Cardiovascular Pharmacotherapeutics
Cardiovascular Pharmacotherapeutics
Third Edition

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For Edmund H. Sonnenblick, MD
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As recently as five decades ago, clinicians had a paucity of effective treatments for treating patients with cardiovascular disease. Since then, no other area of medicine has undergone such a revolution in therapeutics as that in cardiovascular pharmacology, a revolution which has impacted favorably on the morbidity and mortality of patients worldwide.

It is a formidable challenge for the cardiovascular specialist to keep up with the rapid pace of drug discovery and the subsequent introduction of new therapeutic agents into clinical practice. The third edition of *Cardiovascular Pharmacotherapeutics* sheds light on these advances, while pointing to new directions in therapy that will further revolutionize the prevention and care of cardiovascular disease in our patients.

The objectives of the third edition have not changed since the publication of the first edition with Drs. William H. Frishman and Edmund H. Sonnenblick 14 years ago or the second edition 8 years ago with Drs. William H. Frishman, Edmund H. Sonnenblick, and Domenic A. Sica. The third edition is designed to provide a compendium of updated information for the clinician using drug therapy to prevent and treat cardiovascular disease and for those with an academic interest in cardiovascular pharmacology. The scientific and evidence-based rationale for each pharmacotherapy is provided in detail.

The editors have had a long experience in carrying out basic science investigations and clinical trials in the study of cardiovascular drugs. Drawing upon this experience, they have authored or coauthored almost all the book chapters in the volume, while carefully editing the chapters of other noted contributors to bring a consistency in style and content to the entire text.

This edition is organized into 4 main sections. The introductory section includes chapters related to relevant clinical pharmacology, the placebo effect in cardiovascular disease treatments, patient adherence to pharmacotherapy, and pharmacoeconomics.

In the next section, the available cardiovascular drugs are reviewed, and each class of drugs is organized into separate chapters. In these chapters the reader will find detailed discussions on how to use individual drugs for prevention and treatment. New drugs in development for each class of agents are also reviewed. Compared to the first 2 editions, the editors have provided hundreds of updated reference citations, as well as adding new chapters on drugs for pulmonary hypertension, vasopressin and vasopressin antagonists, and drug-eluting stents. Since cardiovascular clinicians do not practice in a vacuum, there are also chapters in this section that deal with the pharmacotherapy of obesity, diabetes mellitus, and smoking cessation as it relates to the cardiac patient.

The third section deals with special topics related to cardiovascular pharmacotherapy that the clinician will often encounter and includes chapters on alternative and complementary medicine, cardiovascular drug–drug interactions, pediatric cardiovascular pharmacology, antibiotic prophylaxis and treatment guidelines for endocarditis and rheumatic fever, and drug therapy of cerebrovascular and peripheral vascular diseases. The section concludes with a chapter on cytokines and myocardial regeneration as a new therapeutic option for cardiac disease and a final chapter which summarizes the status of more than 200 agents that are currently in clinical trials as innovative treatments for cardiovascular disease.

The book concludes with an 8-part appendix section. The first part provides relevant pharmacokinetic information regarding all the available cardiovascular drugs; the second section offers practical drug prescribing information. The remaining 6 appendices provide guides for using cardiovascular drugs in specific patient populations.
This book features an accompanying website, *Advances in Cardiovascular Pharmacotherapeutics* (www.cvptc3.com), which highlights advances in cardiovascular drug therapy. Each chapter in the book is updated periodically online with links to new studies; the updates are overseen by the original chapter authors. In addition, the site reviews new cardiovascular drugs approved by the FDA for clinical use as well as drugs under investigation. Readers may communicate directly with the authors and editors through the website regarding topics related to cardiovascular drug use.

Note that bibliographic references are not listed in the book but available online in the form of downloadable PDFs at www.cvptc3.com.

The editors are indebted to the many contributors to this book, some of whom have worked as research collaborators and trainees with the editors, and who have gone on to develop their own national and international reputations in their areas of interest (Drs. Eberhardt, Gehr, Klapholz, LeJemtel, Peterson, Rosenblum, and Zimetbaum).

A special acknowledgment must be given to Joanne Cioffi-Pryor who has been the editorial assistant for all 3 editions of this textbook and the 2 editions of the supplementary handbooks published in 1998 and 2004. Joanne has worked with the editors for more than 25 years on other textbooks and on peer review journals that include the *American Journal of Medicine*, *Cardiology in Review*, and the *Year Book of Medicine*. Her patience, competence, organizational skills, and meticulous attention to detail have vastly contributed to the successful completion of this latest text.

We wish to acknowledge our publishers, Mike Crouchet and Steven Korn, as well as the production staff at Cardiotext, especially Caitlin Crouchet, and Beth Wright of Trio Bookworks. Also, we wish to acknowledge George Dominguez for his expert work with the illustrations.

Finally, the most important collaborators are our wives, children, and grandchildren, to whom we owe a great debt for their continued love, patience, and forbearance. We also acknowledge our parents for all their love and devotion. We dearly mourn the passing of our colleague Edmund Sonnenblick, who was the inspiration for this current edition.

The editors feel privileged to have been part of the golden era of cardiovascular drug development that began in the early 1970s and continues today. We hope that this new edition of *Cardiovascular Pharmacotherapeutics* will continue to educate and energize health care providers, students, and future investigators in the pursuit of new drug therapies for improving the care of patients with cardiovascular disease.

—William H. Frishman
Domenic A. Sica
**In Memoriam**

Edmund H. Sonnenblick, MD, 1932–2007

Dr. Edmund H. Sonnenblick died in 2007 after a long and courageous battle with cancer. He was just shy of his 75th birthday. He had been coeditor of the first and second editions of *Cardiovascular Pharmacotherapeutics* and the supplementary handbooks and has been an inspiration for this third edition.

Ed was a towering figure in academic cardiology who made seminal contributions in the areas of cardiovascular physiology and energetics, pathophysiology, and therapeutics. The clinical approaches we use now to treat patients with ventricular dysfunction, heart failure, valvular heart disease, and coronary artery disease stem, in great part, from Ed's pioneering research work.

Ed graduated *cum laude* from Harvard Medical School. He completed his postgraduate training in medicine at Columbia Presbyterian Hospital in New York City where he worked directly with Drs. John Laragh and Paul Cannon. At Columbia, Ed was credited as being the first individual to use the electron microscope to image heart muscle structure and the force of its contractions. Subsequently he joined the Cardiovascular Research Laboratories at the National Institutes of Health in Washington DC, working with Drs. Stanley Sarnoff and Eugene Braunwald. At the NIH, Ed carried out fundamental studies on the structure and function of heart muscle that has formed the basis of our current understanding of cardiac ventricular function under normal physiologic and pathophysiologic conditions. In addition to Drs. Sarnoff and Braunwald, his collaborators at the NIH included Drs. John Ross Jr., Dean Mason, William Parmley, Henry Spotnitz, and James Spann.

In 1968 Ed joined Dr. Richard Gorlin at the Peter Bent Brigham Hospital in Boston, where he served as Codirector of Cardiovascular Research and as Associate Professor of Medicine at Harvard Medical School. At Harvard he continued much of the work started at the NIH, while helping to train many of the future leaders of academic cardiology.

In 1975 Ed moved to the Albert Einstein College of Medicine in the Bronx, New York as the Olson Professor of Medicine and Chief of the Division of Cardiology. He was also Director of the Cardiovascular Center. In 1996 he stepped down as Division Chief after 21 years of distinguished leadership, but remained active as a clinical cardiologist and investigator. At Einstein he held the position of the Edmond Safra Distinguished Professor of Medicine until the time of his death.

During his 30 years at Einstein, Ed branched out into translational medicine. Working with collaborators at Einstein, he helped to demonstrate the efficacy and safety of both beta-adrenergic blockers and inhibitors of the renin-angiotensin system in the treatment of congestive heart failure. In reaction to the results of trials with catecholamines and phosphodiesterase inhibitors, Ed was instrumental in overturning the inotropic therapy approach as a first-line therapy for chronic heart failure. In collaboration with Dr. Piero Anversa at New York Medical College in Valhalla, New York, he proposed new theories regarding cardiomyocyte growth and death and the etiology of heart failure. Ed was also involved with Dr. Anversa in the fundamental studies of myocardial regeneration and cardiac stem cell therapy, and he lived to see the early application of these experimental findings applied in clinical medicine.

Ed was a major contributor to the basic science and clinical literature, authoring and coauthoring more than 650 original scientific articles, reviews, and chapters. He was the coeditor of *Progress in Cardiovascular Diseases* with Dr. Michael Lesch and an editor of *Hurst's The Heart* for 4 editions. He was the coauthor with John Ross Jr. and
Eugene Braunwald of the text *Mechanisms of Contraction of the Normal and Failing Heart*, which appeared in 2 editions.

Ed received numerous honors, including the Distinguished Scientific Award of the American College of Cardiology and the Research Achievement Award from the American Heart Association, given posthumously at its 2007 Annual Scientific Sessions.

I had the good fortune to work closely with Ed Sonnenblick for more than 30 years. I joined him as a faculty member at Einstein in 1976. Previously I had followed his remarkable career at the NIH and at Harvard while I was both a medical student and house officer. Ed was an exceptional mentor, whose knowledge of cardiac pathophysiology dramatically influenced my own academic career and that of hundreds of colleagues and trainees. He helped train many of the first heart failure clinical specialists, including Drs. Thierry LeJemtel, Donna Mancini, Uri Elkayam, Joel Strom, Stuart Katz, Hillel Ribner, and Marc Klapholz. He helped form the first academic program in molecular cardiology with Drs. James Scheuer, Leslie Leinwand, Richard Kitsis, and Glenn Fishman. Ed had the ability to bring basic physiologic principles, new concepts in molecular medicine, with a logical clinical approach, to the bedside. He was a revered teacher who was just as excited to be with patients, students and clinical trainees as he was with his colleagues in the basic science laboratory.

After 20 years as colleagues at Einstein, I continued my interactions with him at New York Medical College where I had moved to be Chairman of Medicine in 1997. Fortunately for me, Ed maintained his status as an Adjunct Professor at New York Medical College where he worked with Piero Anversa. It was a privilege to watch him participate at Piero’s weekly research meetings, until the time of his death.

Ed was a remarkable intellect. He had the ability to integrate basic physiologic principles with quantitative parameters of the diseased heart. He brought us such terms as “preload” and “afterload.” His tremendous curiosity and interest in new ideas was contagious and an inspiration to young trainees and colleagues. He had the ability to make the most difficult concepts understandable, both at the lectern and in one-on-one interactions.

Ed was also a true “Renaissance Man,” a “Man for All Seasons.” He had an interest in everything and everybody. He was an avid reader, especially of history, and was a connoisseur of the arts. He did not suffer fools lightly and set the highest standards for himself and those around him. His favorite phrase at our research meetings was “I wonder,” and he left a great legacy and personal example for all of us in cardiovascular medicine.

—William H. Frishman
In Memoriam

Paul Woolf, MD, 1951–2010

During the preparation of this third edition of Cardiovascular Pharmacotherapeutics, Dr. Paul Woolf, a valued colleague, lost his courageous battle with cancer.

Paul coauthored the chapter on pediatric cardiovascular pharmacology for both the second and third editions of the book. At the time of his death, he was an Associate Professor of Pediatrics and Associate Dean for Graduate Medical Education at New York Medical College. He also had served for nearly a decade as the Program Director of the Pediatric House Staff Program at the Maria Fareri Children’s Hospital at Westchester Medical Center. A noted cardiac electrophysiologist, he was Associate Chief of the Division of Pediatric Cardiology in the Department of Pediatrics.

A native of Massachusetts, Paul completed his undergraduate training magna cum laude at Brandeis and his medical studies at Columbia. He completed his house staff and fellowship training in pediatrics and pediatric cardiology at the Children’s Hospital of Philadelphia and joined the faculty at New York Medical College and the Westchester Medical Center in 1984.

Paul was a valued colleague with his steady, even-keeled, and reassuring presence. He was instrumental in the founding of the children’s hospital at the Westchester Medical Center, and he dedicated his entire professional life to improving the health of children. Paul was an outstanding teacher-clinician and the role model of a professional for hundreds of trainees. A devoted husband and father, he was a rabid Red Sox and Patriots fan.

We grieve his untimely passing.

—William H. Frishman
Michael Gewitz
Part 1

Introduction
This chapter focuses on some of the basic pharmacologic principles that influence the manner by which cardiovascular drugs manifest their pharmacodynamic and pharmacokinetic actions. A discussion of drug receptor pharmacology is followed by a review of drug disposition, drug metabolism, excretion, and effects of disease states on pharmacokinetics.

Receptors

For over 100 years, it has been recognized that, in order to elicit a response, a drug must interact with a receptor, which is the interface between drug and body and the principal determinant of drug selectivity. The receptor, (1) recognizes and binds the drug, (2) undergoes changes in conformation and charge distribution, and (3) transduces information inherent in the drug structure (extracellular signal) into intracellular messages, resulting in a change in cellular function. A receptor may be any functional macromolecule and is often a receptor for endogenous regulatory substances, such as hormones or neurotransmitters.

Nature of Receptors

Receptors typically are proteins, lipoproteins, or glycoproteins including (1) regulatory proteins that mediate the action of endogenous substances such as neurotransmitters, hormones, etc.; (2) enzymes, which typically are inhibited by drugs; (3) transport proteins such as Na(+)/K(+) ATPase; and (4) structural proteins such as tubulin.

1. Gated channels involve synaptic transmitters (eg, acetylcholine, norepinephrine) and drugs mimicking their action. These receptors regulate ion flow through membranes, altering transmembrane potentials. The well-characterized nicotinic acetylcholine receptor is a protein consisting of five subunits, two of which selectively bind acetylcholine, opening the Na+ channel through conformational alterations. In the absence of an agonist, the channel remains closed. Other drugs—eg, certain anxiolytics—act similarly at gamma amino butyric acid (GABA)-regulated Cl- channels. The time sequence is extremely fast (milliseconds).

2. G proteins (which interact with guanine nucleotides) diffuse within the cell membrane, interacting with more than one receptor. They regulate enzymes, such as adenyl cyclase, or ion channels. Their large number and great diversity may account for drug selectivity in some cases. A prominent example is the role of a specific G protein in the regulation of muscarinic receptors in cardiac muscle. Activation enhances potassium permeability, causing hyperpolarization and depressed electrical activity. Similarly, the a- and b-adrenergic receptors and the angiotensin II receptors are part of a major class of G protein-coupled receptors.

3. Transmembrane enzymes—eg, protein tyrosine kinases—recognize ligands such as insulin and several growth factors. These bind to an extracellular domain of the receptor and allosterically activate the enzyme site at the cytoplasmic domain, enabling phosphorylation of receptor tyrosines. The signaling process proceeds to phosphorylation of other intracellular proteins, involving serine and threonine as well. Downregulation of these receptors is frequently seen, limiting the intensity and duration of action of the ligand (drug).

4. Intracellular receptors: Here the lipophilic drug (agonist) penetrates the plasma membrane and binds selectively to an intracellular macromolecule. The drug-receptor complex subsequently binds to DNA-
The response time is slow (up to several hours) and duration of hours or days after disappearance of the drug, due to turnover time of the proteins expressed by the affected gene. These four major classes are depicted in Figure 1.

Figure 1-1. This shows the scheme for the four major types of drug receptors and linkage to their cellular effects. Included here are direct control of ion channel, indirect G protein coupling via messenger ion channels, direct control of effector-enzyme, and control of DNA transcription, as well as the various models that are looking at this. Essentially, one gated channel involves synaptic transmitters; an example of this could be acetylcholine and norepinephrine (and drugs mimicking their action). These receptors regulate ion flow through membranes, alternating transmembranal potentials. The well-characterized nicotinic-acetylcholine receptor is a protein consisting of five subunits, two of which selectively bind acetylcholine, opening the sodium channel through conformational alterations. In the absence of an agonist, the channel remains closed. Other drugs, for example, certain anxiolytics, act similarly at GABA-regulated chloride channels. The time sequence is extremely fast, measured in milliseconds.

The indirect G protein interacts with guanine nucleotides, which diffuse within the cell membrane, interacting with more than one receptor. They regulate enzymes such as adenyl cyclase or ion channels. Their large number and great diversity may account for drug selectivity in some cases. A prominent example is the role of specific G protein in the regulation of muscarinic receptors in cardiac muscle. Activation enhances potassium permeability, causing hyperpolarization and depressed electrical activity.

Transmembranal enzymes such as protein tyrosine kinases recognize ligands such as insulin and several growth factors. These bind to an extracellular domain of the receptor and allosterically activate the enzyme site at the cytoplasmic domain, enabling phosphorylation of receptor tyrosines. The signaling process proceeds to phosphorylation of other intracellular proteins involving serine and threonine as well.

With the intracellular receptors, lipophilic drugs permeate the plasma membrane and bind selectively to an intracellular macromolecule. The drug-receptor complex subsequently binds to DNA, modifying gene expression. Response time is slow (up to several hours) and duration of hours or days after disappearance of the drug due to turnover time of the proteins expressed by the affected gene.

The four major classes of receptors are depicted in Figure 1-1. Transmembrane signal transduction also involves a number of second messenger systems that respond to receptor activation. These systems include (1) cyclic AMP, which is formed by the action of ligand-activated adenyl cyclase on ATP and, through activation of selective protein kinases, mediates numerous hormonal and drug responses; and (2) phosphatidyl inositol, which, through hydrolysis by phospholipase C within the cell membrane, yields water-soluble inositol triphosphate, which enters the cell and releases bound Ca2+ and lipidsoluble diacylglycerol, which remains in the membrane, where it activates protein kinase C.

Kinetics of Drug-Receptor Interactions

Drug or agonist interacts with its receptor as follows:

\[
A + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} AR
\]

where \( R \) = unoccupied receptor; \( AR \) = drug-receptor complex.

According to the law of mass action, the forward reaction rate is given by \( k_1[A][R] \) and the reverse reaction rate by \( k_2[AR] \).

The dissociation constant (Kd) is given by:

\[
K_d = \frac{[A][R]}{[AR]}
\]

relates to \( \frac{k_2}{k_1} \)

The binding (affinity) constant (Kd) is given by:

\[
K_a = \frac{1}{K_d}
\]

relates to \( \frac{k_2}{k_1} \)

Each constant is characteristic of a drug and its receptor.

Drug-receptor interaction may involve any type of bond: van der Waals, ionic, hydrogen, covalent. The in-
Receptors are best described in terms of ED50 (dose eliciting 50% of maximal response), it is necessary to plot the response versus the log dose. In this way, the ED50 can be more accurately measured (Figure 1-2B), since it is typically found in a relatively linear part of the curve. This relationship is valid when a graded response is discernible.

The log dose–response curve can also be used to distinguish competitive and noncompetitive inhibition characteristic of many commonly used drugs. Competitive inhibition implies that the agonist and antagonist compete for binding at the active site of the receptor (eg, beta-adrenergic receptor blocking drugs are competitive inhibitors at beta-adrenergic receptor sites). Binding of the antagonist to the active site induces no biological response but causes a shift to the right of the log dose–response curve, indicating that more agonist is required to attain a maximal response (Figure 1-3A). A noncompetitive inhibitor, on the other hand, binds at other than the active site, preventing the agonist from inducing a maximal response at any dose (Figure 1-3B). There may also be blockade of an action distal to the active site of the receptor. For example, verapamil and nifedipine are calcium channel blockers and prevent influx of calcium ions, nonspecifically blocking smooth muscle contraction.

A partial agonist induces a response qualitatively similar to that of the true agonist but quantitatively far less than the maximal response. Of critical importance is the lack of full response to the agonist in the presence of the partial agonist, the latter thereby acting as an inhibitor. The nonselective beta-blocker pindolol exhibits prominent partial agonist activity. The original hope that such a drug would be valuable in cardiac patients with asthma or other lung diseases has not been realized.

Two fundamental properties of drugs, efficacy (intrinsic activity) and potency, must be distinguished (Figure 1-4A). A partial agonist, unable to elicit a full response, has lower efficacy than does a true agonist. Efficacy is actually a property of the drug-receptor complex, since the efficacy of a drug may change from one receptor system to another. Potency refers to the concentration or dose of drug required to elicit a standard response. Figure 1-4B shows that a series of drugs acting on the same receptor and differing in potency may possess similar efficacy; with increasing dose, each can induce the same maximal response. In Figure 1-4C are log dose–response curves for several agonists with similar potencies but with varying efficacies. Potency is often considered to be a function of the drug-receptor binding constant. Clinically, a drug that undergoes extensive first-pass metabolism, is rapidly inactivated, or has other impediments to accessing its receptor may actually require a high dose despite demonstration of high receptor affinity in vitro. High potency in itself is not a therapeutic advantage for a drug. The therapeutic index must always be considered. A twofold increase in potency may be accompanied by a similar increase in toxicity, yielding no net advantage.

**Figure 1-2.** This figure shows the dose-response curve using an arithmetic dose scale, as seen in 2A, and log-dose scale, as seen in 2B. If one measures an effect at varying drug doses and then plots the drug response versus the dose, a rectangular hyperbola is obtained (as shown in 2A). Because quantitative comparisons among drugs and types of receptors are best described in terms of ED50 (dose eliciting 50% of maximal response), it is necessary to plot the response versus the log dose. In this way, the ED50 can be more accurately measured, as shown in 2B, since it is found in a relatively linear part of the curve. This relationship is valid when a graded response is discernible.

A = arithmetic dose scale; B = log-dose scale; ---- = Determination of 50% effect.

A fundamental tenet in receptor theory is that a receptor must be “occupied” by an agonist to elicit a biological response and that the biological response is proportional to the number of receptors occupied. However, the ultimate response—e.g., change in blood pressure, renal function, hormone secretion—may not exhibit a simple proportional relationship owing to the complexity of postreceptor events. The spare-receptor theory states that a maximal response may be attained prior to occupancy of all receptors at a particular site. This is strictly a quantitative concept since the spare (unoccupied) receptors do not differ qualitatively from other receptors at the same site. Spare receptors may represent 10% to 99% of the total and may allow agonists of low affinity to exert a maximal effect.

Modulation of receptor function is frequently seen. Downregulation is the decrease in the number of receptors upon chronic exposure to an agonist, resulting in lower sensitivity to the agonist. The receptor number may later normalize. For example, dobutamine infusion administered to patients with cardiac failure often leads to loss of efficacy of the drug due to downregulation of myocardial beta adrenoceptors. Upregulation was first illustrated by denervation supersensitivity. Sympathetic denervation reduces the amount of neurotransmitter (norepinephrine) to which the postsynaptic adrenoceptor is exposed. Over a period of time, the receptor population increases, resulting in a heightened sensitivity to small doses of agonist.

Drug-induced depletion of sympathetic neurotransmitters (reserpine, guanethidine) elicits a similar response. The increase in cardiac beta receptors with hyperthyroidism increases the sensitivity of the heart to catecholamines. Thus, thyrotoxicosis is accompanied by tachycardia, which in kind responds to the beta blocker propranolol.

**Drug Disposition and Pharmacokinetics**

Although binding of a drug to its receptor is required for most drug effects, the amount bound is a small fraction of the total drug within the body. The mechanisms controlling the movement, metabolism, and excretion of drug within the body are critically linked to the dose, route of administration, onset/duration and intensity of effect, frequency of administration, and, often, toxic adverse effects.

**Passage of Drugs Across Cell Membranes**

Movement of nearly all drugs within the body requires transport across cell membranes by filtration (kidney glomeruli); active transport (renal tubules); passive transport; and/or facilitated diffusion. The movement of drugs across cell membranes occurs most commonly by simple diffusion. Passive flux of molecules down a concentration gradient is given by Fick’s law.
Flux (molecules per unit time)  
\[ \text{Flux} = \frac{(C_1 - C_2) \times \text{permeability coefficient}}{\text{thickness}} \]

where \( C_1 \) and \( C_2 \) = the higher and lower concentrations, respectively; \( \text{area} = \text{area of diffusion; permeability coefficient} = \text{mobility of molecules within the diffusion pathway; \( \text{thickness} = \text{that of the diffusion path.} \)

Therefore, rate and direction of passage depend on (1) concentration gradient across the membrane of unbound drug and (2) lipid solubility of drug. Most drugs, being weak organic bases or acids, will be ionized or un-ionized depending on their \( pK \) and the \( pH \) of their environment. The un-ionized form, being more lipid-soluble, readily diffuses across the membrane, whereas the ionized form is mainly excluded from the membrane. This principle is adhered to most rigidly in the brain, where the tight gap junctions in cerebral capillaries prevent intercellular diffusion of hydrophilic drugs, creating the so-called blood–brain barrier. Drugs having a charge at physiologic \( pH \)—eg, terfenadine (Seldane) and neostigmine—are generally excluded from the brain. By contrast, in the liver, blood passes through sinusoids that are highly fenestrated, allowing plasma constituents, including charged and noncharged drugs, to pass readily into the interstitial space and have direct contact with the liver cells, where selectivity for drug transport is far less.

Absorption

Absorption of drugs from sites of administration follows the general principles described earlier. Other factors include solubility, rate of dissolution, concentration at site of absorption, circulation to site of absorption, and area of the absorbing surface.

Routes of Drug Administration

Sublingual

Sublingual administration avoids destruction due to the acidic environment of the stomach and bypasses the intestine and liver, avoiding loss through absorption and enzymatic destruction (first-pass effect). It is used for nitroglycerin (angina pectoris); ergotamine (migraine); and certain testosterone preparations (avoids prominent first-pass effects).

Oral Route

In addition to the convenience of this route, the structure, surface area, and movement of the intestines are conducive to absorption, which takes place throughout the GI tract. Rules for passive transport are applicable; \( pH \) gradient along the tract influences absorption of drugs with varying \( pK \). Aqueous and lipid solubility of the drug may be competing factors—ie, a drug may be lipid-soluble, favoring absorption, but so insoluble in water that absorption is very poor or erratic. Rate of absorption is partially regulated by intestinal blood flow, which serves to remove the drug from the absorption site, thus maintaining a high GI tract–blood concentration gradient and gastric emptying time (most drugs are mainly absorbed in the intestine). Absorption varies with \( pH \), presence and nature of food, mental state, GI and other diseases, endocrine status, and drugs that influence GI function.

Drugs may be extensively (high extraction) or minimally (low extraction) cleared from both the portal and systemic circulation by the liver. The extent of removal is referred to as the extraction ratio. It follows that the rate of plasma clearance of high-extraction drugs is very sensitive to hepatic blood flow. An increase or decrease in hepatic blood flow will enhance or depress, respectively, drug clearance from the plasma. Conversely, variations in hepatic blood flow have minimal influence on removal of low-extraction drugs, since so little is removed per unit time. Diminished hepatic extraction capacity, as seen in severe liver disease and aging, can significantly decrease the first-pass effect and plasma disappearances of high-extraction drugs.

Rectal Route

This route is reserved mainly for infants, cases of persistent vomiting, and/or patients who have significantly altered mental status without ready vascular access. Absorption follows rules for passive transport but is often less efficient than in other parts of the GI tract. Since blood flow in the lower part of the rectum connects directly with the systemic circulation, portions of rectally administered drugs bypass the first-pass effect.

Pulmonary Route

The pulmonary route is used primarily for gaseous and volatile drugs as well as nicotine and other drugs of abuse, such as crack cocaine. These are rapidly absorbed due to their high-lipid solubility and small molecular size and the vast alveolar surface area (approximately 200 M\(^2\)).

Transdermal Route

This route has come into vogue for the administration of certain cardiac, central nervous system (CNS), and endocrine drugs to produce a slow, sustained effect. The large surface area (2 \( M^2 \)) and blood supply of the skin (30%) are conducive to absorption. Advantages include more stable blood levels, avoidance of first-pass effect, and better compliance (since frequency of administration is greatly diminished, there are no injection risks, and variability in oral absorption is eliminated). The drug must be relatively potent—ie, effective in low dose—sufficiently lipid, and water-soluble to penetrate the several layers of the skin; it
must also be of a nonirritant nature and stable for several days. Inflammation or febrile states, by increasing cutaneous blood flow, may enhance drug absorption. Drugs administered by the transdermal route include scopolamine, nitrates, clonidine, estradiol, and testosterone.

Injection
This route avoids the first-pass effect. The intravenous route allows rapidity of access to the systemic circulation and a degree of accuracy for dosage not possible with other routes. Intramuscular and subcutaneous routes require absorption into the systemic circulation at rates dependent upon the lipid-solubility of the drug and circulation to the injected area. For example, absorption of intramuscularly administered drugs is better from the deltoid than the gluteal muscle. Epinephrine may be added to subcutaneous injection to constrict blood vessels and thus retard absorption. Drugs can also be administered into regional circulations through indwelling catheters (eg, vascular growth factors) and injected directly into the vascular endothelium and myocardium (eg, gene therapy).

Bioavailability
There are two aspects of this concept: (1) Absolute bioavailability, or the proportion of administered drug gaining access to the systemic circulation after oral administration as opposed to IV administration, reflecting the first-pass effect, and (2) Relative bioavailability of different preparations of the same drug.

By plotting plasma concentration versus time, one can calculate the area under the curve (AUC), a measure of bioavailability (Figure 1-5). The curve also indicates peak plasma levels and time to attain peak levels. Bioequivalent preparation should be identical in each of these parameters. However, considerable variation may be seen among different preparations, reflecting extent and rate of drug release from its dosage form (pill, capsule, etc.) within the GI tract. Factors that may affect bioavailability include conditions within the GI tract, pH, food, disease, other drugs, metabolism, and/or binding within the intestinal wall and liver. Ideally, preparations should be tested for bioavailability under identical conditions in the same subject. The narrower the therapeutic index of a drug, the greater the concern for variation in bioavailability. Examples of varying drug bioavailabilities are given in Table 1-1.

Distribution to Tissues
Vascularity and plasma concentration of drug are the main determinants of tissue distribution. Organs receiving a high blood supply—eg, kidney, brain, and thyroid—are rapidly exposed to drugs, whereas bone and adipose

![Figure 1-5. This figure shows theoretical plasma levels of a drug as a function of time. The curve is used to determine bioavailability since it illustrates peak concentration, time of peak concentration, and AUC. Bioequivalent preparations should be identical in each of these parameters. However, considerable variations may be seen among different preparations, reflecting extent and rate of drug release from its dosage form (pill, capsule, etc.) within the GI tract.](image)


<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>46</td>
</tr>
<tr>
<td>Atropine</td>
<td>50</td>
</tr>
<tr>
<td>Bretylium</td>
<td>20</td>
</tr>
<tr>
<td>Caffeine</td>
<td>100</td>
</tr>
<tr>
<td>Digoxin</td>
<td>60–75</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>40–90</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>80</td>
</tr>
<tr>
<td>Flecainide</td>
<td>35</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>35</td>
</tr>
<tr>
<td>Meperidine</td>
<td>52</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>38</td>
</tr>
</tbody>
</table>

tissue receive only a minor fraction of the dose. High plasma concentrations of drugs result in high tissue levels due to mass action and passive diffusion across cell membranes. Lipid-soluble drugs readily pass the placenta, enabling distribution to and possible action on a developing fetus. Therefore, the use of any drug is not recommended during pregnancy if it can be avoided; thiazide diuretics and warfarin, among others, are particularly discouraged. Redistribution of drugs can influence pharmacologic response. For example, it is well established that the actions of benzodiazepines and thiopental are terminated not by metabolism or excretion but by redistribution of the drugs away from the effect compartment in the brain.

Site-specific drug delivery would enhance therapeutic effectiveness and limit side and toxic effects. This has been achieved for very few drugs, since normal body mechanisms are generally conducive to wide distribution to sites unrelated to the desired drug receptors. A type of organ targeting is seen with prodrugs such as L-dopa, which is converted to the active form, dopamine, in the CNS, and sulfasalazine, which is converted to the active salicylate by gut bacteria within the lower bowel.

### Binding to Plasma Proteins

Most drugs are bound to plasma proteins to some extent. Albumin binds a wide spectrum of drugs, particularly those with acidic and neutral characteristics. Binding is usually nonspecific, although some selective sites are known. Basic drugs may also bind to albumin, but mainly to alpha₁-acid glycoprotein, an acute-phase reactant protein. Lipoproteins also bind some lipophilic and basic compounds. Several highly specific proteins exist that bind thyroxine, retinol, transcortin, etc., but these are of little consequence for drugs and other xenobiotics.

Binding to plasma proteins is always reversible, and the half-life of binding and release is exceedingly short (measured in milliseconds). Thus, even in the case of extensive (tight) binding, it is rapidly reversible under physiologic conditions. Since concentration gradients, which determine the rate of passive transport across membranes, are based solely on free drug, it follows that binding to plasma proteins slows the rate of removal of a drug from plasma by diminishing the concentration gradient across capillary cell membranes. Thus, access to all extravascular sites, receptors, metabolism, storage, and excretion are to a great extent regulated by plasma protein binding. It follows that the half-lives of many drugs correlate with the extent of binding. On the other hand, active transport, as in the proximal tubule, is unaffected by plasma protein binding.

For example, nifedipine, which is 96% bound to plasma proteins, has a half-life of only about 2 hours. In this case, the protein-bound portion of the drug serves as a readily accessible reservoir due to rapid reversibility of binding.

Hepatic extraction is sensitive to plasma protein binding. For low-extraction drugs, binding is of considerable importance, whereas hepatic uptake of high extraction drugs is little influenced by binding.

Displacement of drugs from binding sites increases the proportion of free drug in the plasma and thus the effective concentration of the drug in extravascular compartments. Similarly, increasing the dose of a drug beyond binding capacity disproportionately increases the unbound fraction within the plasma and may lead to undesired pharmacologic effects. Plasma-binding proteins may be decreased in concentration or effectiveness under the following conditions:

- **Albumin**: Burns, nephrosis, cystic fibrosis, cirrhosis, inflammation, sepsis, malnutrition, neoplasia, aging, pregnancy, stress, heart failure. Uremia causes decreased binding of acidic but not basic drugs.
- **Alpha₁-acid glycoprotein**: Aging, oral contraceptives, pregnancy.

The possibility of altered drug disposition should be considered in each case.

### Volume of Distribution

Under ideal conditions, drugs are considered to be distributed in one or more of the body fluid compartments. The apparent volume of distribution (Vd) is the body fluid volume that appears to contain the drug.

\[
Vd = \frac{\text{dose}}{\text{plasma concentration (after equilibration)}}
\]

For example, Vd = plasma volume (eg, heparin) implies extensive binding of the drug to plasma proteins, with the bulk of the drug remaining in the plasma. Vd = total body water (eg, phenytoin, diazepam) implies that the drug is evenly distributed throughout the body. However, one should avoid associating Vd values with a specific anatomic compartment, since binding at extravascular sites (eg, procainamide, verapamil, and metoprolol) may significantly affect Vd determinations. The importance of Vd values lies in the fact that they can vary with age, gender, disease, etc. Thus, changes in plasma protein synthesis, skeletal muscle mass, adipose tissue mass, adipose/muscle ratio, and body hydration will be reflected in Vd and may markedly alter the therapeutic as well as the toxic response to a drug. Values of Vd, if used intelligently, can provide information on the body's distribution of a drug, changes in body water compartments, implications for intensity of effect, and rate of elimination.

### Half-Life and Clearance

The half-life (T₁/₂) of a drug is the time for the plasma concentration to be decreased by one-half. It is usually...
independent of route of administration and dose. Assuming equilibration among all body fluid compartments, it theoretically is a true reflection of the T½ within the total body and correlates closely with duration of action. T½ is derived from a first-order reaction calculated from a semilog plot of the plasma concentration versus time during the elimination phase, which reflects metabolism and excretion of the drug (Figure 1-6). Linearity of this phase reflects exponential kinetics (first order), in which plasma concentrations of drug do not saturate the rate-limiting step in elimination. The process may be expressed as a rate constant, k, the fractional change per unit time. T½ and k are related by the following equation:

\[ T_{\text{½}} \times k = 0.693 \text{ (In 0.5)} \]

or

\[ T_{\text{½}} = \frac{0.693}{k} \]

After oral administration, the initial period is called the absorption phase. Here too, T½ is calculated from the elimination phase. In a few cases (alcohol, phenytoin, high-dose aspirin), the rate-limiting step is saturated and the plasma disappearance rate is zero order. For phenytoin, this may lead to difficulty in controlling blood levels to maintain efficacy while avoiding toxicity.

Total body clearance (Clτ) is an expression of the fluid Vd cleared per unit time. It is calculated as the product of the elimination rate constant and the Vd.

\[ \text{Cl}_\tau = iVd \]

It follows that

\[ T_{\text{½}} = \frac{0.693}{\text{Cl}_\tau} \]

This concept assumes clearance from a single body fluid compartment and is the sum of renal and hepatic clearances. Disease states, aging, and other conditions where Vd may be altered would change clearance. Clearance can be used to determine correct dosage when the desired plasma concentration has been predetermined but changes in physiologic parameters governing drug disposition occur, thus altering clearance.

Dosage = Cl × Css

where Cl = clearance; Css = steady-state plasma drug concentration. Dosage therefore is a replacement of cleared drug.

Caution: Since clearance is calculated from Vd, a theoretical rather than a physiologic term, the number derived may itself not be truly physiologic. In therapeutics, it is the change of clearance that is a marker for altered drug disposition.

Steady-State Kinetics

During chronic oral administration of a drug, its steady-state plasma level is not a set concentration but a fluctuating concentration, reflecting periodic absorption and continual removal. When drug administration is begun, in accord with first-order kinetics, the elimination rate gradually increases with increasing plasma levels, and, eventually, a steady state is attained where input equals output. This is the plateau effect (Figure 1-7). The following can be shown:

- 50% of steady state is attained after one half-life
- 75% of steady state is attained after two half-lives
- 87.5% of steady state is attained after three half-lives
- 93.75% of steady state is attained after four half-lives

The rule of thumb is that steady state is attained in four to five half-lives.

After drug withdrawal, the converse of the plateau effect is seen—ie, plasma levels are reduced by

- 50% in one half-life
- 75% in two half-lives
- 87.5% in three half-lives
- 93.75% in four half-lives

...
When a long half-life—eg, 14 hours—and therapeutic demands preclude waiting four to five half-lives to attain desired plasma concentration of drug, a loading dose is used, calculated as follows:

\[ LD = \frac{Vd \times C}{F} \]

where \( Vd \) = apparent volume of distribution; \( C \) = desired plasma concentration; \( F \) = fraction of oral dose that reaches the systemic circulation (first pass effect). This is based on the need to fill the entire \( Vd \) to the desired concentration as rapidly as possible. The dose is limited by toxicity, distribution rate, and other variables.

For a drug given by intravenous infusion,

\[ LD = \text{infusion rate} \times T_{1/2} \]

**Drug Metabolism (Biotransformation)**

**Mechanisms and Pathways**

Most drugs and other xenobiotics are metabolized prior to excretion. Although most drugs are ultimately converted to inactive products, many are transformed to pharmacologically active metabolites. In some instances, a drug is metabolized via several pathways, some of which represent inactivation, while others involve activation to active moieties or toxic products.

For many drugs, the first step (phase I) in metabolism is being catalyzed by the cytochrome P450 (mixed-function oxidase) system of the endoplasmic reticulum (microsomal fraction). Cytochrome P450 is actually a large family of isozymes, members of which vary with species, gender, and age. Each has its own spectrum of substrates and can be independently influenced by induction and inhibition. Selective forms of cytochrome P450 (CYP) are shown in Table 1-2. Among the implications of this table is that patients lacking the CYP2D6 isozyme will obtain little or no pain relief from codeine, since CYP2D6 converts codeine to morphine, the active analgesic metabolite of codeine.

The mixed-function oxidase system exists mainly in the liver but has been detected in nonhepatic tissue as well, particularly at other sites of xenobiotic entry—eg, lung, skin, etc. Total metabolism in these tissues is a fraction of that of the liver. Nevertheless, since environmental chemicals often enter the body through the lungs and skin, these tissues are of considerable importance in their initial metabolism.

Major phase I pathways, microsomal and nonmicrosomal, include (1) aliphatic and aromatic hydroxylation, (2) \( N \)-dealkylation, (3) \( O \)-dealkylation, (4) sulfoxidation, (5) \( N \)-hydroxylation (commonly associated with toxic activation of aromatic amines, including a number of chemical carcinogens), (6) azo and nitro reduction, (7) \( O \)-methylation, and (8) hydrolysis by plasma esterase.

Conjugation (synthetic) pathways (phase II) often but not always follow phase I. They include (1) acylation, a common pathway for aliphatic and aromatic primary amines; (2) glucuronide formation; (3) sulfate formation; and (4) glutathione conjugate formation. Phase II
reactions increase drug polarity and charge and thus promote renal excretion (see below).

Glutathione conjugation is a major inactivation mechanism for toxic metabolic intermediates of numerous drugs. For example, in normal dosage, a toxic metabolite of acetaminophen is effectively removed as a glutathione conjugate. In extreme overdose (10 g–15 g and even less when glutathione depletion exists), the demand for glutathione exceeds its rate of hepatic biosynthesis and the accumulation of toxic intermediate leads to liver toxicity and, in rare cases, necrosis and death. Acetaminophen hepatotoxicity is best treated with acetylcysteine, which serves to restore liver glutathione.

Factors Affecting Drug Metabolism

Species
This is a major problem in drug development and research.

Age
Few drugs are studied in young children prior to their approval by the US Food and Drug Administration (FDA), presenting a considerable challenge in the treatment of this population. In the neonate, factors affecting drug disposition include prolonged gastric emptying time, fluctuating gastric pH, smaller muscle mass, greater cutaneous absorption of toxic substances (eg, hexachlorophene), changing body water/fat ratio, less effective plasma protein binding, poor hepatic drug metabolism, and low renal blood flow. Drugs that pass the placenta present problems of disposition to the fetus. The newborn often exhibits a deficiency in glucuronyl transferase, which catalyzes the essential step in bilirubin excretion. If this deficiency is unattended, kernicterus may ensue. The postneonatal period is also a time of rapid structural and physiologic changes, including the capacity to metabolize drugs. Therefore calculation of dosage based solely on body weight or surface area may not always be appropriate. In the elderly, one sees diminished renal plasma flow and glomerular filtration rate; decreased hepatic phase I but not phase II drug metabolism; diminished Vd due to loss of body water compartment; decreased muscle mass; decreased or increased adipose tissue; and decreased first-pass effect.

Genetic Factors
Marked differences in rates of drug metabolism are often attributable to genetic factors. Approximately half the male population in the United States acetylates aromatic amines such as isoniazid rapidly and the other half acetylates slowly (Figure 1–8). The slow-acetylator phenotype is inherited as an autosomal recessive trait. Neither slow nor fast acetylation is an advantage, since the toxicity of both isoniazid (peripheral neuropathies, preventable by pyridoxine administration) and its acetylated metabolite (hepatic damage) is known. Other drugs with genetic factors influencing their clearance include procainamide, hydralazine, and sulfasalazine.

A small percentage (< 1% of the population) has an abnormal form of plasma pseudoesterase and is unable to hydrolyze succinylcholine at the normal rapid rate, leading to a prolonged duration of action. Three forms of cytochrome P450 (CYP2D6, CYP2C19, and CYP2C9) exhibit polymorphism. The phenotypes are slow and rapid metabolizers of many drugs: CYP2D6—debrisoquin, tricyclic antidepressants, phenformin, dextromethorphan, and several beta blockers; CYP2C19—mephenytoin; and CYP2C9—warfarin. Approximately 3% to 10% of the population has the slow trait, inherited in an autosomal recessive fashion.

Nutritional Deficiency

Multiple manifestations of malnutrition may significantly affect drug disposition. These include changes in GI and renal function; body composition (fluids, electrolytes, fat, protein, etc.); hepatic drug metabolism; endocrine function; and immune response. Multiple manifestations are most likely among economically depressed populations and in diseases such as cancer, which are often accompanied by malnutrition.

Effects of Disease

Obviously, hepatic or renal disease can have major consequences for drug disposition. Half-lives for many drugs increase in those with cirrhosis, hepatitis, and obstructive jaundice. Chronic liver disease has the most impact on drugs that are normally cleared in large amounts by the liver. Both drug metabolizing activity and hepatic blood flow may be reduced by portosystemic shunting, which diverts portal blood directly to the systemic circulation. For most drugs, a reduction in drug dosage or a dose interval is necessary. In drugs where the therapeutic effect of the agent is dependent on active metabolites (eg, enalapril), another agent should be selected that is not affected by hepatic metabolism. Liver disease can also influence pharmacokinetics of drugs by decreasing the production of drug-binding proteins.

Kidney disease may manifest itself as altered renal blood flow and depressed glomerular filtration, active transport, or passive reabsorption. Renal disease can affect protein binding (hypoalbuminemia) and urinary pH (alkalization can alter tubular reabsorption drugs because of a change in the ionization of weak bases, thereby resulting in diminished excretion). In drugs that are mainly eliminated by renal excretion (eg, nadolol, digoxin), one can expect a decrease in clearance and a prolongation of the elimination half-life in direct proportion to the creatinine clearance.
In cardiac failure, the decreased cardiac output and the increased sympathetic activation result in poor perfusion of the GI system, liver, and kidneys. These changes have implications for drug absorption, metabolism, distribution, and elimination. There may be delayed and incomplete absorption of drugs from a hypoperfused and edematous gut (eg, diuretics). A decreased volume of distribution has been described for lidocaine. A significant decrease in drug clearance may be observed with those agents whose clearance is dependent on hepatic (high hepatic extraction ratios) and/or renal perfusion. Decreased hepatic metabolizing enzymatic activity has also been described in patients with CHF. In patients with heart failure, drugs should be used initially in low doses. A prolongation of drug half-life in heart failure will require less frequent changes in drug dose since the length of time to reach steady state will be prolonged.

The patient with AMI may have changes in drug-binding proteins (eg, lidocaine) where a drug is more readily protein bound, requiring higher doses to achieve a clinical benefit. Conversely, decreases in cardiac output with MI can influence the metabolism and excretion of drugs, as described earlier, if hepatic and renal perfusion is impaired. In an area of decreased myocardial perfusion, as is seen with coronary thrombosis, cardiac drugs may reach their myocardial targets later and be eliminated at a slower rate.

Cardiac Surgery with Cardiopulmonary Bypass
The utilization of extracorporeal circulation using cardiopulmonary bypass can affect drug pharmacokinetics during cardiac surgery. The effects of cardiopulmonary bypass that can influence drug kinetics include an acute hemodilution action, which can decrease the plasma concentrations of almost any drug. Hemodilution will increase the volume of distribution of propranolol, thereby increasing the drug's elimination half-life. Hemodilution can also cause hypoalbuminemia, which may increase free plasma levels of highly protein-bound drugs. Heparin administration with cardiopulmonary bypass can also increase the free fraction of highly protein-bound drugs. Hypothermia may influence metabolic activity in the liver, decreasing the hepatic clearance of drugs. In addition, there may be sequestration of drugs into the bypass equipment due to absorption.

Induction
Chronic exposure to any of a large number of drugs and other environmental chemicals induces the synthesis of specific forms of cytochrome P450 (Table 1-3); conjugation with glucuronic acid and glutathione may also be affected. The duration of action of some drugs is thereby shortened, their blood levels are lowered, and their potency is diminished. The half-lives of drugs with low hepatic extraction are mainly affected, whereas drugs not metabolized by these enzymes are not affected. Examples of well-known inducing agents are (1) lipid-soluble drugs such as phenobarbital, phenytoin, rifampin, and ethanol; (2) glucocorticoids; and (3) environmental pollutants such as benzo(a)pyrene and other polycyclic hydrocarbons formed in cigarette smoke, polychlorinated biphenyls, and dioxin. The effect of smoking on plasma drug levels is shown in Figure 1-9.

Inhibition
Inhibition of drug metabolism will have the opposite effect (Table 1-3), leading to a prolonged half-life and an exaggerated pharmacologic response. Drugs well known for their inhibitory effects include chloramphenicol, cinmetidine, allopurinol, and monoamine oxidase inhibitors. Alcohol acutely depresses certain drug metabolism pathways (although chronically it induces them) and may lead to enhanced and prolonged effects of other drugs. Erythromycin and ketoconazole block the conversion of terfenadine, a prodrug, to its active metabolite. Since the parent compound is arrhythmogenic, serious cardiac toxicity may be seen with such drug combinations. For this reason, terfenadine was banned, although its active metabolite is marketed as fexofenadine (Allegra), which lacks cardiotoxicity and adverse CNS effects. It is suspected that there are many more such inhibitory drugs,
but it is difficult to predict a priori when inhibition will occur.

Metabolism by Intestinal Microorganisms
The abundant flora of the lower gut includes many organisms capable of metabolizing drugs as well as their metabolic derivatives. Since the microflora consist mainly of obligate anaerobes and the gut environment is anaerobic, only pathways not requiring oxygen are seen. These bacteria make a significant contribution to drug metabolism, and suppression of the gut flora by oral antibiotics or other drugs will appreciably alter the fate and thus the effects of many other drugs. The various pathways include hydrolysis of glucuronides, sulfates, and amides; dehydroxylation; deamination; and azo and nitro reduction.

Enterohepatic Circulation
Many conjugated drugs are transported into the bile and pass into the intestine. Here, intestinal microorganisms hydrolyze the conjugate (glucuronides in particular), yielding the original, less polar compound, which can then be reabsorbed. This cycle tends to repeat itself and makes a major contribution to maintenance of drugs and certain endogenous compounds within the body. For example, bile salts are 90% recirculated through this mechanism. Suppression of gut bacteria by oral antibiotics will appreciably affect the half-lives and thus the plasma levels of compounds that undergo extensive enterohepatic circulation.

Excretion
All drugs are ultimately eliminated from the body via one route or another. Elimination rate, as reflected in plasma disappearance rate for most drugs, is generally proportional to the total amount in the body, following first-order kinetics.

1. The kidney is the major organ of excretion for most drugs and associated metabolites. Its large blood supply (25% of cardiac output) is conducive to efficient excretion. Drugs not bound to plasma proteins are filtered in the glomeruli with nearly 100% efficiency. Reabsorption within the tubule is mainly by passive diffusion. Thus, highly charged drugs (or metabolites) will be poorly reabsorbed and readily excreted. Changes in tubular pH alter excretion rates by influencing the net charge on the compound. Appropriate manipulation of urinary pH is helpful in facilitating excretion in cases of drug overdose. For example, raising the pH increases excretion of phenobarbital, an organic acid, while lowering the pH increases excretion of amphetamine, an organic base. Active transport of organic anions and cations takes place in the tubules. Penicillin, a weak organic acid, is actively pumped into the tubule's lumen by the organic lumen of the tubular anion transport system, which is competitively suppressed by probenecid, an inhibitor of the anion transport system. Renal failure presents a major therapeutic problem due to accumulation of renally cleared drugs as well as toxic metabolites. Hemodialysis filters

---

**TABLE 1-3. Major Inhibitors and Substrates of Different Cytochrome P450 (CYP450) Enzymes**

<table>
<thead>
<tr>
<th>CYP450 Enzymes</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Cimetidine, ciprofloxacin, clarithromycin, erythromycin, fluvoxamine, grapefruit juice, isoniazid, ketoconazole, levofloxacin, paroxetine</td>
<td>Phenobarbital, phenytoin, rifampin, ritonavir, smoking</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Amiodarone, chloramphenicol, cimetidine, fluvoxamine, omeprazole, zafirlukast</td>
<td>Carbamazepine, phenobarbital, phenytoin, rifampin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Amiodarone, cimetidine, desipramine, fluoxetine, fluphenazine, haloperidol, paroxetine, propafenone, quinidine, ritonavir, sertraline</td>
<td>Carbamazepine, phenobarbital, phenytoin, rifampin, ritonavir</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Amiodarone, clarithromycin, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, indinavir, itraconazole, ketoconazole, metronidazole, nefazodone, ritonavir, saquinavir, sertraline, zafirlukast</td>
<td>Carbamazepine, dexamethasone, ethosuximide, phenobarbital, phenytoin, rifabutin, rifampin, troglitazone</td>
</tr>
</tbody>
</table>

out unbound drugs from the plasma, thus assisting in overall drug clearance. Drugs with a large Vd have their total body burden less affected by dialysis than drugs with a smaller Vd.

2. Biliary excretion is usually reserved for highly polar compounds with a molecular weight greater than 500. Bile empties into the duodenum, and drugs passing via this route are frequently reabsorbed in the intestinal tract (see "Enterohepatic Circulation," above). Unlike the mechanisms involving urine, those of bile formation and biliary excretion are poorly understood. Biliary secretion is greatly but not entirely dependent on bile salt transport. Bile salts may facilitate or inhibit biliary excretion of drugs, depending on the drug and the concentration of bile salts.

3. Lungs are the excretion route for many general anesthetics and other volatile substances. A clever utilization of the lungs as a route of excretion is the "aminopyrine breath test." Aminopyrine that has been labeled with radioactive carbon in its methyl moiety is administered. It is demethylated by the liver's P450 system, ultimately forming radioactive carbon dioxide, which is then collected from the expired air and counted. The amount of radioactivity is a reflection of hepatic drug metabolism and has been used as a noninvasive assessment of liver function in, for example, liver cirrhosis. In recent years erythromycin has been used as the test substance.

4. Considerable concern has been raised regarding drugs in breast milk in view of the increase in the past two decades in the number of nursing mothers. Drug entry into plasma is affected by the pK of the drug, the pH of milk and plasma, binding to plasma and milk proteins, and the fat composition of milk. Drugs enter the milk by passive diffusion. The pH of milk (6.5–7.0), its varying volume, and its high content of fat globules and unique proteins influence drug secretion, especially for lipid-soluble compounds. Drugs known to be secreted into milk include cardiovascular drugs (hydralazine, digoxin), CNS drugs (caffeine, amitriptyline, primadone, ethosuximide), drugs of abuse (nicotine, narcotics, cocaine), and others (metronidazole, medroxyprogesterone, nortestosterone). This does not necessarily imply an incompatibility between nursing and taking any of these drugs. However, drugs contraindicated or to be used with caution during lactation include alcohol, amiodarone, atropine, chlorpromazine, cimetidine, cocaine, cyclosporine, doxorubicin, lithium, morphine, nitrofurantoin, phenytoin, phenindione, salicylates, tetracyclines, and tinidazole. At present, drugs must be evaluated individually when deciding on the safety of nursing infants. Similar considerations are valid for cow's milk, since these animals may be given drugs to increase milk production.

Another route of excretion being developed for noninvasive assessment of blood levels of drugs is saliva. For some drugs, a known equilibrium exists between the plasma and saliva. Although the work is only in its infancy, one can foresee the day when, if plasma levels are required, a patient will simply spit for the physician rather than being stuck with a needle five or six times.

Note: Recommended reading for this chapter can be found here: www.cvpct3.com

Figure 1-9. This figure shows blood levels of phenacetin in smoking and nonsmoking populations, reflecting the inducing effect of components of cigarette smoke on drug metabolizing enzymes.

The Placebo Effect in the Treatment of Cardiovascular Disease

William H. Frishman, MD
Stephen P. Glasser, MD

There are 3 general reasons for improvement in a patient’s clinical condition: (1) natural history and regression to the mean; (2) the specific effects of the treatment; and (3) the nonspecific effects of the treatment attributable to factors other than the specific active components (this latter effect being included under the heading of “placebo effect”).1 Each time a physician recommends a diagnostic or therapeutic intervention for a patient, there is built into this clinical decision the possibility of a placebo effect being involved, a clinical effect unrelated to the intervention itself.2–4 A beneficial response to an inert therapy is a placebo response; an adverse effect to an inert substance is a nocebo response.

Simple diagnostic procedures such as phlebotomy or more invasive procedures such as cardiac catheterization have been shown to have important placebo effects associated with them.7,8 Indeed, Chalmers has stated that one only has to review the graveyard of therapies to realize how many patients would have benefited by being assigned to a placebo control group.9 In fact, what might represent the first known clinical trial and one in which the absence of a placebo control group led to erroneous conclusions is a summary attributed to Galen in 150 BCE, where he stated that “some patients that have taken this herb have recovered, while some have died; thus, it is obvious that this medicament fails only in incurable diseases.”

Placebo effects are commonly observed in patients with cardiac disease who also receive drug and surgical therapies as treatments (Figure 2-1). In this chapter, the placebo effect in cardiovascular disease treatment is reviewed and the implications of this clinical phenomenon to the study of new drug treatments are discussed.

Definition

Stedman's Medical Dictionary gives 2 meanings for the word placebo, which originates from a Latin verb meaning "I shall please": (1) an inert substance prescribed for its suggestive value, and (2) an inert substance identical in appearance with the compound being tested in experimental research, which may or may not be known by the physician and/or the patient; and which is given to distinguish between a compound’s action and the suggestive effect of the compound under study.10

Currently, there is some disagreement as to the exact definition of a placebo.11–13 Many articles on the subject include a broader definition, as described by Shapiro in 196114:

Any therapeutic procedure (or that component of any therapeutic procedure) which is given deliberately to have an effect or unknowingly has an effect on a patient, symptom, syndrome, or disease, but which is objectively without specific activity for the condition being treated. The therapeutic procedure may be given with or without conscious knowledge that the procedure is a placebo, may be an active (non-inert) or nonactive (inert) procedure, and includes, therefore, all medical procedures no matter how specific—oral and parenteral medication, topical preparations, inhalants, and mechanical, surgical and psychotherapeutic procedures. The placebo must be differentiated from the placebo effect which may or may not occur and which may be favorable or unfavorable. The placebo effect is defined...
as the changes produced by placebos. The placebo is also used to describe an adequate control in research.

A further refinement of the definition was proposed by Byerly in 1975: “any change in a patient's symptoms that is the result of the therapeutic intent and not the specific physiochemical nature of a medical procedure.”

**The Placebo Effect in Clinical Trials**

Placebo controls in medical research date to 1753, when Dr. James Lind advocated their use when he evaluated the effects of lime juice on scurvy. After World War II, research protocols designed to assess the efficacy and safety of new pharmacologic therapies began to include the recognition of the placebo effect. Recognition of placebos and their role in controlled clinical trials occurred in 1946, when the Cornell Conference on therapy devoted a session to placebos and double-blind methodology. At that time, placebos were associated with increased heart rate, altered respiration patterns, dilated pupils, and increased blood pressure. In 1951, Hill concluded that for a specific treatment to be attributable to a change for better or worse in a patient, this result must be repeatable a significant number of times in similar patients. Otherwise, the result was merely due to the natural history of the disease or simply the passage of time. He also proposed the inclusion of a control group that received identical treatment except for the inclusion of an “active ingredient.” Thus, the active ingredient was separated from the situation within which it was used. This control group, also known as a placebo group, would help in the investigations of new and promising pharmacologic therapies.

Beecher was among the first investigators to promote the inclusion of placebo controls in clinical trials. He emphasized the importance of ensuring that neither the patient nor the physician know what treatment the experimental subject was receiving and referred to this as the “double unknown technique.” Today, this is called the “double-blind trial” and ensures that the expectations and beliefs of the patient and physician are excluded from evaluation of new therapies. In 1955, Beecher reviewed 15 studies that included 1082 patients and found that an average of 35% of these patients benefited from placebo therapy. He also concluded that placebos can relieve pain from conditions in which either physiologic or psychologic etiologies were present. He described many diverse objective changes from placebo therapy. Some medical conditions improved, including severe postoperative wound pain, cough, drug-induced mood changes, pain from angina pectoris, headache, seasickness, anxiety, tension, and the common cold.

**Characteristics of the Placebo Effect**

There appears to be an inverse relationship between the number of placebo doses that need to be administered and treatment outcomes. In a study of patients with postoperative wound pain, 53% of the subjects responded to one placebo dose, 40% to two or three doses, and 15% to four doses.

In analyzing the demographics of placebo responders and nonresponders, Beecher and his associates could find no differences in gender ratios or intelligence quotients between the 2 groups. They did find significant differences in attitudes, habits, educational backgrounds, and personality structure between consistent responders and nonresponders. In attempting to understand the repro-
ducibility of the placebo effect, they observed that there was no relationship between an initial placebo response and subsequent responses with repeated placebo doses of saline.19 Beecher concluded that placebos are most effective when stress, such as anxiety and pain, is greatest.18

Placebos can produce both desirable and adverse reactions. Beecher and his associates described over 35 different adverse reactions from placebo;19 the most common ones are described in Table 2-1.20,21 These reactions were recorded without the patient’s or physician’s knowledge that a placebo had been administered. In one study where lactose tablets were given as a placebo, major adverse reactions occurred in 3 patients.22 The first patient experienced overwhelming weakness, palpitation, and nausea after taking placebo. The second patient experienced a diffuse rash that disappeared after discontinuing placebo administration. The third patient experienced epigastric pain followed by watery diarrhea, urticaria, and angio-neurotic edema of the lips after receiving placebo.22

Indeed, due to the substantial evidence of placebo “efficacy” and placebo “adverse effects” or nocebo effects, some have wittingly suggested that if placebo were submitted to the US Food and Drug Administration (FDA) for approval, the agency, although impressed with the efficacy data, would probably recommend disapproval based on the high incidence of adverse effects. Some have questioned whether placebos are truly inert. Davis points out that “part of the problem with the placebo paradox is our failure to separate the use of an inert medication (if there is such a substance) from the phenomenon referred to as the placebo effect.”23 It might help us if we could rename the placebo effect the ‘obscure therapeutic effect.” That is, in lactase deficiency, could the amount of lactose in placebo tablets actually cause true adverse effects? Due to the small amount of lactose, this seems unlikely, but it is perhaps more likely that allergies to some of the so-called inert ingredients in placebos could cause reactions in predisposed individuals (although in the latter case it would seem unlikely that this could explain more than a small percentage of placebo adverse effects).

The most recent validation of the placebo effect occurred in 1962, when the United States enacted the Harris-Kefauver Amendments to the Food, Drug, and Cosmetic Act. These amendments require proof of efficacy as well as documentation of relative safety, in terms of the risk-to-benefit ratio for the disease to be treated, before an experimental agent can be approved for general use.24 In 1970, the FDA published rules for “Adequate and Well-Controlled Clinical Evaluations.” The federal regulations identified 5 types of controls (ie, placebo, dose-comparison, active, historical, and no treatment) and identified utilization of the placebo control as an indispensable tool to achieve the standard.25 However, it should be pointed out that the FDA does not mandate placebo controls, and

<table>
<thead>
<tr>
<th>Table 2-1. Most Common Adverse Reactions from Placebo Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Sensation of heaviness</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Dry mouth</td>
</tr>
<tr>
<td>Relaxation</td>
</tr>
<tr>
<td>Warm glow</td>
</tr>
</tbody>
</table>


in fact has stated that placebo groups are “...desirable, but need not be interpreted as a strict requirement... the speed with which blind comparisons with placebo and/or positive controls can be fruitfully undertaken varies with the nature of the compound.”26 In the FDA publication regarding “General Considerations for the Clinical Evaluation of Drugs,” it further states that “it should be recognized that there are other methods of adequately controlling studies. In some studies, and in some diseases, the use of an active control drug rather than a placebo is desirable, primarily for ethical reasons.”26

An important statistical concept and one that may mimic a placebo response is regression to the mean, which addresses the fact that in biologic systems, most variables increase and decrease around a mean (one might envision a sine wave to conceptualize this). Thus, it is likely that any value measured at a specific point in time will, by chance, either be above or below the mean, and that a second measurement will be at a different point around the mean and therefore different from the first measurement (Figure 2-2). This change between measurements could then represent an improvement or worsening and thereby mimic a placebo response. The presumption is that this variability about the mean will be the same in the placebo group as the active treatment group (assuming adequate sample size and randomization), so that differences between the 2 groups relative to regression to the mean will “cancel out.”

A meta-analysis of randomized clinical trials with 3 arms—a treatment arm, a placebo arm, and a non-treatment arm—demonstrated a clear placebo effect when comparing continuous variable outcomes among subjects in the placebo arm with subjects in the nontreatment arm.27 The beneficial effect, however, decreased with in-
creasing sample size. The authors suggest that although placebo should continue to play a role in future clinical trials, it should not be used as an actual treatment.

**Placebo in Ischemic Heart Disease and Chronic, Stable, Exertional Angina**

The rate of improvement in the frequency of symptoms in patients with chronic, stable, exertional angina with placebo therapy has been assessed to be from 30% to 80%. A summary of subjective and objective placebo effects in cardiovascular disease is provided in Tables 2-2 and 2-3. Due to the magnitude of the placebo effect, studies of new anti-anginal therapies had generally been performed with a placebo control. However, the safety of this practice came under scrutiny in the late 1980s due to the concern that patients with coronary artery disease would have periods of no drug treatment. As a result of this, Glasser et al explored the safety of exposing patients with chronic, stable, exertional angina to placebos during short-term drug trials with an average double-blind period of 10 weeks. The study samples were taken from new drug applications (NDAs) submitted to the FDA. The results of these drug trials were submitted, whether favorable or not, and all adverse events were reported. Qualifying studies used symptom-limited exercise tolerance testing as an endpoint. No anti-anginal medication except sublingual nitroglycerin was taken after a placebo or drug-free washout period. The placebo-controlled samples consisted of 12 studies, 6 studies using beta-adrenergic blockers and 6 studies using calcium antagonists. A total of 3,161 patients entered the studies, and 197 withdrew due to adverse cardiovascular events. Beta-blocker therapy was not significantly different when compared to placebo therapy. Conversely, calcium antagonist therapy had a significantly higher cardiovascular event rate compared to placebo therapy, leading to withdrawal from the trials. However, this significantly higher cardiovascular event rate was due to one calcium antagonist study reporting a disproportionately higher number of adverse events than the other 5 studies. This study found evidence supporting the safety of a placebo group in short-term drug trials for chronic, stable, exertional angina.

In contrast, the safety of using placebo in longer-term drug trials for chronic, stable, exertional angina has not been established. A placebo-controlled trial by a European group in 1986 enrolled 35 patients and followed them while administering a placebo and short-acting nitroglycerin for 6 months. This study of the long-term effects of placebo treatment in patients with moderately severe, stable angina found a shift toward the highest dosage during the titration period. Seven patients were kept on the lowest dosage. The average ending dosage was 65% more than the initial dose. The adherence for 27 patients, when determined by pill count, was > 80%. During the first 2½ months of the trial, all the patients who were nonadherent or could not physically continue the study were determined. No patients died or had a myocardial infarction (MI).

There is a paucity of data regarding any gender differences in placebo response. Female patients represented 43% of the population in the aforementioned European

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**Figure 2-2. If one measures a variable at its peak value (A in the example), the next measurement is likely to be lower (B, x, or y in this example). Conversely, if one were to measure a variable at its lowest point (B), the next measurement is likely to be higher.**


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**Table 2-2. Symptomatic Placebo Effects in Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Placebo Effect</th>
<th>Placebo Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic, stable angina</td>
<td>30%-80%²⁸</td>
</tr>
<tr>
<td>improvement</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>25%-35%⁴⁶</td>
</tr>
<tr>
<td>improvement</td>
<td></td>
</tr>
</tbody>
</table>

The Placebo Effect in the Treatment of Cardiovascular Disease

Table 2-3. Objective Placebo Effects in Cardiovascular Disease

<table>
<thead>
<tr>
<th>Placebo Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Exercise tolerance testing</td>
</tr>
<tr>
<td>with 1–2 baseline measurements</td>
</tr>
<tr>
<td>with 3–10 baseline measurements</td>
</tr>
<tr>
<td>Increase in ejection fraction of 5%</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Measured by noninvasive, automatic, ambulatory 24-hour monitoring</td>
</tr>
<tr>
<td>Arrhythmias</td>
</tr>
<tr>
<td>based on comparison of one control 24-hour monitoring period to one 24-hour treatment period (variability is so great that it may be inadvisable to pool individual patient data to detect trends in ectopic frequency in evaluating new potential antiarrhythmic agents in groups of patients).</td>
</tr>
<tr>
<td>Mean hourly frequency of ventricular tachycardia</td>
</tr>
<tr>
<td>Mean hourly frequency of couplets</td>
</tr>
<tr>
<td>All ventricular ectopics, without regard for complexity</td>
</tr>
</tbody>
</table>
| When differentiating proarrhythmia in patients with mixed cardiac disease and chronic ventricular arrhythmias from spontaneous variability, with a false-positive rate of only 1%.
| When baseline VPCs > 100/h | < 3 times baseline<sup>27</sup> |
| When baseline VPCs < 100/h | < 10 times baseline<sup>76</sup> |
| Silent ischemic coronary disease |
| Reduction in the frequency of ischemic events | 44%<sup>34</sup> |
| Reduction of ST-segment integral | 50%<sup>34</sup> |
| Reduction in duration of ST-segment depression | 50%<sup>34</sup> |
| Reduction of total peak ST-segment depression | 7%<sup>34</sup> |
| Other |
| Adherence with treatment at a rate ≥ 75% | < 3 times baseline<sup>80,82</sup> |
| VPCs, ventricular premature contractions |


...study<sup>31</sup> and were more likely to have angina despite normal coronary arteries. Since the placebo effect may be more pronounced in patients with normal coronary arteries, data from male patients were analyzed separately to be compared with the overall results. However, the data from male patients were very similar to the overall results. In fact, the functional status of males showed more improvement due to placebo (61%) than overall (48%) at 8 weeks. The results of this study showed no adverse effects of long-term placebo therapy with 65% of patients reporting subjective clinical improvement and 27% of patients reporting objective, clinical improvement on exercise performance.<sup>31</sup> It is noteworthy that improvement in exercise performance can occur when patients are repeatedly exposed to testing.<sup>32</sup>

There are two problems inherent in all modern trials of anti-anginal therapy. One problem relates to the fact that since anginal patterns vary and, with modern day treatments, attacks of angina are rather infrequent, a surrogate measure of anti-anginal effect has been adopted by the FDA and relates to treadmill walking time to the point of moderate angina. Also, just as there is a placebo effect on anginal frequency, a patient’s treadmill walking time frequently (50%–75%) improves with placebo therapy.
There are other potential mechanisms that partially explain the improvement unrelated to a treatment effect in exercise walking time in anti-anginal studies: the so-called learning phenomenon and the training effect. Patients frequently show an improvement in exercise walking time between the first and second treadmill test in the absence of any treatment. The presumption is that the first test is associated with anxiety and unfamiliarity, which are reduced during the second test. Of greater importance is the training effect, where the frequency of treadmill testing might result in a true improvement of exercise performance irrespective of treatment.

The effect of placebo on exercise tolerance in patients with angina was demonstrated in the Transdermal Nitrate Therapy Study, which compared various doses of nitroglycerin administered for 24-hour durations from transcutaneous patch formulations to placebo patch treatment. This study was particularly important because it was the first large study to address the issue of nitrate tolerance with transcutaneous patch drug delivery in outpatient ambulatory subjects. The net result of the study was the demonstration of tolerance in all treated groups in that the treated groups performed no better than placebo at study end. However, in both the placebo and active treatment groups there was a striking improvement of 80 to 90 seconds in the primary efficacy endpoint of exercise walking time on a treadmill. This improvement in placebo could have masked any active treatment effect, but it also demonstrated the importance of placebo control, since without such a control one could have deduced a significant improvement due to active therapy.

Myocardial ischemia was assessed via 48-hour ambulatory electrocardiographic (ECG) monitoring for ST-segment analyses in 250 males with stable angina and coronary artery disease based on at least 70% stenosis of one major coronary artery, previous MI at least 2 months prior to screening, coronary artery bypass surgery, angioplasty, or a positive exercise tolerance test within the last 12 months prior to screening. These participants were reassessed after 7 weeks of therapy with amlopidine or placebo by repeating the 48-hour ambulatory ECG monitoring. The monitoring showed the well-known circadian pattern of ischemic activity with peaks in the morning and afternoon. Amlodipine significantly reduced ischemia compared to placebo. However, transient silent myocardial ischemia was less frequent in all groups, including the placebo group.

It was once thought that internal mammary artery ligation improved angina until studies showed similar benefit in patients where a sham operation was performed—that is, skin incision with no ligation. Beecher tried to analyze the effect of physicians’ personalities on clinical outcomes by comparing the results of the same placebo procedure performed by 1 of 2 groups, the “enthusiasts” or the “skeptics.” His analysis indicated that the enthusiasts achieved nearly 4 times more “complete relief” for patients than the skeptics, in spite of the fact that the procedure has no known specific effects. Five patients receiving the sham operation emphatically described marked improvement. Objectively, a patient undergoing the sham operation had an increase in work tolerance from 4 to 10 minutes with no inversion of T waves on ECG and no pain. This procedure was utilized in the United States for 2 years before it was discontinued, when it was disproven by 3 small, well-planned, double-blind studies.

Carver and Samuels also have addressed the issue of sham therapy in the treatment of coronary artery disease. They point out that although the pathophysiology of coronary artery disease is well known, the awareness of many of the expressions of myocardial ischemia are subjective, rendering the placebo effect more important. This has resulted in a number of treatments that are based upon “testimonials” rather than hard scientific evidence and have been touted as “miracle cures” and “breakthroughs,” etc. Among therapies cited by these authors are chelation therapy, various vitamin therapies, and mineral supplements (see Chapter 30, Alternative and Complementary Medicine for Preventing and Treating Cardiovascular Disease). Chelation therapy is probably one of the most instructive examples of a sham and is briefly discussed here. It has been estimated that 500,000 patients per year are treated by this technique in the United States alone. Prior to 1995, the data to support claims regarding the effectiveness of chelation therapy were uncontrolled open-label studies. In 1994, van Rij and associates performed a double-blind, randomized, placebo-controlled study in patients with intermittent claudication and demonstrated no benefits of chelation over placebo. A number of variables were evaluated, including both objective and subjective measures, with improvement in many of the measures of both therapies. Again, without the use of a placebo control, the results could have been interpreted as improvements related to chelation treatment.

The results of a large multicenter, placebo-controlled trial by the NIH revealed no apparent clinical benefit from chelation therapy in patients with CAD; the trial was terminated in 2008 for procedural reasons.

The Placebo Effect in Heart Failure

Until recently, the importance of the placebo effect in patients with congestive heart failure (CHF) had not been recognized. In the 1970s and early 1980s, vasodilator therapy was administered to patients in clinical trials without placebo control. Investigators believed that the cause of heart failure was predictable, so placebo-controlled trials were unnecessary. Another view of the unfavorable course of heart failure concluded that with-
holding a promising new agent was unethical. The ethical issues regarding placebo use in cardiovascular disease are discussed further on in this chapter.42–45

With the inclusion of placebo controls in clinical trials, a 25%–35% improvement in patients' symptoms was documented. This placebo response occurred in patients with mild to severe symptoms and did not depend on the size of the study. The assessment of left ventricular (LV) function can be determined by several methods, including noninvasive echocardiography, radionuclide ventriculography, or invasive pulmonary artery balloon-floatation catheterization. These methods measure the patient's response to therapy or the natural progression of the patient's heart failure.46

Noninvasive measurements of LV ejection fraction vary, especially when the ventricular function is poor and the time interval between tests is 3 to 6 months. Packer found that when a 5% increase in ejection fraction is used to determine a beneficial response to a new drug, 20%-30% of patients show improvement while receiving placebo therapy. Overall, changes in noninvasive measures of LV function have not been shown to correlate closely with observed changes in clinical status of patients with CHF. Most vasodilator and inotropic drugs can produce clinical benefit without a change in LV ejection fraction. Conversely, LV ejection fraction may increase significantly in heart failure patients with worsening clinical status.46

When Swan Ganz catheterization is used to evaluate the efficacy of a new drug, the interpretation must be done carefully, since there may be spontaneous fluctuations in hemodynamic variables in the absence of drug therapy. To avoid recognition of spontaneous variability attributable to drug therapy, post-drug effects should be assessed at fixed times and threshold values should eliminate changes due to spontaneous variability. Another factor that can mimic a beneficial drug response by favorably affecting hemodynamic measurements is measurement performed immediately after catheterization of the right side of the heart or after ingestion of a meal. Following intravascular instrumentation, systemic vasoconstriction occurs and resolves after 12 to 24 hours. When pre-drug measurements are done during the post-catheterization period, any subsequent measurements will show beneficial effects, since the original measurements were done during the vasoconstricted state. Thus, comparative data must be acquired after the post-catheterization vasoconstricted state has resolved.46

The most common test to evaluate drug efficacy for heart failure is the exercise tolerance test (ETT). An increased duration of ET represents a benefit of therapy. However, this increased duration is also recorded during placebo therapy, possibly due to the familiarity of the patient with the test and the increased willingness of the physician to encourage the patient to exercise to exhaust-
with pretherapy. In 6 of 9 hospitalized patients, there was a blood pressure reduction of 39/28 mm Hg.

An important factor to consider is the method used to measure blood pressure. In using standard sphygmomanometry, blood pressure falls initially. During placebo therapy, intra-arterial pressures and circadian curves measured over 24 hours did not show a decline in blood pressure or heart rate. Intra-arterial blood pressure was lower at home compared to measurements at the hospital. The circadian curves from intra-arterial ambulatory blood pressure monitoring were reproducible on separate days several weeks apart. Similar to 24-hour invasive intra-arterial monitoring, 24-hour noninvasive automatic monitoring of ambulatory blood pressure also has been reported to be devoid of a placebo effect. Upon the initial application of the blood pressure device, a small reduction of ambulatory blood pressure values in the first 8 hours occurred with placebo therapy. This effect, however, did not change the mean 24-hour value. The home monitoring values were lower than the office measurements. Heart rate was also measured, with no variance in either setting. The office measurement of blood pressure but not the 24-hour blood pressure was lower after 4 weeks of placebo therapy. This study confirms the absence of a placebo effect in blood pressure, 100 patients were followed for a 2-week single-blind period and for a 2-week double-blind period.

In a study on the influence of observer’s expectation on the placebo effect in blood pressure, 100 patients were followed for a 2-week single-blind period and for a 2-week double-blind period. During this time, the patients’ blood pressures were measured by 2 methods: a 30-minute recording with an automatic oscillometric device and a standard sphygmomanometric measurement performed by a physician. All patients were seen in the same examining room, monitored by the same automatic oscillometric device, and seen by the same physician. The results during the single-blind period showed a slight but statistically significant decline in diastolic blood pressure detected by the automatic oscillometric device and no decline measured by the physician. During the double-blind period, there was no additional decline in diastolic blood pressure measured by the oscillometric device, but the physician measured significant decreases in both systolic and diastolic blood pressures. Overall, the blood pressures measured by the automatic oscillometric device in the absence of the physician were lower than those measured by the physician. However, there was significant correlation of the 2 methods. The investigators concluded that in correcting for the placebo effect in clinical trials in hypertension, the use of ambulatory monitoring should adhere to the same design standards as those in using conventional sphygmomanometry.

Although there was a placebo effect in the measurement of blood pressure using auscultatory technique in the Systolic Hypertension in the Elderly Program (SHEP), this was not as significant as the reduction of blood pressure produced by active therapy in patients 60 years of age and older with isolated systolic hypertension. In a subsequent study of patients with isolated systolic hypertension, it was observed that a substantial portion of the long-term blood pressure change observed during active treatment could be attributed to a placebo effect. Twenty-four-hour blood pressure monitoring was no more reliable than conventional sphygmomanometry in correcting for the actions of placebo.

As was true with angina studies, questions have been raised about the safety of placebo-controlled studies in hypertension. As a result, 2 publications have addressed this issue. Al-Khatib et al performed a systematic review of the safety of placebo controls in short-term trials. In their meta-analysis, they combined the data for death, stroke, MI, and CHF from 25 randomized trials. Each study was small (n = 20-734) but the combined sample size was 6,409 subjects. They found a difference between the 2 treatment groups and, at the worst, there were no more than 6/10,000 differences between placebo and active therapy. Lipicky et al reviewed all original case report forms for deaths, and dropouts were reviewed from all antihypertensive drug trials submitted to the FDA between 1973 and 2001. The population at risk was 86,137 randomized patients (64,438 randomized to experimental drug and 21,699 randomized to placebo). Of the 9,636 dropouts, more were from the placebo group. The majority of the dropouts were due to treatment failures, and the patients were returned to their original therapies with no sequelae. When serious adverse effects were compared (death, irreversible harm, etc.), there were no differences between placebo and experimental drug.

**The Placebo Effect in Arrhythmia**

Spontaneous variability in the natural history of disease or in its signs and/or symptoms is another reason that placebo controls are necessary. In a study of ventricular arrhythmias, Michelson and Morganroth found marked spontaneous variability of complex ventricular arrhythmias such as ventricular tachycardia and couplets. Their study followed 20 patients for 4-day periods of continuous ECG monitoring. They recommended that, in evaluating therapeutic agents, a comparison of one 24-hour control period to four 24-hour test periods must show a 41% reduction in the mean hourly frequency of ventricular tachycardia and a 50% reduction in the mean hourly frequency of couplets to demonstrate statistically signifi-
cant therapeutic efficacy. They also suggested that individual patient data not be pooled to detect trends because the individual variability is so great.

A study by Morganroth et al provides an algorithm to differentiate spontaneous variability from proarrhythmia in patients with benign or potentially lethal ventricular arrhythmias. A total of 495 patients were evaluated with 2 or more Holter tracings during placebo therapy. The algorithm defines proarrhythmia as an increase of more than 3 times when the hourly frequency of baseline ventricular premature complexes (VPCs) is > 100 and > 10 times when it is < 100. The false-positive rate is 1% with this algorithm.

The Cardiac Arrhythmia Suppression Trial (CAST) evaluated the effect of antiarrhythmic therapy in patients with asymptomatic or mildly symptomatic ventricular arrhythmia. Response to drug therapy was determined by ≥ 80% reduction of ventricular premature depolarizations or ≥ 90% reduction of runs of unsustained ventricular tachycardia as measured by 24-hour Holter monitoring 4 to 10 days after the initiation of pharmacologic treatment — this response having previously been considered an important surrogate measure of antiarrhythmic drug efficacy. Ambulatory ECG (Holter) recording screened for arrhythmias. The CAST Data and Safety Monitoring Board recommended that encainide and flecainide therapy be discontinued based on the increased number of deaths from arrhythmia, cardiac arrest, or any cause compared to the placebo group (1455 patient were assigned to drug regimens). The CAST investigators’ conclusion emphasized the need for more placebo-controlled clinical trials of antiarrhythmic drugs with a mortality endpoint.

Hypertrophic Cardiomyopathy

Linde et al evaluated the placebo effect of pacemaker implantation in 81 patients with obstructive hypertrophic cardiomyopathy in a 3-month multcenter, double-blind, crossover trial. In the first study period, 40 patients were assigned to inactive pacing and compared to 41 patients with active pacing. During inactive pacing there was an improvement in chest pain, dyspnea, palpitations, and the left ventricular outflow gradient. The change in the active pacing group for most parameters was greater.

The Relationship of Treatment Adherence to Survival in Patients with and without History of Myocardial Infarction

One important consideration in determining study results is adherence to therapy and the presumption that any differences in adherence rates would be equal in the active versus the placebo treatment groups. The Coronary Drug Project planned to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term treatment of coronary heart disease. This randomized, double-blind, placebo-controlled, multicenter clinical trial found no significant difference in the 5-year mortality of 1103 men treated with the fibric acid derivative clofibrate compared to 2789 men given placebo. However, good adherers, patients taking ≥ 80% of the protocol drug, had lower mortality than poor adherers in both the clofibrate and placebo groups.

A similar association between adherence and mortality was found in patients after MI in the Beta-Blocker Heart Attack Trial (BHAT) data. This phenomenon was extended to women after MI. On analysis of the BHAT data for 505 women randomized to both beta-blocker therapy and placebo therapy, there was a 2½-3-fold increased mortality within the first 2 years in patients taking < 75% of their prescribed medication. Adherence among men and women was similar at about 90%. However, the cause of the increased survival resulting from good adherence is not known. There is speculation about good adherence reflecting a favorable psychological profile — an individual’s ability to make lifestyle adjustments that limit disease progression. Alternatively, adherence may be associated with other advantageous health practices or social circumstances not measured. Another possible explanation is that improved health status may facilitate good adherence.

The Lipid Research Clinics Coronary Primary Prevention Trial did not find a correlation between adherence and mortality. They randomized 3806 asymptomatic hypercholesterolemic men to cholestyramine or placebo. Over 7 years, the main effects of the drug compared to placebo on cholesterol and death or nonfatal MI were shown. In the active drug group, a relationship between adherence and outcome existed, mediated by lowering cholesterol. However, no effect of adherence on cholesterol or outcome was observed in the placebo group. The Physicians’ Health Study randomized 22,000 US male physicians between the ages of 40 and 84 years who were free of MI and cerebral vascular disease. This study analyzed the benefit of differing frequencies of aspirin consumption on the prevention of MI. Additionally, the study identified factors associated with adherence and analyzed the relationship of adherence with cardiovascular outcomes in the placebo group. In this study, an average adherence of 80% in the aspirin and placebo groups over the 60 months of follow-up was observed. Adherence during the trial was associated with several baseline characteristics in the aspirin and placebo groups. Trial participants with poor adherence (< 50% adherence with pill consumption) were more likely to be younger than 50 years at randomization, to smoke cigarettes, to be overweight, to not exercise regularly, to have a parental history of MI, and to have angina relative to those with good adherence. These associations were statistically signifi-
cant. In a multivariate logistic regression model, cigarette smoking, being overweight, and angina remained significant predictors of poor adherence. The strongest predictor of adherence during the trial was adherence during the run-in period. Baseline characteristics with little relationship to adherence included regular alcohol consumption and a history of diabetes mellitus and hypertension.84

Using an intention-to-treat analysis, the aspirin group had a 41% lower risk of MI compared to the placebo group. On subgroup analysis, participants reporting excellent (≥ 95%) adherence in the aspirin group had a significant (51%) reduction in risk of first MI relative to those with similar adherence in the placebo group. Lower adherence in the aspirin group did not produce a statistically significant reduction of first MI compared to the placebo group with excellent adherence. Excellent adherence in the aspirin group was associated with a 41% lower relative risk of MI than in those with lower adherence in the aspirin group. Excellent adherence in the placebo group did not show a reduction of relative risk.

The rate of stroke was different from MI. Using an intention-to-treat analysis, the aspirin group had a non-significant (22%) increased rate of stroke than the placebo group. Excellent adherence in the placebo group produced a lower rate of strokes than among participants in the aspirin and placebo groups with poor (< 50%) adherence. Excellent adherence in the placebo group was associated with a 29% lower risk of stroke than among those with excellent adherence in the aspirin group.

The overall relationship of adherence to aspirin therapy with cardiovascular risk considered a combined endpoint of all important cardiovascular events—including first fatal or nonfatal MI or stroke or death from cardiovascular disease with no prior MI or stroke. Using an intention-to-treat analysis, there was an 18% decrease in risk of all important cardiovascular events in the aspirin group compared to the placebo group. Participants with excellent adherence in the aspirin group had a 26% reduction of risk of a first major cardiovascular event compared to those with excellent adherence in the placebo group. However, those participants in the aspirin group with poor adherence had a 31% increased risk of a first cardiovascular event compared to those in the placebo group with excellent adherence. Within the placebo group, there was no association between level of adherence and risk of first cardiovascular event.

In analysis of death from any cause with no prior nonfatal MI or stroke, poor adherence in both the aspirin and placebo groups was associated with a fourfold increase in the risk of death. In analysis of the 91 deaths due to cardiovascular causes, similar risks were found to be associated with poor adherence in both the aspirin and placebo groups relative to excellent adherence in the placebo group.

The Physicians’ Health Study found similar results to the Coronary Drug Project when all-cause mortality and cardiovascular mortality were considered.79,84 These relationships remained strong when adjusted for potential confounding variables at baseline. The strong trend for higher death rates among participants with poor adherence in both the aspirin and placebo groups may be due to the tendency for individuals to lessen or discontinue study participation as individuals’ health declines with serious illness. Acute events such as MI did not accompany an increased risk associated with poor adherence in the placebo group. Thus, placebo effects seem to vary depending on the cardiovascular outcome considered.

Clinical Trials and the Ethics of Using Placebo Controls

Since the 1962 amendments to the Food, Drug, and Cosmetic Act, the FDA has had to rely on the results of “adequate and well-controlled” clinical trials to determine the efficacy of new pharmacologic therapies. Regulations governing pharmacologic testing recognize several types of controls that may be used in clinical trials to assess the efficacy of new pharmacologic therapies. These include (1) placebo concurrent control, (2) dose-comparison concurrent control, (3) no-treatment concurrent control, (4) active-treatment concurrent control, and (5) historical control. However, regulations do not specify the circumstances for the use of these controls because there are various study designs that may be adequate in a given set of circumstances.85,86

There is an ongoing debate concerning the ethics of using placebo controls in clinical trials of cardiac medications.42,43,87 The issue revolves around the administration of placebo in lieu of a proven therapy. Two articles illustrate the debate.43,44

Rothman and Michels44 state that patients in clinical trials often receive placebo therapy instead of a proven therapy for the patient’s medical condition and assert that this practice is in direct violation of the Nuremberg Code and the World Medical Association’s adaptation of this code in the Helsinki Declaration. The Nuremberg Code, a 10-point ethical code for experimentation in human beings, was formulated in response to the human experimentation atrocities that were recorded during the post–World War II trial of Nazi physicians in Nuremberg, Germany. According to Rothman and Michels,44 violation occurs because the use of placebo as control denies the patient the best proven therapeutic treatment. It occurs despite the establishment of regulatory agencies and institutional review boards, although these authors seem to ignore the fact that informed consent is part of the current practice, as certainly was not the case with the Nazi atrocities.
placebo-controlled trials are approved by institutional review boards is that this type of trial is part of the FDA's general recommendation for demonstrating therapeutic efficacy before an investigational drug can be approved. When the investigational drug is found to be more beneficial than placebo, therapeutic efficacy is proven. As more drugs are found to be more effective than placebo in treating disease, the inclusion of a placebo group is often questioned. However, this question ignores the fact that, in many cases, drug efficacy had been established by surrogate measures and—as new and better measures of efficacy become available—additional study becomes warranted. For instance, the suppression of ventricular arrhythmia by antiarrhythmic therapy was later proven to be unrelated to survival; in fact, results with this therapy were worse than with placebo. Likewise, in studies of inotropic therapy for heart failure, exercise performance rather than survival was used as the measure of efficacy, and, in fact, a presumed efficacious therapy performed worse than placebo. In the use of immediate short-acting, dihydropyridine calcium antagonist therapy for the relief of symptoms of chronic stable angina, again, a subject might have fared better had he or she been randomly assigned to placebo therapy.

Also important in the concept that established beneficial therapy should not necessarily prohibit the use of placebo in the evaluation of new therapies is that the natural history of a disease may change, and the effectiveness of the so-called established therapy (eg, antibiotic agent for treatment of infection) may diminish. In deciding on the use of an investigational drug in a clinical trial, the prevailing standard is that there should be enough confidence to risk exposure to a new drug but also enough doubt about the drug to risk exposure to placebo. Thus, in this situation, the use of a placebo control becomes warranted, particularly as long as other life-saving therapy is not discontinued.

The use of placebo-controlled trials may be advocated on the basis of a scientific argument. When pharmacologic therapy has been shown to be effective in previous placebo-controlled clinical trials, conclusions drawn from trials without placebo controls may be misleading because the previous placebo-controlled trial becomes a historical control. These historical controls are the least reliable for demonstrating efficacy. In active-controlled clinical trials, there is an assumption that the active control treatment is as effective under the new experimental conditions as it was in the previous placebo-controlled trial. This assumption can result in misleading conclusions when results with an experimental therapy are found to be equivalent to those with active, proven therapy. This conclusion of equivalence can be magnified by conservative statistical methods, such as the use of "intent to treat" approach, an analysis of all randomized patients regardless of protocol deviations, and an attempt to minimize the potential for introduction of bias into the study. Concurrent placebo controls account for factors other than drug-effect differences between study groups. When, instead of a placebo-control group, an untreated control group is used, blinding is lost and treatment-related bias may occur.

Clark and Leaverton agree that the use of placebo controls is ethical when there is no existing treatment to affect morbidity and mortality or survival favorably. Furthermore, there are chronic diseases for which treatment exists but does not favorably alter morbidity and mortality or survival. For example, no clinical trial has found the treatment of angina to increase a patient's survival. In contrast, treatment after an MI with beta-blocking agents has been convincingly proven to increase a patient's survival. However, Clark and Leaverton disagree with Rothman and Michels in asserting that, for chronic disease, a placebo-controlled clinical trial of short duration is ethical because there is usually no alteration in long-term outcome for the patient. The short duration of the trial represents a small segment of the life-time management of a chronic disease. For instance, the treatment of chronic symptomatic CHF and a low-ejection fraction (< 40%) with enalapril was shown to decrease mortality by 16%. This decrease in mortality was most marked in the first 24 months of follow up, with an average follow-up period of 40 months. Therefore, only long-term adherence with pharmacologic therapy resulted in some decrease in mortality. Hypertension is another example of a chronic medical condition that requires long-term treatment and in which short-term placebo is probably not harmful. In some studies, men and women with a history of MI and with ≥ 80% adherence with treatment, including placebo therapy, had an increased survival. This increased survival was also described in patients in a 5-year study of the effect of lipid-influencing drugs on coronary heart disease.

Therefore, Rothman and Michels agree that a placebo should not be included in a trial when there is a proven therapy that favorably affects morbidity and mortality, but they disagree with regard to chronic cardiovascular diseases and short-term trials. Brief interruption of effective therapy has not been found to alter long-term outcome when the effective treatment is a long-term therapy. The claim that the use of placebos in clinical trials violates the Nuremberg Code and the Helsinki Declaration if a proven therapy exists does not account for all of the information currently available. The proven therapies for chronic congestive heart failure and hypertension are long-term therapies. The belief that patients receiving placebo are being harmed is not accurate because there is no adverse effect on morbidity and
mortality or survival when proven, long-term therapy is withheld for a short time.

A different argument for the ethical basis of using placebo controls relies on the informed consent process. Before a patient's participation in a clinical trial, the patient is asked to participate in the trial. The informed consent process includes a description of the use of placebo and other aspects of the trial. In this written agreement the patient is responsible for notifying the physician of any medical problems and is informed of his or her right to withdraw from the study at any time, as described in the Nuremberg Code and Helsinki Declaration. During this disclosure, patients are presented with some new concepts and with risks and benefits to understand. On the basis of this information, a patient voluntarily decides whether to participate, knowing that he or she may receive a placebo or investigational medication.

However, despite physicians' efforts to inform the patient of research methods and the risk and benefits of trial participation, some patients agree to participate simply because of their trust in their physician. This situation may produce conflict between the physician-patient relationship and the physician's role as investigator. A partial resolution of this conflict is the double-blind technique, in which neither the patient nor the investigator knows which therapy a patient is receiving. This technique allows the physician and patient to make medical decisions on the basis of clinical signs and symptoms. In addition, because of the requirement for informed consent, the decision about participation in a clinical trial is shifted to the patient rather than left solely with the physician. However, the patient's physician evaluates the suitability of the patient for a particular trial before asking the patient to participate.

For every pharmacologic therapy, an assumption is made about patient adherence with the regimen. In clinical trials, investigators try to keep track of adherence by having patients bring their pill bottles to their appointments and counting the pills. Ultimately, the patient decides whether the beneficial effects of therapy outweigh the adverse effects. If a medication produces annoying and adverse effects, then the patient may not continue to take the medication. Other factors affecting adherence are the number of pills taken per day or the frequency of dosing. For instance, it is easier to take a medication once a day rather than 3 times a day. Furthermore, studies of patient adherence have found increased survival in patients with at least an 80% rate of adherence with therapy, including placebo therapy. All parties should be responsible for their research and accountable for the ethical conduct of their research. Clinical trials failing to comply with the Nuremberg Code and the Helsinki Declaration must be used as universal standards.

Until the mechanism of the placebo action is understood and can be controlled, a clinical trial that does not include a placebo group provides data that should be interpreted with caution. The absence of a placebo group makes it difficult to assess efficacy of a therapy. It is easy to attribute clinical improvement to a drug therapy if there is no control group. As was found with heart failure, chronic diseases have variable courses. Until the variability in chronic diseases is understood, placebo controls are needed to help explain it. In addition, because each clinical trial has a different setting and different study design within the context of the physician-patient relationship, a placebo group helps the investigator differentiate true drug effects from placebo effects.

More important than the inclusion of a placebo group is a careful study design that includes frequent review by a data and safety monitoring board of each patient's medical condition and trends affecting the patient's mortality, morbidity, and survival. This monitoring is crucial to protect study participants, as is the requirement that trials must include provisions that require a patient to be removed from a trial when the patient or physician believe that removal is in the best interest of the patient. The patient can then be treated with currently approved therapies.

Patients receiving placebo may report subjective, clinical improvements and show objective, clinical improvements, for instance, on ETT or Holter monitoring of ischemic events. Findings such as these dispel the implication that placebo therapy is the same as no therapy and may occur because many factors are involved in the physician-patient relationship, such as the psychological state of the patient, the patient's expectations and conviction regarding the efficacy of the method of treatment, and the physician's biases, attitudes, expectations, and methods of communication. An explanation of improvement in patients participating in trials is the close attention received by patients from the investigators. Baseline laboratory values are checked to ensure the safety of the patient and adherence with the study protocol. This beneficial response by the patient is called a positive placebo effect when found in control groups of patients receiving placebo therapy.

Conversely, the condition of patients receiving placebos has also, in some cases, worsened in response to placebo therapy. Every drug has side effects. When these side effects are actually adverse effects related to placebo
therapy, they may be so great that they preclude the patient’s continuation with the therapy. This phenomenon is reported by patients in clinical trials receiving placebo. Finally, placebos can act synergistically and antagonistically with other specific and nonspecific therapies. Therefore, much is still to be discovered about the effect of placebo in cardiovascular medicine.

**Conclusion**

The effect of placebo on the clinical course of systolic hypertension, angina, silent myocardial ischemia, CHF, and ventricular tachyarrhythmias has been well described and continues to be the focus of much investigative interests. In the prevention of MI, there appears to be a direct relation between adherence with placebo treatment and favorable clinical outcomes. The safety of short-term placebo-controlled trials has now been well documented in studies of drug treatment of angina and hypertension. The ethical basis of performing placebo-controlled trials continues to be challenged in the evaluation of drugs for treating cardiovascular diseases however, as long as life-saving treatment is not being denied, the performance of placebo-controlled studies remains a prudent approach for obtaining reliable scientific information regarding the efficacy and safety of new treatments.

*Note: References for this chapter can be found here: www.cvpct3.com*
More than 79 million American adults are estimated to have 1 or more types of cardiovascular disease (CVD). It is estimated that 1 in 3 adults has some form of CVD and that 72 million persons suffer from hypertension alone in the United States. The concern over this high disease prevalence is warranted, since CVD is associated with high rates of mortality and morbidity.

Essential hypertension is associated with an increased risk for cardiovascular (CV) events. For every 20-mmHg increase in systolic blood pressure (SBP) and 10-mmHg increase in diastolic blood pressure (DBP), there is a twofold increase in the risk of stroke and ischemic heart disease. If hypertension is left untreated, or if treatment does not bring patients to goal blood pressure (BP), there is a significant risk of coronary heart disease (CHD) and heart failure (HF).

The prevalence of CHD is estimated at 15.8 million American adults, with 7.9 million estimated to suffer from myocardial infarction (MI). The prognosis for these patients is not always favorable, as men and women in the United States are more likely to die of CHD than of any other disease. Data also indicate that patients suffering an MI have a poor prognosis: 25% of men and 38% of women will die within 1 year of an MI; within 6 years of an MI, 18% of men and 35% of women will have another MI.

The prevalence of HF is estimated at 5.2 million American adults. Data show that patients with HF are also at a high risk for poor outcomes. Repeat hospitalizations stemming from HF are common: 40% to 50% of HF patients are readmitted to the hospital for worsening HF or HF-related morbidity within 6 months of their initial hospital discharge.5

While the current prevalence and prognosis for patients with CVD is not encouraging, numerous clinical trials have shown the efficacy of various pharmacotherapies in post-MI patients as well as in those with hypertension and HF. These recent trials have shown that impressive reductions in the risks of mortality and rehospitalization associated with hypertension, MI, and HF are possible. The controlled environment of a clinical trial allows for observations in a “perfect world”; however, the large reductions in morbidity and mortality seen in clinical trials may not translate into better prognoses in patients in the “real-world” setting.

In order to obtain reductions in risks associated with CVD such as those seen in clinical trials, adherence to a prescribed medication regimen is crucial, but adherence to medication regimens has been shown to be a challenge in CVD. Reports have shown that as many as 40% to 50% of patients with CVD (including post-MI patients, patients with hypertension or hypercholesterolemia, and patients with diabetes mellitus and ischemic heart disease) fail to follow prescribed regimens. For patients being treated for chronic conditions (such as coronary artery disease, hypertension, and post-acute coronary syndromes), a marked reduction in adherence may be observed after just 6 months of therapy. Poor adherence to treatment, as a problem, has received attention in the literature for many years, and it remains a significant problem in disease management, especially in CVD.

Recently this has come to the forefront with the observation that nonadherence to antiplatelet therapy contributes to an increased risk of late site thrombosis in patients who had undergone coronary artery stenting. Because adherence to medical regimens is a critical mediator between the physician’s expertise and a patient’s outcomes, it is incumbent upon physicians to do more than follow care recommendations; they must stress the importance of adherence and make an effort to simplify the prescribed regimen.
of this review is to discuss the importance of treatment adherence in CVD, the common barriers to adherence, and the value of once-daily dosing in improving adherence rates.

Assessment of Adherence and Compliance

Adherence to a medication regimen has been defined as the extent to which a patient takes a medication as prescribed by the physician or health care provider. The term “adherence” is often used interchangeably with “compliance,” but adherence is currently the preferred term because it implies a responsibility shared by both the patient and the physician.6,24

There are a number of ways to assess whether a patient is correctly adhering to a medication regimen. In studies that have examined this issue, adherence rates are commonly reported as the percentage of the prescribed dose of medication actually taken by the patient over a period of time. Laboratory measurements of blood or urine drug metabolites or serum drug concentrations can be used to determine adherence.10 These methods do not have practical applications in a primary care setting, however, as they are invasive and potentially costly. Physicians are more inclined to evaluate adherence by questioning the patient, taking pill count assessments at checkup, and using electronic medication caps that record when a bottle is opened by the patient. Unfortunately, patients do not always report their nonadherent behavior, and other indirect measures can mislead health care providers into overestimating patient adherence.

Impact of Adherence in Hypertension, HF, and the Post-MI Patient

Adherence has been demonstrated to be directly linked to a favorable treatment outcome for a variety of chronic therapies.31 In a quantitative review of 63 studies assessing patient adherence for several chronic conditions (including arthritis, cancer, diabetes, heart disease, and hypertension), adherence (compared with nonadherence) reduced the risk of no significant benefit or a poor treatment outcome by 26%. Specifically, patients with hypertension who adhered to their medication regimens had a 30% reduction in the risk for a poor outcome.11 Patients with acute conditions, conditions that they know are associated with a high mortality (such as heart failure), or patients who are asymptomatic are more likely than those with chronic conditions to adhere to their therapeutic regimens. In chronic diseases, medication use is a daily commitment, and disease symptoms may not be as noticeable, which may lead patients to forget to take their medication.5

One chronic condition with relatively poor pharmacologic adherence rates is systemic hypertension, in which failure to take prescribed medications properly can have important implications for both BP control and CV complications.24,25 Treatment of hypertension usually requires daily lifelong treatment, with rigid adherence to therapy for the maintenance of proper BP control and the avoidance of hypertensive complications. Studies examining adherence in hypertension have pointed to a direct relation between BP control and medication adherence. A study that interviewed hypertensive patients identified a subgroup whose uncontrolled BP was potentially a direct result of their lack of adherence to medication.29 In another study, during the first 6 months of therapy more than 50% of 134 newly diagnosed hypertensive patients with poor BP control also had problems with adherence.31 BP control has been demonstrated to be significantly better in hypertensive subjects with medication adherence rates of 80% or greater than in those with adherence rates lower than 50%.32

The overall goal in the treatment of hypertension is to prevent CV complications that arise as a result of uncontrolled BP. If poor adherence results in reduced BP control, it logically follows that poor adherence will also have an effect on long-term outcomes in patients with hypertension. Decreased adherence to drug therapy prescribed for the treatment of hypertension and its relation to hospitalizations was evaluated in a retrospective study by Maronde et al.32 Adherence and readmission status was measured for a minimum of 1 year in patients admitted to an acute-care hospital with the diagnosis of hypertension during a 6-month period. Medication adherence in patients who were readmitted to the hospital was compared with the patients who were not readmitted. The readmitted group had a significantly higher ratio of days when they were without any antihypertensive agents relative to the length of time in the study. These findings indicate that the underutilization of antihypertensive agents was associated with increased hospitalizations. In a population-based, case-controlled study by Psaty et al, the risk of CHD complications was studied in hypertensive patients who were on antihypertensive therapy for 2 years.34 Patients categorized as recently nonadherent to β-blocker therapy (<80% adherent, stopping their medication during the preceding month) demonstrated a 4.5-fold increased risk for CHD complications.

In addition to being a large problem in hypertension therapy, poor adherence to treatment is also a major concern in post-MI patients or those suffering from acute coronary syndromes.35 For example, elderly patients have been found to have very poor rates of adherence to statin therapies, regardless of the presence of known CVD.15,36 In addition, the 2-year adherence rates to statin therapy for patients ≥66 years of age were observed to be only 40% for acute coronary syndrome, 36% for chronic coronary
artery disease, and 25% for primary prevention. Yet adherence to statin therapies for the treatment of CVD has been shown to be a critical factor in preventing poor outcomes. In the post-MI patient, a risk reduction of 81% for recurrent MI was observed for patients with at least 80% adherence to their statin medication. A 53% reduction in all-cause mortality was observed for this same group of patients. Post-MI patients who were documented as being less than 80% adherent had no significant reduction in risk for recurrent MI or all-cause mortality.

Results of the Lescol Intervention Prevention Study (LIPS) demonstrated a twofold increase in the risk of a major adverse cardiac event for post-MI patients who discontinued their statin medication. It has been demonstrated that the long-term survival advantages associated with improved drug adherence in post-MI patients appear to be drug-class specific, suggesting that adherence outcomes benefits are mediated by the drug’s effects rather than “healthy adherer, behavioral attributes.” 

HF is an additional CVD that requires chronic pharmacotherapy; a variety of studies have raised concern about medication adherence in its management. Chronic rehospitalization for HF is common. By 6 months after initial discharge, between 40% and 50% of HF patients are readmitted to the hospital. Poor adherence has been identified as a significant contributor to this problem. Studies indicate that between 20% and 64% of rehospitalization cases have been linked to poor adherence to prescribed HF treatments. A small study by Hope et al observed that only 30% to 38% of HF patients who visited the emergency department were adherent to their medication. Results from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study demonstrated that adherence to prescribed HF therapy was associated with a significant reduction in the risk of all-cause mortality. This reduction was observed irrespective of assigned treatment in the study. Adherence is also a problem in patients with HF, although a number of studies have shown adherence rates to be higher in HF than other CVDs. For instance, 71% of HF patients followed for 3 months were 85% to 100% adherent with their daily regimen of angiotensin-converting enzyme (ACE) inhibitor. In another small study, 72% of HF patients were adherent to diuretic therapy after 6 months. This variation in adherence rates may reflect differences in patient knowledge regarding the prognosis of their condition and the benefits of their medication as well as provider-patient communication.

**Impact on Costs**

In addition to poor outcomes, an impact on overall increased health care costs is also observed with poor adherence. An analysis of the association between the interruption or termination of antihypertensive drug therapy and total health care costs was performed by McCombs et al. This analysis used paid claims data from the California Medicaid program, with a primary outcome variable of total cost of health care in the first year after the initiation of antihypertensive therapy. Each patient with interrupted antihypertensive drug therapy accumulated an additional $873 in health care costs during the first year. These increased costs were primarily the result of increased hospital expenditures. Use of the MEDIPLUS database, which details patient primary care information in the United Kingdom, also demonstrated an increase in hospital and general physician costs associated with the discontinuation of antihypertensive treatment.

**Adherence Barriers in the Treatment of Cardiovascular Disease**

**Asymptomatic Disease**

Barriers to adherence can involve both modifiable and nonmodifiable factors (Table 3-1). Specific disease characteristics associated with CV conditions may also have a significant impact on adherence. The asymptomatic state associated with hypertension and hyperlipidemia has been observed to be a common barrier. A prospective study investigating adherence to the Joint National Committee (JNC) 6 hypertension treatment guidelines in the New York metropolitan area demonstrated that only 37% of the 821 patients surveyed reported consistent adherence to their antihypertensive regimen. This is not a new phenomenon, as evidenced by the results of a 1982 cross-sectional study of 800 adults in Detroit, Michigan, in which 21% of the 206 hypertensive patients interviewed had stopped drug treatment without being advised to do so. The factor that was most commonly found to distinguish dropouts from those adherent to their medication regimens was the perception of their health status. The poorer a patient perceived his or her health to be, the more likely he or she was to adhere to the prescribed treatment regimen. The reason given most often for discontinuation was that the patient felt well without the medication.

There are hypertensive patients who are more likely to adhere to their medication regimen. Patients who viewed hypertension as a symptomatic disease and who believed their treatment had beneficial effects on their symptoms have been shown to be more adherent and to have better BP control. These tendencies are not exclusive to hypertensive patients. Hyperlipidemia is another disease in which the asymptomatic condition has been observed to affect medication adherence, particularly in patients without CHD. Two-year adherence rates to statin therapies were studied in elderly patients with and without acute coronary syndromes. Elderly patients taking statins...
Adverse Effects

Adverse effects are another common reason for discontinuation of prescribed therapy. These may be more apparent in hypertensive patients because the illness itself is so often asymptomatic, which may increase a patient's awareness of common adverse effects associated with prescribed therapies. A drug's adverse-effect profile has been demonstrated to contribute to poor adherence by affecting a patient's quality of life.\textsuperscript{54} A survey by Düsing et al of 1603 patients with hypertension demonstrated that

<table>
<thead>
<tr>
<th>Table 3-1. Characteristics That Influence Medication Compliance</th>
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</thead>
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<td><strong>Patient's sociodemographic characteristics:</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Educational level</td>
</tr>
<tr>
<td>Occupational status</td>
</tr>
<tr>
<td>Family stability and level of support</td>
</tr>
<tr>
<td>Race and ethnicity</td>
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<tr>
<td>State of knowledge of disease process or consequences and</td>
</tr>
<tr>
<td>medication regimen</td>
</tr>
<tr>
<td>General attitude toward health care</td>
</tr>
<tr>
<td>Expectations of prescribed regimen</td>
</tr>
<tr>
<td>Appointment attendance</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>Living status (alone vs not alone)</td>
</tr>
<tr>
<td>Mental stability; level of forgetfulness</td>
</tr>
<tr>
<td>Religious beliefs</td>
</tr>
<tr>
<td>Strength of belief in treatment value</td>
</tr>
<tr>
<td>Previous history of compliance</td>
</tr>
<tr>
<td>Appropriateness of health beliefs</td>
</tr>
</tbody>
</table>

| **Characteristics of health care provider:**                  |
| Length of time between start of problem and referral of      |
| patient to provider                                          |
| Interviewing and listening ability of provider               |
| Length of time between contacts between provider and patient |
| Provider's ability to keep appointments                      |
| Continuity of care with provider                             |
| Degree and ease of access that provider has to the patient   |
| Patient level of satisfaction with initial contact with      |
| provider                                                     |
| Ability level of provider to assess patient compliance       |
| and potential barriers to compliance                        |
| Length of waiting time for provider services                 |
| Length of time provider spends with patient                  |
| Level of support, empathy, and feedback that provider gives   |
| to the patient                                               |
| Quality of instruction given for taking prescribed regimen   |

| **Medication characteristics:**                               |
| Type of medication                                            |
| Complexity of dosing schedule                                 |
| Medication packaging                                          |
| Degree of lifestyle changes required to adhere to prescribed |
| medication regimen                                            |
| Duration of therapy                                           |
| Number of prescribed medications                              |
| Side effects                                                  |
| Cost                                                          |

| **Disease characteristics:**                                  |
| Symptomatology                                               |
| Duration of illness                                          |
| Previous hospitalization                                     |
| Severity of illness                                          |
| Previous history of disease                                  |
| Level of disability caused by disease process                 |

Importance of Medication Adherence in Cardiovascular Disease Treatment

approximately 10% of poor adherence reported was due to adverse effects associated with the prescribed medication. In addition to adverse effects, new symptoms that may be unrelated to the medication regimen can also dramatically impact adherence. It is therefore important to advise patients of adverse effects that may be related to their medications, as patients tend to blame their drugs for any new symptoms they experience.

Pill Burden and Dosing Complexity

The complexity of a drug regimen, including the number of drugs required, has been observed to affect a patient's adherence to therapy. This barrier to adherence is especially problematic in the treatment of hypertension and HF, as the complexity of dosing and number of medications increases with the severity of these diseases. This is a problem that has been growing as the number of available medications has increased. From 1998 to 1999, elderly HF patients were discharged on a mean of 6.8 drugs, which represented 10.1 daily doses. From 2000 to 2001, this number increased to 7.5 drugs, an average of 11.1 doses daily. An average of 2 to 4 antihypertensive medications are required for BP control in most high-risk hypertensive patients with comorbid conditions such as renal disease or diabetes. As seen in Figure 3.1, Bakris and colleagues noted that 2 or more different antihypertensive agents were needed to achieve target BP goals in 5 separate randomized control trials. As new treatment strategies are added for patients with HF and hypertension, the increased pill burden may contribute to problems with adherence.

The frequency of medication dosing has also been shown to have a direct impact on adherence: an inverse relationship has been observed between the number of daily doses and the rate of adherence (Figure 3.2). Mean dose-taking adherence declines as the number of daily doses increases. A meta-analysis of 76 studies assessing medication adherence for a variety of chronic conditions (including 26 studies in CVD) showed that mean dose-taking adherence was 79% for 1 dose, 69% for 2 doses, 65% for 3 doses, and 51% for 4 doses (P < .001 among dose schedules) (Table 3-2). These data show that it is important for physicians to identify patients at risk for poor adherence and to prescribe therapies that will help to alleviate pill burden.

Once-Daily Dosing Improves Medication Adherence in the Treatment of CVD

Medications that offer once-daily dosing options (such as long-acting and/or slow-release oral drugs) are prevalent in the treatment of chronic CVD. Reduction in dose frequency through the selection of once-daily agents has

Figure 3.1. The number of different antihypertensive agents in 5 separate randomized control trials necessary to achieve BP goal in patients with diabetes and/or kidney disease. AASK = African American Study of Kidney Disease and Hypertension; ABCD = Appropriate Blood Pressure Control in Diabetes; BP = blood pressure; HOT = Hypertension Optimal Treatment; MDRD = Modification of Diet in Renal Disease; UKPDS = UK Prospective Diabetes Study. Reprinted with permission from Bakris GL. Maximizing cardio-renal benefit in the management of hypertension: achieving blood pressure goals. J Clin Hypertens (Greenwich). 1999;1:141.

Figure 3.2. Adherence to medication according to frequency of doses. Vertical lines represent 1 SD on either side of the mean rate of adherence (horizontal bars). Data from Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23:1296.
been shown to improve medication adherence in several chronic conditions, particularly in the treatment of hypertension. A systematic review of dosing regimens and medication adherence demonstrated that use of once-daily drug formulations has a significant effect on medication adherence. Included in this meta-analysis were 76 studies (studies included covered a range of therapeutic areas, 26 of which were CV disorders) that measured adherence to prescribed regimens through the use of medication event monitoring systems (MEMS). Once-daily dosing was shown to have the highest adherence rate among dosing schedules. As the number of doses per day increased, the adherence rates declined significantly (Table 3-2).

A meta-analysis by Iskedjian et al also demonstrated a significant correlation between daily-dose frequency and adherence to antihypertensive therapy. A total of 11,485 observations with captured data on adherence to antihypertensive therapy were pooled to determine if statistical differences in adherence rates existed when comparing once-daily dosing (QD), twice-daily dosing (BID), and multiple daily dosing (MDD; either 3 or 4 times daily). Reducing daily dose frequency was found to produce a significant improvement in adherence. The average adherence rate was significantly higher for QD dosing compared to MDD dosing (91.4% versus 83.2%, \( P < .001 \)). The average adherence rate for QD dosing compared to BID dosing was also significantly higher (92.7% versus 87.1%, \( P = .026 \)).

The value of once-daily dosing in improving medication adherence can be analyzed by several different parameters. MEMS recording systems can report not only the number of times a medication bottle is opened, but also the time at which the prescribed dose is taken, which is important because proper timing of a medication regimen is a key measure of adherence. Once-daily drug formulations have been shown to improve adherence rates for medication regimens by increasing correct dose timing. In the meta-analysis by Claxton et al mentioned previously, dose timing as a measure of adherence to a prescribed drug regimen was also shown to be improved with reductions in dosing frequency (Table 3-3).

In a study of 320 hypertensive patients taking either once-daily amlodipine or twice-daily nifedipine, 5 different parameters of adherence were analyzed: 1) pill count (number of pills dispensed / number of pills prescribed); 2) taking adherence (number of openings / total number of days); 3) days with correct adherence rate was significantly higher for QD dosing compared to MDD dosing (91.4% versus 83.2%, \( P < .001 \)). The average adherence rate for QD dosing compared to BID dosing was also significantly higher (92.7% versus 87.1%, \( P = .026 \)).

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Table 3-4. Innovative Strategies for Improving Patient Compliance

| Electronic monitoring devices                  |
| Pill containers with daily compartment for medication |
| Phone call refill reminders from pharmacies       |
| Augmented medication counseling by pharmacists at time prescription is filled |
| Computerized lay-language medication instructions written by manufacturer for distribution at local pharmacies |
| Computerized dosage-schedule charts from pharmacies incorporating medication interactions of a prescribed regimen in over-the-counter medications and food products |
| Contact with pharmaceutical companies to provide medications for economically needy patients |
| Contact with pharmaceutical companies who offer compliance reminder programs |
| Community-based programs for patients by health care providers at schools and community centers |
| Compliance programs educating patients to be resourceful health care consumers |
| Compliance teams within health care facilities to educate and monitor patient compliance |
| Continuing education programs for health care providers on ways to increase patient compliance |


acceptable level of hypertension medication adherence (80% of correct time intervals for bottle opening within a 24-hour period) was observed in 49% of patients when once-daily formulations of antihypertensive agents were used but in only 5% of patients when twice-daily formulations were used. BP was within goal in 50% of the patients who were adherent to therapy but in only 14% of patients who were identified as being nonadherent. The MEMS cap system was also used in a study by Leenen et al to assess differences in various adherence parameters for patients with hypertension. Use of once-daily amlodipine demonstrated significant improvements in adherence compared with twice-daily therapy, as measured by the percentage of doses taken on schedule and the percentage of days with correct dosing (P < .01 for both parameters).

The importance of adherence is demonstrated in a number of studies that have shown both better BP control and improved outcomes for patients with CVD. A study comparing the once-daily controlled-release formulation of isosorbide mononitrate to twice-daily 5-isosorbide mononitrate demonstrated significant differences in the 2 regimens for patients suffering from angina pectoris. Patients randomized to the once-daily formulation showed significant improvement in adherence as measured by the correct number of doses taken as well as correct timing of doses compared to the twice-daily formulation. This improved adherence was correlated with improvements in outcomes. Patients on the once-daily regimen had fewer angina attacks (1.7 per week for QD compared to 3.3 per week for BID) and used fewer supplemental nitroglycerin tablets for symptom relief than patients on BID therapy (1.1 per week for QD compared to 1.6 per week for BID).

One concern regarding the use of once-daily formulations is that when patients are not adherent to their therapeutic regimens, they miss an entire day’s worth of medication as opposed to missing half a day or less with multiple dosing. Although this is an important consideration, the properties of long-acting oral formulations may help to provide protection from adverse events even when adherence is not perfect. In the study by Leenen et al that defined partial adherence as less than 80% of prescribed pills taken, although BP control was significantly reduced in patients who were only partially adherent to the short-acting, twice-daily diltiazem therapy, this was not the case in patients who were only partially adherent to the long-acting, once-daily formulation of amlodipine. This suggests that the negative consequences of partial compliance for BP control may be offset by selecting agents with a longer duration of action beyond the dosing intervals. Overall, the use of once-daily drug formulations provides a significant improvement in adherence to a prescribed regimen and may improve outcomes in the treatment of CVD.
Conclusions

The burden of CVD remains high in the United States, with a widespread prevalence and a poor prognosis despite significant advances in treatment. A number of factors can prevent the CVD population from receiving the best care possible, and less than optimal treatment of CVD poses a significant risk for poor and potentially fatal outcomes. Physicians must not only provide evidence-based care but must also pay attention to whether or not the therapy they prescribe is optimal. It is essential that physicians consider whether the drugs they prescribe have significant adverse effects that will cause the patient to discontinue therapy. They must also factor in the possibility that the patient may forget to take multiple doses of the agent or skip doses if the pill burden or complexity of regimen is too great. Moreover, as additional therapies show benefit when included in a treatment regimen, or as a patient’s disease becomes more severe, it may be necessary to add medications that could hinder adherence with the entire drug regimen.

Adherence to a prescribed CVD drug regimen is critical to effective treatment.\(^{31}\) Despite the advances in pharmacological therapies, adherence remains a significant issue facing the practitioner, and it is an issue that must be addressed aggressively (Table 3-4). The excellent therapeutic regimens for diseases such as hypertension and HF and for post-MI patients will be beneficial only if physicians can find ways to improve patient adherence.\(^{67-71}\) In addition to initiating an honest dialogue with patients about their medications, expected adverse effects, and the importance of adherence, the use of once-daily, long-acting oral drugs is a treatment strategy that has been shown to improve both adherence to therapy and patient outcomes. When available, a once-daily agent should be prescribed in lieu of agents that require multiple dosing.

Note: References for this chapter can be found here: www.cvpcpt3.com
Health Economic Considerations in Cardiovascular Drug Utilization

Renée J. G. Arnold, RPh, PharmD
William H. Frishman, MD

The age of evidence-based medicine is upon us. As stated in a recent American College of Physicians position paper, “given the as-yet uncontrolled explosion of health care costs, the de facto rationing produced by having 47 million uninsured patients denied access to health care [in the United States], and the limited resources of our society, the time has come for patients, physicians, insurers, and health care policymakers to explicitly and transparently factor the comparative effectiveness, comparative cost, and cost-effectiveness of both new and existing health care interventions into their decisions.”

Recent studies in the field of health economics (HE)/pharmacoeconomics (PE) show the types of analyses being used to help determine its place in therapy/market advancement/characterization, market segmentation, post-marketing surveillance, guideline development, break-even analyses, and policy decisions among others. Countless examples in other areas of health care demonstrate the enormous importance of these studies.

With limited health care dollars, an increasing burden is being placed on health care professionals to provide the best possible care while consuming the fewest possible resources. This is particularly the case when high-technology but costly interventions are a potential option, as in the treatment of patients with cardiovascular disease. The total economic burden of cardiovascular disease and stroke in the United States, consisting of both direct and indirect costs, is estimated at $503.2 billion for 2010, more than twice the estimated cost of all cancer and benign neoplasms ($228 billion) in 2008.

Of particular interest, then, is the incremental benefit associated with the additional cost of a new therapeutic option. For example, tissue plasminogen activator (t-PA) has been demonstrated to reduce post-myocardial infarction (MI) mortality by 1.1% over streptokinase, but at an additional cost of approximately $2,800 per patient. Another example is the up-front cost associated with angiotensin-converting enzyme (ACE) inhibitor therapy as a treatment for heart failure, which may be associated with lower “downstream” hospitalization costs. A further example was the $3,225 incremental cost per patient to avoid a new thrombosis for heparin-induced thrombocytopenia (HIT) without thrombosis treated with the direct thrombin inhibitor argatroban, compared with patients who discontinued heparin and were treated with standard therapy.

Often, therapies with improved efficacy and/or safety profiles are more expensive than less effective treatments, and it is not always clear whether the incremental benefit from the more expensive therapy is worth the additional cost. The science of HE allows one to determine whether this trade-off of effectiveness for cost is worthwhile. Cost-effectiveness analyses first became of interest in the 1970s and have assumed greater importance through the development of more sophisticated analytic techniques. Because of the increasing prominence of these analyses in all areas of decision-making, it is incumbent upon the practicing cardiologist to understand the basic tenets of HE analyses and how these may be applicable to daily practice. Indeed, several comprehensive reviews of the cost-effectiveness of heart disease treatments, primarily those in the US literature, were published 15 years ago and have not been updated since. The science of HE is more far-reaching than the question of which therapeutic options should be available within a particular setting. In fact, they are sometimes conducted in some institutions to help determine which health professionals should initially be treating patients (eg, generalist versus specialist) and even which setting should be recommended. Many influential groups, including the American Heart Association, support the tenet that cost-effectiveness, in addition to clinical effectiveness, must be determined to...
allow for appropriate treatment while maximizing allocation of scarce medical resources.38,39

**Features of Health Economic Analyses**

**Cost-Effectiveness**

An effective HE or cost-effectiveness analysis is designed to answer certain questions, such as: Is the treatment effective? What will it cost? How do the gains compare with the costs? By combining answers to all of these questions, the technique helps decision makers to weigh the factors, compare alternative treatments, and decide which treatments are most appropriate for specific situations. Typically, one chooses the option with the least cost per unit of measure gained; the results are represented by the ratio of cost to effectiveness (C:E). With this type of analysis, called a cost-effectiveness analysis (CEA), various disease endpoints that are affected by therapy (risk markers, disease severity, death) can be assessed by corresponding indexes of therapeutic outcome (degree of blood pressure reduction, number of hospitalizations averted, and life-years saved, respectively).

“Average” cost-effectiveness is the result of dividing mean total costs by outcomes. Although this type of analysis allows one to view the actual numbers involved in the computation, average cost-effectiveness does not illustrate differences between competing strategies.40,41 Thus, many researchers discuss the merits of an “incremental” cost-effectiveness ratio (ICER), ie, additional cost for additional benefit, which may be calculated as follows:

\[
\frac{\text{AC}}{\text{AE}} = \frac{\text{cost}_1 - \text{cost}_2}{\text{effectiveness}_1 - \text{effectiveness}_2}
\]

where effectiveness$_1$ is greater than effectiveness$_2$.

The term incremental is commonly used interchangeably with the term marginal to denote the additional cost and outcome of an intervention.40 For example, consider the analysis by Eckman and colleagues42 of the comparative cost-utility of aspirin, anticoagulation, and no anticoagulation in atrial fibrillation. Over a lifetime, providing anticoagulation therapy for a patient costs on average $2,200 more than aspirin therapy (ie, cost$_1$ - cost$_2$) and results in an average gain of 0.12 quality-adjusted life-years (QALYs) (ie, effectiveness$_1$ - effectiveness$_2$), concluding in a marginal CER, or ICER, of $2,184/0.12$ or $18,200 per QALY (Table 4-1). This type of analysis is useful in the following two instances: (1) where the new strategy is more costly but expected to be more effective, or (2) where the new strategy is less costly but less effective.

In cases where these conditions do not apply, a negative cost-effectiveness ratio occurs—ie, when the competing strategy produces cost savings without reducing effectiveness or when the comparator results in a net increase in costs and reduction in health. Such a strategy is said to be dominated by the more effective strategy. The CER for a dominated strategy is, therefore, negative. Logically, no one would choose a treatment that costs more and is less effective; this results in a negative CER and results may be considered uninterpretable.41,43 As an example, again consider the analysis by Eckman and colleagues.42 Since the CER of “do not anticoagulate” is negative, ie, less effective than either comparative strategy, only the aspirin and “anticoagulate with warfarin” strategies are evaluated.

An efficiency envelope illustrates the concept of incremental effectiveness versus cost. The curve of the outermost points forms the envelope or frontier and represents the most efficient options. Points within the envelope are dominated by at least one point along the envelope.44 Relatively steep slopes from one strategy to another indicate a substantial increase in effectiveness for a modest increase in cost. As an example, once more consider the analysis by Eckman and colleagues (Figure 4-1).42 Here, aspirin and anticoagulation correspond to two points along the envelope where incremental cost-effectiveness is calculated; “do not anticoagulate” corresponds to the inside of the envelope.

The concepts that are of importance in understanding an HE analysis include its type, perspective, method used, data source(s), ultimate use, time frame, patient subgroups, and robustness. Each of these is discussed in detail below and examples of cardiovascular analyses in the literature given.

**Types of Analyses**

Analyses may characterize differences between therapies and/or procedures used for treatment of disease. They can also be used to determine the cost-effectiveness of preventive measures. Several types of economic analyses have been developed to facilitate choices among therapies competing for the same health care dollars. HE analyses are generally categorized according to the type of analysis to be performed (Table 4-2).45-47 Cost-minimization analysis (CMA) is most appropriately used when therapies are equally effective and only costs need be compared: the least expensive drug is preferred. Cost-benefit analysis (CBA) uses monetary terms to measure effectiveness; because it is difficult to place a monetary value on life and health, this approach has limited utility.

When a single dimension of effectiveness characterizes the relevant outcome for all therapies and alternative treatments do not have the same clinical effectiveness, CEA may be the most appropriate method of evaluation. It assesses the incremental gain in therapeutic benefits derived from additional costs, and it measures effective-
iness in terms of health outcomes, such as life-years saved, cases of disease prevented, or complication-free therapy-months. Cost-utility analysis (CUA), which may be considered a type of CEA, evaluates the impact of a certain therapy on quality of life and measures effectiveness in terms of quality-adjusted units, such as the QALY. All of these methodologies may be carried out using either a retrospective or prospective approach, although the reliability of a CUA may be questionable when such a study is conducted retrospectively.

For example, prevention of primary and secondary MI and stroke via use of lysine acetylsalicylate was shown to be a cost-effective strategy in patients at high risk of cardiovascular and cerebrovascular events in a French model that used the Social Security perspective. CERs varied according to underlying disease and dose of acetylsalicylate (Table 4-3). Likewise, Augustovski and colleagues designed a Markov model to evaluate the utility of aspirin for primary prevention of cardiovascular events on expected length and quality of life for a hypothetical cohort over 10 years. Risk factors that were considered included gender, age, cholesterol levels, systolic blood pressure, smoking status, diabetes mellitus, and presence of left ventricular hypertrophy. Outcomes were MI, stroke, gastrointestinal bleed, ulcer, and death. The model indicated that those patients with the highest risk would garner the greatest benefit (gain of 11.3 quality-adjusted life-days), while those with the lowest risk would actually lose benefit (loss of 1.8 quality-adjusted life-days). The decision was extremely sensitive to variations in patient preference for taking aspirin and to aspirin’s effects on cardiovascular mortality.

### Perspective

The perspective of the analysis is typically that of the primary decision maker. Perspective dictates whether charges or actual costs to the payer should be recorded and employed in the evaluation. Examples of perspective include those of the patient, the third-party payer (e.g., Medicare, insurance companies), the institution (e.g., hospital or managed care organization), the provider, or society at large. The societal perspective frequently includes indirect costs, such as loss of productivity, home health care, and caregiver loss of wages, as well as direct costs of therapy, whereas the institutional perspective does not take indirect costs into consideration. Although studies done in countries with a primarily socialized (nationalized) health care system frequently take the societal viewpoint, US-based studies may not, especially since

---

**Table 4-1. Cost-Effectiveness Analysis**

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Cost</th>
<th>Effectiveness (QALYs)</th>
<th>Marginal Cost (cost)</th>
<th>Marginal Effectiveness (QALYs)</th>
<th>Marginal Cost-Effectiveness Ratio (per additional QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (ASA)</td>
<td>$8,544</td>
<td>6.74</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Do not anticoagulate</td>
<td>$9,889</td>
<td>6.37</td>
<td>$1,345</td>
<td>$-0.37 (vs ASA)</td>
<td>Dominated</td>
</tr>
<tr>
<td>Anticoagulate with warfarin</td>
<td>$10,728</td>
<td>6.86</td>
<td>$2,184</td>
<td>0.12 (vs ASA)</td>
<td>$18,200</td>
</tr>
</tbody>
</table>

*Quality-adjusted life-years.

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**Figure 4-1.** Aspirin and anticoagulation correspond to two points along the efficiency envelope where incremental cost-effectiveness is calculated; “do not anticoagulate” corresponds to the inside of the envelope.
indirect costs are frequently difficult to measure. Approaching the analysis from the appropriate perspective helps to ensure that the results will be useful. Importantly, different perspectives may be driving the issue, such as the individual physician’s desire to hospitalize the patient and the managed care organization’s (MCO’s) desire to maximize profit margin.

Resource and Cost Components

The frequency and cost of resources that are typically incorporated into the cost component (numerator) of the CER include outpatient visits, hospital days, emergency or urgent care visits, laboratory studies, treatment of adverse events, concomitant medications, monitoring for therapeutic effect and adverse events, generalist and specialist visits, primary drug therapy, and devices.

Costs may be recorded as charges or actual costs to the payer, depending on the perspective of the analysis. If costs are desired and only charges are available (as with patient bills), charges may be multiplied by cost-to-charge ratios (which may be available through accounting departments at institutions) to convert charges to costs. Care must be taken in this endeavor, however, since different cost centers may have a variety of cost-to-charge ratios. In addition, interpretation of results may be obscured by cost-shifting, ie, shifting costs of procedures away from less profitable cost centers.52 Several national sources of charges include the Medicare databases.

<table>
<thead>
<tr>
<th>Type of Economic Analysis</th>
<th>Appropriate Uses</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-consequence, cost-identification, or component enumeration</td>
<td>Costs and/or consequences of each therapy are presented in disaggregated form.</td>
<td>No combinational analysis is attempted; difficult to ascertain total comparative costs</td>
</tr>
<tr>
<td>Cost-minimization analysis (CMA): Identifies least costly selection among equally effective therapies</td>
<td>Selecting among equally effective therapies (eg, generic substitutions)</td>
<td>Difficult to establish identical clinical effectiveness in same/similar patient(s)</td>
</tr>
<tr>
<td>Cost-benefit analysis (CBA) Expresses effectiveness in monetary terms; monetary value placed on health-related outcomes as well as costs</td>
<td>Choosing drugs or other therapy with highest net benefit or greatest cost: benefit ratio; comparing therapeutic regimens with different objectives</td>
<td>Difficult to place monetary value on life or health</td>
</tr>
<tr>
<td>Cost-effectiveness analysis (CEA): Assesses incremental gain in therapeutic benefits derived from additional costs; measures effectiveness in terms of health outcomes; compares regimens that measure effectiveness in terms of health outcomes and computes cost-effectiveness ratio for comparison</td>
<td>Selecting among alternative treatments that do not have same clinical effectiveness. Used when single dimension of effectiveness (eg, cost/life years saved) characterizes outcome of all therapies</td>
<td>Cannot compare different types of treatments; treatment strategies compared only for specific disease rather than across diseases</td>
</tr>
<tr>
<td>Cost-utility analysis (CUA): Evaluates impact of certain therapy on quality of life and measures effectiveness in terms of quality-adjusted units</td>
<td>Simultaneously synthesizing or summarizing several outcomes into single measure (eg, impact of drugs on both pain and physical functioning)</td>
<td>Difficult to compare therapeutic impact across individuals. Preference for health state may differ according to current condition</td>
</tr>
<tr>
<td>Quality-adjusted life-year (QALY): Commonly used health outcome in CEA and CUA</td>
<td>When considering net gain in value or utility of state of health in addition to net gain in duration of life</td>
<td>Assumes that preferences for state of health do not change over time</td>
</tr>
</tbody>
</table>

Table 4-2. Types of Economic Analysis

Health Economic Considerations in Cardiovascular Drug Utilization

Considerations in Cardiovascular Drug Utilization

43

(eg, Medicare Provider Analysis and Review [MEDPAR] available through the Centers for Medicare and Medicaid Services [formerly the US Health Care Financing Administration]) and the resource-based relative value scale (RBRVS) of charges for physician-initiated procedures.53 Costs may be collected, for example, via institutional examination (eg, cost-accounting systems in hospitals and health maintenance organizations [HMOs]), wholesale drug prices (eg, Red Book), and time and motion studies.

Resources may be broadly grouped as direct or indirect. Direct resources are those that are consumed in the immediate care of the patient, such as outpatient visits, while indirect resources are incurred as a consequence of the treatment or illness and are not directly consumed in carrying out the treatment strategy; indirect resources are those that may impact the patient or society at large, such as loss of income or leisure time.41 On occasion, known costs may be used as proxies for unknown costs of items if these are felt to be comparable. For example, as a proxy for an adverse event cost, Podrid et al54 used the cost of a typical inpatient stay for a primary diagnosis of this event in a study of three antiarrhythmic agents. Sometimes, a cost-of-illness or burden-of-illness evaluation is undertaken. Such an analysis takes into consideration direct and indirect costs of illness and may be useful in determining the potential impact of the intervention on the total cost of treating the disease.

Time Frame (Discounting and Time Horizon)

Future costs and effects are discounted to reflect the fact that, in general, individuals and society have a positive rate of time preference.57-59 In general, they prefer desirable consequences to occur earlier and undesirable consequences to occur later. Thus, future benefits are discounted to reflect the fact that they are worth less simply because they occur in the future rather than now. Similarly, future costs are discounted to reflect the fact that we prefer them to occur in the future rather than the present.28 Although the appropriate discount rate is controversial, the most accepted figures are 3% or 5%, since they are based on the real rate of return on long-term government bonds.60 However, sensitivity analyses (see below) should encompass rates from 0% (ie, no discounting) to 7%.

Time horizon (the length of time into the future considered in the analysis over which costs and outcomes are projected) is also very important.40 For example, if a clinical trial or the published literature report only short-term results for a chronic condition, the study outcome may come into question. This is where decision-analytic models may come into play, allowing one to project study results to clinically realistic time frames. In addition, these models can help in projecting thresholds (see "Robustness," below).61

Efficacy Versus Effectiveness

Efficacy is typically considered as the measurement of therapeutic effect in clinical trials. Thus, it is a determination of the optimal benefit in an ideal setting which may or may not be seen in routine clinical practice. In contrast, effectiveness is the therapeutic effect in a "real world" setting and is generally less favorable than efficacy because it includes effects such as nonadherence and less-than-ideal care. Effectiveness, rather than efficacy, is used in HE analyses because it is more representative of what clinicians experience in routine clinical practice.

Life expectancy is a frequently used as effectiveness criterion.62-67 Edelson et al published a long-term cost-effectiveness study that compared propranolol, hydro-

<table>
<thead>
<tr>
<th>History</th>
<th>Follow-Up</th>
<th>C/E Metric</th>
<th>C/E Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>1 year</td>
<td>Cost per avoided MI</td>
<td>$5,703 to $5,761 (1996 prices)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>2 years</td>
<td>Cost per avoided MI</td>
<td>$15 (300-mg dose) to $494 (75-mg dose) (5% discount rate)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3 years</td>
<td>Cost per avoided MI</td>
<td>$610 to $2,082</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cost per avoided stroke</td>
<td>$176 to $599</td>
</tr>
<tr>
<td>Stable angina</td>
<td>4 years</td>
<td>Cost per avoided MI</td>
<td>$4,375 to $3,608</td>
</tr>
</tbody>
</table>

*In US dollars.
C/E = cost effectiveness.

Table 4-3. Prevention of Primary and Secondary Myocardial Infarction (MI) and Stroke via Use of Acetylsalicylate
chlorothiazide, nifedipine, prazosin, and captopril as monotherapy for mild to moderate hypertension. These authors used the Coronary Heart Disease Policy Model (a computer simulation model) to calculate the cost per years of life saved (YLS) over 20 years of simulated therapy. Probabilities for cardiovascular events were determined from the Framingham Heart Study. The effects of the five agents on blood pressure and cholesterol were obtained via meta-analysis of 153 reports. The cost per YLS (1987 dollars discounted at 5% annually) varied from $10,900 for propranolol to $72,100 for captopril. The analysis included savings due to avoided cardiovascular events but did not consider reduction in the risk of stroke.

In addition, adherence with these regimens was not considered. In fact, the Treatment of Mild Hypertension Study (TOMHS) examined this issue and demonstrated that after 4 years, 67.5% of patients remained on chlorthalidone, 77.8% on acebutolol, and 82.5% on amlopidine. Similarly, discontinuation rates of antihyperlipidemic drugs in clinical trials were demonstrated in a study by Andrade et al not to be reflective of (higher than those of) managed care patients—eg, 41% versus 31% for bile acid sequestrants, 46% versus 4% for niacin and 37% versus 15% for gemfibrozil in the managed care and clinical trials, respectively. Moreover, as demonstrated in Table 4-4, Kozma and coworkers showed that, regardless of initial diastolic blood pressure, full adherence with the medication regimen would result in a cost per QALY that was about half that associated with partial adherence.70

A similar finding of reduced total costs among compliant patients was noted in a retrospective review of administrative claims data for congestive heart failure (CHF) patients. Clearly, these issues must be considered in long-term cost-effectiveness models.

Other measures may be employed to define the effectiveness component if the therapies being evaluated are not necessarily lifesaving, if the time frame of the analysis does not lend itself to YLS, or if this measure is not clinically relevant to the question being studied. Examples of these include complication-free therapy months; coronary heart disease (CHD) events potentially avoided; percentage reduction in total cholesterol; low density lipoprotein (LDL), high density lipoprotein (HDL) cholesterol and LDL/HDL; degree of stenosis found; blood pressure control; surgical cure; and thromboembolism averted.

### Utility Assessment and Quality of Life

CUAs have gained increasing popularity since they incorporate a patient-oriented measure or subjective component (patient preferences) into the effectiveness portion of the equation. In this regard, YLS may be "qualified" by the decrement in quality of life (QOL) during this time span, giving an effectiveness criterion such as QALYs. Quality adjustment is important in that a treatment may not change life expectancy but may change QOL dramatically, so the net effect of a strategy will be completely missed if one does not consider QOL. For example, drugs to treat angina pectoris may not improve survival but may improve QOL. There are also strategies that may increase survival but reduce QOL, such as a pacemaker, where the patient is continually concerned about premature electrical discharge. For the remainder of the patient's life, his or her lifestyle will be dominated by this negative component of the therapy.

Quality adjustment is usually performed by polling a representative population (depending on the perspective of the analysis) to elicit their preferences for being in a particular state of health. These results, called “utilities,” are typically expressed as numbers between “0” (death) and “1” (perfect health), which are then multiplied by the number of years in that health state. For example, 2 years with angina might be worth 1.6 years (2 years × 0.8 utilities or quality-adjustment factor) of perfect health. A number of methods, such as the standard gamble and time trade-off, have been developed to allow one to measure health-state utilities. Although time trade-off has been generally considered easier to use than standard gamble, the latter may be more consistent or reliable. Debates in this area have focused on potential states worse than death and on the definition of the utility of “1” (ie, whose idea of perfect health?). That is, while “0” is meant to represent the worst state of health, some believe that death is not always the worst health state.

Nonetheless, the importance of taking effectiveness and QOL into consideration may be illustrated as:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>QALYs</th>
<th>Cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>$10,000.00</td>
<td>10</td>
<td>$1,000.00</td>
</tr>
<tr>
<td>B</td>
<td>$8,000.00</td>
<td>6</td>
<td>$1,333.00</td>
</tr>
</tbody>
</table>

At face value, treatment B would be preferred because it is less expensive. However, if one takes into consideration...
the number of years lived and QOL during this time period for the average patient, treatment A is the preferred strategy.

**Method Used**

A variety of methods have been used to structure HE evaluations to assure inclusion of all applicable parameters. Some of these include decision trees (decision-analytic models), mathematical spreadsheets (eg, using Lotus or Microsoft Excel), simulation models, and cost enumeration, among others.

**Decision-Analytic Models**

Decision-analytic models are structured methods of incorporating probabilities and costs of likely events for expected therapeutic pathways. These models use a tree structure and principles of expected utility to calculate both cost and effectiveness. Numerous evaluations have used this method for determining the most cost-effective strategy.6,34-38 An example of this type of analysis was that undertaken by Danford and colleagues,39 in which echocardiography for evaluation of a pediatric heart murmur followed by referral to the cardiologist was found to be more costly than initial evaluation by a cardiologist.

An example of a decision-analytic model that illustrates the need to target specific patient subgroups is the economic analysis carried out by Barrett and researchers to estimate the incremental cost per QALY of low (LOCM)- vs high (HOCM)-osmolality contrast media for cardiac angiography.40 These strategies include unrestricted use of LOCM or HOCM and selective use of LOCM in patients at high risk for contrast medium-related adverse events (eg, those with unstable angina, recent MI, severe valvular disease). Nonfatal adverse events were characterized as severe (MI and stroke); moderate (ischemic, hemodynamic, electrophysiologic, and symptomatic events, including ventricular fibrillation and moderate to severe angina); and minor (nausea, mild angina). Data sources included clinical trial results and review of a large registry of cardiac catheterization complications. Incremental cost per QALY gained was dramatically different, depending on the study perspective and subgroup assessed—$649 to $17,264 in high-risk and $35,509 to $47,874 in low-risk patients, depending on the perspective taken. The results showed that only selective use of LOCM—ie, in high-risk patients—would give a favorable CER. Similarly, Steinberg and colleagues examined this issue and determined that there would be a 3.5-fold increase in incremental cost of each moderate adverse event avoided if LOCM were given to all rather than just high-risk patients.81

Another example of a decision-analytic model that illustrates the need to consider temporal effects of the drug(s) and disease is the economic analysis carried out by Arnold and colleagues6 to evaluate the financial implications associated with using the direct thrombin inhibitor argatroban for early treatment (< 48 hours after thrombocytopenia onset), compared with delayed treatment (≥ 48 hours after thrombocytopenia onset), of immune-mediated HIT with or without thrombosis. The decision-analytic model (Figure 4-3) that was developed using Excel shows the strategies that were examined. The total per-patient cost included: hospital days, diagnostic tests, heparin, argatroban, major hemorrhagic events, and patient outcomes (ie, amputation, new thrombosis, stroke, or death), multiplied by the probability of each event. The ICER was calculated by dividing the incremental cost between patients with and without argatroban treatment by the incremental effectiveness or the cost per new thrombosis event avoided. The evaluation indicated that the mean cost per HIT patient without thrombosis decreased by 6.85% for patients who were treated earlier with argatroban therapy, representing a $2,605 saving per
A further example of a decision-analytic model is one that examined the comparative cost-effectiveness of urokinase and alteplase for the treatment of acute peripheral artery disease (PAD) since urokinase is generally associated with higher costs and higher treatment success than alteplase. Similar to the HIT model above, data were from published clinical trials and the analysis was done from the perspective of a health care institution. Cost data were obtained from the literature, the Physicians’ Fee Reference 2005, the Agency for Healthcare Research and Quality’s Healthcare Cost and Utilization Project (H-CUP) database, and the 2005 Red Book. The authors stated that H-CUP database charges were converted to costs using a cost:charge ratio of 0.55 based on a 2001 analysis conducted by the Centers for Medicare and Medicaid Services. The effectiveness (success) criterion was clot lysis with a subsequent 30-day survival post-treatment. Using alteplase as the baseline, the ICER for urokinase was $332,309 per additional treatment success. Sensitivity analysis revealed that the model was most sensitive to the cost of intervention (ranging from the least costly intervention [angioplasty] to the most costly [revascularization]).

There are also special types of decision-analytic models, such as Markov models, that can account for issues of time-sensitivity. That is, continuous risk and uncertain timing of events may depend on when events occur. For example, Eckman and colleagues employed a Markov model in atrial fibrillation to discern the comparative cost-utility (using QALY as the effectiveness parameter) of anticoagulation versus no anticoagulation. Patients go on to develop three potential types of events—thromboembolic events, major bleeding events, or death from age-, gender-, race- and comorbidity-related causes. Using results from five nonvalvular atrial fibrillation trials, aspirin was shown to be both more effective and less costly than “do not anticoagulate”; thus, aspirin was the dominant strategy (Table 4-1).

Reynolds and colleagues developed a Markov model to evaluate the comparative cost-effectiveness of radiofrequency catheter ablation (RFA) with or without antiarrhythmic drug therapy or drug therapy alone with an effectiveness outcome measure of QALYs. The ICER for RFA versus drug therapy was $51,431 per QALY. Thus, the authors concluded that RFA with/without drug therapy for symptomatic, drug-refractory paroxysmal atrial fibrillation appeared to be reasonably cost-effective in comparison with drug therapy alone. Model results were sensitive to time horizon, relative utility weights and to the cost of an ablation procedure.

Likewise, a Markov model was used to evaluate the benefits and costs of nine diagnostic strategies—transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), sequential approaches, selective imaging, and no imaging—to identify potential cardiovascular sources of emboli in patients who have had strokes. Values for event rates, anticoagulation effects, utilities, and costs were obtained from the literature and Medicare data. Once again, it was more cost-effective to selectively perform diagnostic procedures ($9,000 per QALY versus $13,000 per QALY for TEE in patients with and without previous cardiac history, respectively). Cost savings and decreased morbidity and mortality rates associated with reduction in preventable recurrent strokes substantially offset examination costs and risks of anticoagulation. Since the major advantage of a computerized decision-analytic model is the ability to alter values for key variables and reevaluate the options (ie, perform a sensitivity analysis) or to project long-term effectiveness when only short-term data are available, several “what-if” scenarios were undertaken. These sensitivity analyses demonstrated that the study results were moderately sensitive to efficacy of anticoagulation and incidence of
intracranial bleeding during anticoagulation and were mildly sensitive to prevalence of left atrial thrombus, rate of recurrent stroke in patients with thrombus, QOL after stroke, cost of TEE, and specificity of TEE. TTE, alone or in sequence with TEE, was not cost-effective compared with TEE.

There is an increasing likelihood that genomics will play a role in decisions about drug use. For example, a recent theoretical Markov model showed pharmacogenomic-guided dosing for anticoagulation with warfarin to be not cost-effective in patients with nonvalvular atrial fibrillation. Variations in hepatic microsomal enzyme activity primarily responsible for warfarin metabolism have shown serious or life-threatening bleeding events to be associated with slow metabolizers of warfarin. Therefore, Eckman and colleagues examined two strategies—standard versus genotype-guided induction of warfarin therapy—for a hypothetical 69-year-old male with nonvalvular atrial fibrillation at average risk for stroke (CHADS\textsubscript{2} score = 2) and without specific risk factors for bleeding (HEM-MORR_HAGES score = 0). The clinical data (rates of bleeding, stroke, severe or mild permanent illness, resolution, and death) used to inform the Markov model were a meta-analysis of three, randomized published studies; the Red Book for medication costs; and average Medicare reimbursement for Current Procedural Terminology or diagnosis-related group codes for procedures, office visits, and hospitalizations. Costs and effectiveness were discounted at 3% per year. Assumptions included:

- Pharmacogenetic-guided dosing only decreased the risk for major hemorrhage during the first month of warfarin induction
- A pharmacogenetic-based algorithm would have been used to titrate warfarin doses to a lower dose for slow metabolizers
- Patients receiving genotype-guided therapy would reach a therapeutic INR an average of 2.7 days earlier than those receiving standard anticoagulant therapy induction
- Genotyping would cause a 3-day delay in initiating warfarin therapy

They used a lifelong time horizon, which may have diluted out the early benefit of the pharmacogenetic-guided dosing hemorrhagic risk reduction during the first month of warfarin induction. In addition, the authors considered a societal perspective for the study, perhaps not appropriate in the United States as mentioned in the Perspective section above. In the base case, genotype-guided dosing cost $367 more and had a marginal cost-effectiveness ratio of $144,100 per QALY gained versus standard induction of warfarin therapy. If one considers $50,000 per QALY gained as the upper threshold for cost-effectiveness (an admittedly arbitrary but typically used number), genotype-guided dosing would not be considered cost-effective. These results, however, were quite sensitive to some of the modeling assumptions. For example, if genotype testing takes 1 rather than 3 days and is done in, rather than out, of hospital, the marginal CER of genotype-guided dosing was $51,000 per QALY. Other assumptions that influenced results included the efficacy of genotype-guided dosing and cost of genotyping (see “Robustness” below).

### Mathematical Spreadsheets

These models calculate the cost and cost-effectiveness of therapeutic strategies by multiplying the probability of an event by its cost. An example of this type of methodology is an Excel spreadsheet model developed by Arnold and colleagues to assess CHD events potentially avoided (CEPA) in patients at risk for CHD. In the base case, four HMG-CoA reductase inhibitors—lovastatin (L), pravastatin (P), simvastatin (S), and fluvastatin (F)—were evaluated. A multivariate regression equation used the following data to estimate the costs associated with CEPA: World Health Organization definition of CHD, Framingham Heart Study coefficients for CHD based on relative risk, National Cholesterol Education Program II Guidelines for initiation of treatment, National Health and Nutrition Examination Survey II for distribution of LDL cholesterol in the US population, HCFA’s MEDPAR CHD treatment costs, and Red Book (1994) for daily drug cost. Efficacy (LDL-cholesterol reduction), drug monitoring, and CHD treatment costs were analyzed. The average annual cost of CHD events per 1000 patients was $561,300 (F); $1,035,000 (P); $1,038,650 (S); and $1,108,000 (L) for the majority of patients. Compared to F, the marginal cost per CEPA was $473,700 (P); $477,350 (S); and $546,700 (L). To improve relevance to cost- and budget-conscious managed care clinicians, a matrix of the two population segments was developed to assess the drug budget impact.

Another example is an analysis performed by Najib and coauthors to examine costs associated with managing patients with CHF in an MCO. Computerized administrative, clinical chart, and claims data from seven individual health care plans affiliated with the MCO were obtained. Medical records and claims data for 275 subjects (128 carvedilol and 147 control) were evaluated. The carvedilol patients were initially identified through the pharmacy and medical claims databases. Patients in the case group were health plan members with a pharmacy benefit chosen for this study. They also met all of the following criteria: (1) at least one carvedilol prescription, (2) a valid diagnosis of CHF defined as a minimum of two claims with ICD-9-CM codes (428.x) at least 30 days apart between 5/1/1997 and 3/31/1999 in the outpatient setting, (3) aged 16 to 84 as of the date of their first claim.
with a CHF diagnosis, (4) continuous carvedilol treatment for at least 4 months (continuous treatment was defined by having a prescription gap less than 90 days), (5) at least one of the concomitant drugs (diuretic, ACE inhibitor, or digoxin) taken within the 10-month period starting at the carvedilol index prescription date (the evaluation period), and (6) the latest start with the carvedilol index prescription date occurring before April 1, 1998. Control patients were included in the study if they met criteria two and three and three listed above but were not receiving carvedilol or any other beta blocker. Case patients were matched in approximately a one-to-one ratio with noncarvedilol (control) patients.

Using the claims data, the facility, professional services, and medication costs to the health plan during the 10 months following the index date for each patient were calculated. Charges submitted by providers to the health plan for their services were used to evaluate the costs associated with health care utilization. Costs were further divided into two groups: those for services with a corresponding CHF ICD-9-CM code plus carvedilol (carvedilol-related costs), and those services with a CHF ICD-9-CM code with no beta-blocker medication (non-carvedilol-related costs). All costs were adjusted to 1999 dollars using the medical care component of the Consumer Price Index. In addition to costs, the rates of facility and professional service utilization were calculated.

Even though no statistically significant differences were detected between treatment groups in terms of facility expenditures, the overall facility expenditures were lower for patients in the carvedilol group than for patients in the control group (Table 4-5). The difference detected was approximately $9,000 in favor of carvedilol. This is consistent with the findings from the 1996 clinical trial conducted by Packer et al,\textsuperscript{107} which showed carvedilol to have a significant influence on reducing hospitalization-related expenditures. Indeed, in the current study, the mean cost of inpatient stay was approximately $6,500 greater in the control group than in the carvedilol group. The economic evaluation performed on the 6-month data from the clinical trial showed a difference of approximately $9,400 in favor of carvedilol,\textsuperscript{108} which is also consistent with findings from the current study.

In another study, Murdock and colleagues\textsuperscript{109} compared the clinical effectiveness and cost to convert recent-onset atrial fibrillation or flutter to sinus rhythm with intravenous ibutilide after 3 to 4 weeks of anticoagulation with direct-current cardioversion. Physician cost consisted of the summation of Medicare charges (CPT codes) submitted by cardiology and anesthesiology departments; hospital costs were obtained from charge data adjusted by cost-to-charge ratios appropriate for each cost center at the authors' hospital; and average wholesale price was used as a proxy for pharmaceutical costs. The low success rate with ibutilide made direct-current cardioversion the more cost-effective method to restore sinus rhythm. As noted by the authors, this is in contrast to a study by Zarkin and colleagues,\textsuperscript{110} where ibutilide was shown to be more cost-effective as first-line therapy followed by direct-current cardioversion for patients who failed to convert versus proceeding directly to direct-current cardioversion. This discrepancy may have resulted from a number of confounding factors: Zarkin used published literature efficacy rates (and primarily for arrhythmia of recent onset) and assumed resource utilization and a lower cost for ibutilide, while Murdock et al used actual efficacy rates in their hospital (although with an admittedly small sample size of 30) and included patients with arrhythmia of duration up to 90 days (although mean duration of arrhythmia in each group was not noted); a preponderance of atrial fibrillation (versus atrial flutter) patients (both groups would be expected to reduce the efficacy of ibutilide); and average wholesale price (which is typically quite a bit greater than the price negotiated by institutions).

**Data Source(s)**

**Prospective**

The randomized, prospective, clinical trial may be a good source of clinical data; however, one must take care not to include costs of resource use required by protocols (so-called protocol-driven resource use), as these are artificially derived and may not be experienced in routine clinical care.\textsuperscript{72,98} Perhaps a more reliable way to examine health care resource utilization is the prospective, observational, economic trial, in which patients are randomized to technologies to be evaluated, and data on resource use are collected. However, this procedure may be lengthy and expensive. Moreover, there is no guarantee of external validity—that is, the ability to transfer resource use from one country or situation to another.\textsuperscript{111} Califf and Eisenstein\textsuperscript{29} attempted to account for this potential of nongeneralizability by prospectively enrolling typical patients undergoing percutaneous intervention in examining the cost-effectiveness of abciximab versus placebo (EPIC trial),\textsuperscript{85,86} then versus a lower dose of heparin (EPILOG trial),\textsuperscript{112} and then versus or in combination with stenting (EPISTENT trial).\textsuperscript{113} Although these researchers demonstrated very favorable CERs of $6,213 per YLS for stents plus abciximab in comparison with stenting alone and $5,291 per YLS compared with abciximab alone, the use of glycoprotein IIb/IIIa agents in patients undergoing percutaneous intervention remained at approximately 50% for these procedures.

Ligthart and coworkers\textsuperscript{114} conducted a systematic review of 19 CEAs comparing drug-eluting and bare-metal stents to identify external factors involved in the study.
outcome. They found that the study's quality, funding source, and country of origin affected recommendations from the study. That is, lower study quality, sponsored studies, and studies from the United States tended to support more widespread use of drug-eluting stents.

Another method of using prospective or clinical trial data to project future events was undertaken by Caro and colleagues to estimate the cost-effectiveness of primary prevention with pravastatin compared to diet alone.\textsuperscript{115} Using a generalized model of cardiovascular disease prevention, these researchers quantified the effect in terms of the avoidance of cardiovascular disease based on treatment-specific risks derived from West of Scotland Coronary Prevention Study data. Country-specific costs were accounted for by expressing these in terms of the ratio of monthly treatment to that of managing an MI. Over multiple sensitivity analyses, CERs were consistently below $25,000 per life-year gained.

<table>
<thead>
<tr>
<th>TYPE OF SERVICE FACILITY</th>
<th>Total (n = 211) Mean (SD) [Median]</th>
<th>Cases (n = 105) Mean (SD) [Median]</th>
<th>Controls (n = 106) Mean (SD) [Median]</th>
<th>P value\textsuperscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>$12,426 ($34,075) [$0]</td>
<td>$9,157 ($22,585) [$0]</td>
<td>$15,664 ($42,376) [$0]</td>
<td>.165</td>
</tr>
<tr>
<td>Outpatient Hospital</td>
<td>$3,225 ($11,323) [$339]</td>
<td>$2,186 ($5,411) [$151]</td>
<td>$4,254 ($15,009) [$464]</td>
<td>.185</td>
</tr>
<tr>
<td>Emergency Room</td>
<td>$338 ($868) [$0]</td>
<td>$368 ($873) [$0]</td>
<td>$309 ($780) [$0]</td>
<td>.605</td>
</tr>
<tr>
<td>Total Facility Expenses</td>
<td>$16,454 ($40,829) [$2,880]</td>
<td>$11,987 ($25,620) [$1,410]</td>
<td></td>
<td>.113</td>
</tr>
<tr>
<td>PROFESSIONAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiologist</td>
<td>$1,735 ($2,347) [$903]</td>
<td>$1,886 ($2,456) [$930]</td>
<td>$1,585 ($2,236) [$864]</td>
<td>c353</td>
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<tr>
<td>Internist</td>
<td>$436 ($1,181) [$0]</td>
<td>$445 ($1,502) [$0]</td>
<td>$428 ($745) [$116]</td>
<td>0.914</td>
</tr>
<tr>
<td>Family Practitioner</td>
<td>$333 ($751) [$39]</td>
<td>$287 ($733) [$0]</td>
<td>$399 ($769) [$136]</td>
<td>.281</td>
</tr>
<tr>
<td>Other Medical Specialty</td>
<td>$2,812 ($4,814) [$756]</td>
<td>$2,444 ($4,690) [$510]</td>
<td>$3,176 ($4,929) [$936]</td>
<td>.270</td>
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<tr>
<td>Total Professional Service Expenses</td>
<td>$6,831 ($8,981) [$3,616]</td>
<td>$6,559 ($9,050) [$3,509]</td>
<td>$7,101 ($8,947) [$3,696]</td>
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<tr>
<td>MEDICATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>$508 ($594) [$0]</td>
<td>$1,020 ($428) [$1,009]</td>
<td>$0 ($0) [$0]</td>
<td>.0001</td>
</tr>
<tr>
<td>Angiotensin-converting Enzyme Inhibitors</td>
<td>$361 ($359) [$310]</td>
<td>$449 ($403) [$364]</td>
<td>$273 ($284) [$239]</td>
<td>.0003</td>
</tr>
<tr>
<td>Diuretics</td>
<td>$89 ($207) [$25]</td>
<td>$119 ($264) [$28]</td>
<td>$59 ($121) [$22]</td>
<td>.0347</td>
</tr>
<tr>
<td>Digoxin</td>
<td>$29 ($26) [$27]</td>
<td>$33 ($26) [$35]</td>
<td>$2,116 ($2,609) [$1,313]</td>
<td>.8351</td>
</tr>
<tr>
<td>Other Medications</td>
<td>$2,149 ($2,291) [$1,589]</td>
<td>$2,182 ($1,929) [$1,876]</td>
<td>$2,116 ($2,609) [$1,313]</td>
<td>.8351</td>
</tr>
<tr>
<td>Total Medication Expenses</td>
<td>$3,135 ($2,552) [$2,593]</td>
<td>$3,804 ($2,200) [$3,329]</td>
<td>$2,472 ($2,709) [$1,740]</td>
<td>.0001</td>
</tr>
</tbody>
</table>
with patients at higher baseline risk being the most cost-effective to treat.

Retrospective

A number of pharmacoeconomic researchers advocate retrospective analyses and modeling as alternatives to prospective trials. Sources for retrospective studies include patient charts, individual or meta-analyses of clinical trials in the literature, medical and pharmacy claims data, and Medicare databases, among others. Claims or administrative databases have, in particular, recently gained favor as they are frequently computerized and reflect actual charges and payments for specific plans and populations. The disadvantages of these databases are as follows:

- Diagnosis and procedure codes reflecting reimbursement strategies instead of clinically accurate diagnoses
- Limited information on important covariates
- Sparse outcomes data
- Lack of representativeness
- Lack of structure for research purposes

Indeed, in two comparisons of clinical and insurance claims databases in patients with ischemic heart disease, claims data failed to identify more than one half of patients with prognostically important conditions, including mitral insufficiency, CHF, peripheral vascular disease, old MI, hyperlipidemia, angina, and unstable angina. Similar inconsistencies were noted in a study of coronary artery bypass surgery in which miscoding of diagnoses could be linked with the lack of specificity for an ICD-9-CM grouping and lack of reporting of coexisting conditions on discharge abstracts and claims. Given the current state of these types of analyses, collection of original data for a representative percentage (typically 10%) of the patient population should be undertaken to validate the clinical information contained therein.

Expert Opinion

Expert opinion is a source, frequently elicited by survey, used to obtain information where no or little data are available. For example, in our experience with a multicountry evaluation of health care resource utilization in atrial fibrillation, very little country-specific published information was available on this subject. Thus, the decision-analytic model is being supplemented with data from a physician expert panel survey to determine the following:

- Initial management approach: rate control versus cardioversion
- First-, second-, and third-line agents
- Doses and durations of therapy
- Type and frequency of studies that would be performed to initiate and monitor therapy
- Type and frequency of adverse events by body system and the resources used to manage them
- Place of treatment
- Adverse consequences of lack of atrial fibrillation control and cost of these consequences, eg, stroke, CHF

This method may also be used in testing the robustness of the analysis.

Ultimate Use

Economic evaluations are used in a variety of settings; they serve, among other things, as decision aids and for assisting in reimbursement strategies for national formularies. In fact, Australia and Canada have implemented guidelines for economic technology assessment. Although these and other countries do not yet require HE studies for drug registration, many countries in the European Union, and recently, Korea and China, strongly suggest that these be undertaken. They are useful for policy makers who are concerned with health care resource allocation on a statewide or individual institutional level. End users may include insurance companies, pharmaceutical manufacturers (who are interested in demonstrating the comparative cost-effectiveness of their agents to gold standards and/or to the most commonly used therapeutic options), government agencies (for establishing levels of reimbursement), MCO executives (to aid in establishing therapeutic guidelines), employers (who use these analyses as an aid in benchmarking the MCOs they are evaluating for their employees' health plans), and pharmacy benefits managers (who also wish to demonstrate that they have evaluated managed care plans to offer the most cost-effective one to employers). Similarly, individual clinicians are becoming increasingly interested in documenting that they have systematically identified the most cost-effective therapeutic options for their patients.

Application to Patient Subgroups (Targeting)

Age, Gender, and Pretreatment Lipid Levels

Some therapies are cost-effective only in certain patient subgroups, and a number of patient-specific factors may influence economic outcomes. This observation may be illustrated by CEAs of the drug treatment of hypercholesterolemia. In general, these analyses have shown that the cost to produce health benefits of increased longevity and improved QOL are lowest in groups with the highest near-term risk for CHD.
to investigate the cost-effectiveness of lipid-lowering therapy in the primary prevention of CHD, Oster and Epstein examined the effects of cholestyramine therapy on men between 35 and 74 years of age with elevated levels of total plasma cholesterol.67 The researchers found a wide range of values of cost-effectiveness of treatment, ranging from $36,000 to over $1 million per YLS. Cost-effectiveness was greatest for younger patients, for those with additional coronary risk factors such as smoking or hypertension, and for those whose course of treatment was of less-than-lifelong duration. These therapies were less cost-effective in older patients, for those with no additional coronary risk factors, and for patients who were treated for a lifetime. The investigators concluded that pharmacologic therapy may not be cost-effective for all patients with elevated cholesterol levels, especially those over 65 years of age.

To determine the cost-effectiveness of HMG-CoA reductase inhibitors for the primary and secondary prevention of CHD, Goldman et al conducted an analysis based on the Coronary Heart Disease Policy Model.63 This computer-simulation model estimates the risk factor–specific annual incidence of CHD and the risk of recurrent coronary events in persons with prevalent CHD. Primary prevention with HMG-CoA reductase inhibitors had favorable CERs only in selected subgroups based on cholesterol levels and other established risk factors. When used for secondary prevention, 20 mg of lovastatin was estimated to save lives and save costs in younger men with cholesterol levels above 250 mg/dL and to have a favorable CER regardless of the cholesterol level. The only exception cited was in younger women with cholesterol levels below 250 mg/dL. Lovastatin doses of 40 mg daily had a favorable incremental CER in men with cholesterol levels above 250 mg/dL.

Similarly, Grover and colleagues124 performed simulations using the Cardiovascular Life Expectancy Model to estimate the long-term costs and benefits of treatment with simvastatin in diabetics with varying pretreatment LDL cholesterol values. Treatment with simvastatin for patients with cardiovascular disease was found to be cost-effective for both men and women with or without diabetes mellitus. Among diabetic individuals without cardiovascular disease, the benefits of primary prevention were also substantial and the CERs attractive across a wide range of assumptions (approximately $4,000 to $40,000 per YLS). In the absence of diabetes mellitus, CERs associated with primary prevention were substantially higher, ranging from $28,000 to $51,000 per YLS for men and $16,000 to $65,000 per YLS for women. The presence of diabetes mellitus was found to substantially increase the absolute risk of cardiovascular events and thereby to lower the cost-effectiveness of treating even modest levels of hyperlipidemia. These conclusions were robust even among diabetics with lower baseline LDL values and smaller LDL reductions.

Likewise, Weinstein and Stason125 used the regression coefficients from the Framingham Study to calculate the expected changes in the numbers of strokes and MIs resulting from treatment. The benefit of this treatment was found to vary by patient age and duration of therapy, being less for MI than for stroke and ranging from about 40% in younger subjects to around 10% in 60-year-olds. Gender was also an important influence, such that, as in the previously described study, cost-effectiveness improved as women aged but declined as men aged (Table 4-6).125 This may reflect the propensity for women to develop cardiovascular disease later in life and the improved expected therapeutic effectiveness as a result. Low (good) CERs were also found in the Swedish Trial in Old Patients with Hypertension study of men and women aged 70 and above, especially with beta blockers and diuretics.126 In general, it appears cost-effective to treat patients 45 years of age and older with a diastolic blood pressure $≥90 mm Hg.127 The presence of other risk factors improves the cost-effectiveness of treatment, since these would be sicker patients, more likely to manifest hypertensive end-organ disease.

In contrast to Edelson,62 Kawachi and Malcolm128 reported a range of the cost-effectiveness of antihypertensive therapy from £11,058 to £63,760 per QALY gained in men and from £22,060 to £194,989 per QALY gained in women (costs and benefit discounted at 5%). Diuretic therapy produced the best (lowest) CERs, using as an example a 60-year-old woman with a diastolic pressure of 90 mmHg (£17,980 per QALY). For this woman, the cost per QALY was £67,678 on beta-blocker therapy and £111,230 per QALY on ACE inhibitors.

Pre-Treatment Blood Pressure

In addition to age and duration of therapy, the benefit (eg, primary prevention of MI, prevention of CHD, QALYs, YLS) and cost-effectiveness of antihypertensive treatments vary according to pretreatment blood pressure.129,130 These and other influences on the cost-effectiveness of antihypertensive treatment are summarized in Table 4-7. For example, evaluating data from the Hypertension Optimal Treatment trial, researchers noted that the CERs, expressed as cost per year of life gained, were most favorable for the ≤90 mm Hg treatment target group ($4262) and for added aspirin treatment ($12,710). For moderately aggressive treatment (blood pressure ≤85 mm Hg), the CER escalated incrementally to $86,360 and with intensive treatment to $658,370 per year of life gained. Thus, treatment to a target of 90 mm Hg and co-administration of aspirin were considered highly cost-effective, whereas treatments to lower the blood pressure
further to 85 mm Hg were marginally cost-effective; intensive blood pressure lowering down to 80 mm Hg was not cost-effective.129

Comorbid Conditions

However, in patients with comorbid conditions that may accelerate the development of hypertensive sequelae, such as in those with type 2 diabetes mellitus, tight control of blood pressure has been shown to substantially reduce the cost of complications, increase the interval without complications and survival, and have a CER that compares favorably with many accepted health care programs. Indeed, the incremental cost per extra year free from diabetes mellitus-related endpoints amounted to £1,049 (costs and effects discounted at 6% per year) for patients randomized to tight control of blood pressure (n = 758) and £434 for patients in the less tight control group (n = 390) (costs discounted at 6% per year and effects not discounted). The incremental cost per life years gained was £720 (costs and effects discounted at 6% per year) and £291 (costs discounted at 6% per year and effects not discounted) for the two groups, respectively.131

These studies have demonstrated that HE analyses can aid decision making in the prevention of hypertensive complications. Indeed, HE analyses can clarify the value of alternative strategies for CHD prevention in specific populations, thereby helping to choose among them, given limited health care resources. Modification of major cardiovascular risk factors (blood cholesterol, high blood pressure, and smoking) is very cost-effective but needs to be better targeted if potential health gain is to be realized.133 For example, the most CERs in the treatment of hypertension are typically found in men of late middle age with the most severe hypertension and in those with multiple risk factors.125,128,134-137 Population screening, stratified according to these cost-effectiveness criteria, can help identify patients in whom aggressive intervention via these disease management techniques is most desirable and in whom the best value is derived from treatment of hypertension. The utility of pharmaecoconomics in assisting in these decisions depends to a great extent upon the assumptions made and the quality of the data used for the analyses (eg, the degree to which the data are evidence based).134

Robustness

In all analyses, there is uncertainty about the accuracy of the results that may be dealt with via sensitivity analyses.120 In these analyses, one essentially asks the question “What if”? These allow one to vary key values over clinically feasible ranges to determine whether the decision remains the same—that is, if the strategy initially found to be cost-effective remains the dominant strategy. Sensitivity analyses also allow one to determine threshold values for the key parameters at which the decision would change. For example, amiodarone was found to be a preferred strategy over implantable cardioverter-defibrillators when QOL (utility) on amiodarone decreased to 40% lower than that with an implantable cardioverter-defibrillator.116 By performing sensitivity analyses, one can increase the level of confidence in the conclusions. Indeed, varying the effectiveness of a new therapy in reducing death, nonfatal MI, and revascularization (assuming all components contributed equally to the reduction in death) from 0.25 to 7.0% demonstrated a broad range of very cost-effective results (Figure 4-4).132

Table 4-6. Effect of Age and Gender on CEA (cost/QALY*)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Initial Diastolic Blood Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>20</td>
<td>$5,500</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>$8,700</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>$50,100</td>
</tr>
<tr>
<td>Female</td>
<td>100</td>
<td>$14,700</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>$8,500</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>$3,300</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>$5,700</td>
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<td>60</td>
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<tr>
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<td>$8,500</td>
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<tr>
<td></td>
<td>110</td>
<td>$14,700</td>
</tr>
</tbody>
</table>

*Quality-adjusted life-year; CEA = cost-effective analysis.

Table 4-7. Influences on Cost-Effectiveness of Cardiovascular Treatment

- Patient age
- Comorbidities
- Duration of therapy
- Pretreatment goal (eg, blood pressure)
- Benefit sought (eg, YLS, CHD event prevention, QALYs)
- Medication adherence

CHD = coronary heart disease; QALYs = quality-adjusted life-years; YLS = years of life saved.
Probabilistic Sensitivity Analysis may be employed in addition to deterministic (standard) sensitivity analysis because probabilistic sensitivity analyses:
1. Characterize uncertainty in input parameters, defining inputs as a probability distribution, rather than best-estimate-plus range.
2. Propagate the uncertainty through the model using Monte Carlo simulations or micro simulation models.
3. Present the implications of parameter uncertainty in an appropriate format for the results, e.g., confidence intervals around an incremental ratio or a cost-effectiveness acceptability curve (CEAC).

As discussed by Eckman and colleagues, the CEAC demonstrated (Figure 4-5) that genotype-guided dosing had a 10% chance of costing less than $50,000 per QALY and a 30% chance of costing less than $100,000 per QALY, the latter sometimes indicated as being an upper-ranging figure for cost-effectiveness.

**Conclusion**

HE analyses of cardiovascular therapies is a timely topic, especially in light of the fact that a number of governmental regulatory agencies are attempting to set reimbursement guidelines based upon these data. At this time, numerous studies have been completed for a variety of therapeutic options. However, there are no standardized guidelines for these studies; inclusion of resource use (e.g., direct, indirect), effectiveness criteria (e.g., CHD event avoided, QALYs), centralized cost sources, perspective, and incorporation of sensitivity analyses into the evaluation are quite variable. This underlies clinicians’ concerns about premature efforts by regulatory agencies to dictate therapeutic options based upon an incomplete understanding of the true costs to payers and society and the benefits to the patient. Moreover, in addition to the societal and governmental perspectives regarding these analyses, there is inadequate information for the individual clinician attempting to treat an individual patient in terms of cost, general estimates of life expectancy, and overall likelihood of success of one particular treatment regimen versus another.

Furthermore, as newer and potentially more expensive therapies become readily available, decisions based on state-of-the-art analyses will be required to determine their place in therapy. Indeed, Eisenstein and colleagues developed a decision model to evaluate the potential “economic attractiveness” of new therapies in patients with non-ST elevation acute coronary syndrome. Event probabilities at 30 days and 6 months were estimated from US patients in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndrome IIb trial, and cost estimates were derived from patients enrolled in the Economics and Quality of Life substudy of this trial. Study results found that new therapies costing up to $2,000 per episode that reduce 6-month mortality by 0.5%, death and nonfatal MI by 1%, or a composite endpoint of death, nonfatal MI, and revascularization by 3% may be cost-effective by current

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**Figure 4-4.** Cost-effectiveness of new therapies that reduce death, myocardial infarction (MI), and revascularization. YOLS = years of life saved; * indicates that the therapy becomes dominant.


**Figure 4-5.** The figure shows the Cost-Effectiveness Acceptability Curve (CEAC) reported by Eckman and colleagues that demonstrates, through a willingness-to-pay (WTP) scenario, the probability that pharmacogenetic-guided testing is cost-effective in comparison with standard testing for warfarin dosing.
standards. New therapies costing up to $1,000 per episode reduce the absolute rate of death, nonfatal MI, and revascularization at 6 months by 6.5% or more and may be cost saving.

Especially since the psychological component of many of these therapies—such as pacing, surgery, and implantable devices—has not yet been sufficiently addressed, any future prospective observational studies should probably incorporate QOL assessments. Such assessments of patients’ desires, anticipated QOL with a variety of interventions, and evaluators’ perceptions about the representative nature of the study population from which the original cost estimates were derived will hopefully allow modulation of these and future HE analyses. It is likely that these decisions will become increasingly common as health care reforms—such as capitation, initiated by organized health care delivery systems—become more evident.36,52,138

Although HE analyses will have an increasingly important role in resource allocation and even in individual health care decisions, there are some limitations to these assessments.139 As mentioned throughout this chapter, although decision-analytic technique is an objective and well-established methodology, many other questions persist regarding basic issues such as uncertainty about costs and benefits, attribution of resources (eg, if an adverse event requires a therapeutic switch, should future costs be attributed to the initial agent or to the switch agent), perspective, appropriateness of retrospective (eg, claims) databases, appropriate time horizon and projection to clinically relevant time frames, QOL utility measurements (eg, health states worse than death), and discount rate (eg, if same for benefits as for costs, which value should be used), among others.

Despite these limitations, sensitivity analyses and ongoing updated evaluations will allow health care policy analysts to make the most informed decisions about the allocation of limited monetary resources to best treat the population with cardiovascular illnesses.122 Podrid and colleagues140 (adapted from Wong141) and Kupersmith and coworkers29-31 have published tables of comparative values or dollar cost (US$) per year or per QALY for cardiovascular therapies. More recently, Neumann142 developed the US federally-funded Tufts Medical Center Cost-Effectiveness (CEA) Registry to investigate the use of perspective and costing methodology in published CUA. The CEA Registry contains over 3000 cost-utility ratios and utility weights for roughly 4000 health states from 1164 published CUA through 2005. The Registry also provides an online-based searchable database (available at: www.cearegistry.org). These types of analyses may be of use in performing comparative evaluations of available therapeutic options. HE analysis will also help guide the individual physician in making cost-effective decisions for individual patients. Moreover, these decisions will be guided by political forces and health care system requirements.

Note: References for this chapter can be found here: www.cvptct3.com
Part 2

Drug Classes
Catecholamines are neurohumoral substances that mediate a variety of physiologic and metabolic activities in humans. The effects of the catecholamines ultimately depend on their chemical interactions with receptors, which are discrete macromolecular structures located on the plasma membrane. Differences in the ability of the various catecholamines to stimulate a number of physiologic processes were the criteria used by Ahlquist in 1948 to separate these receptors into 2 distinct types: alpha and beta-adrenergic. Subsequent studies have revealed that beta-adrenergic receptors exist as 3 discrete subtypes called beta₁, beta₂, and beta₃ (Table 5-1). It is now appreciated that there are 2 subtypes of alpha receptors, designated alpha₁ and alpha₂ (Table 5-1). At least 3 subtypes of both alpha₁- and alpha₂-adrenergic receptors are known, but distinctions in their mechanisms of action and tissue location have not been well defined.

This chapter examines the adrenergic receptors and the drugs that can inhibit their function. The rationale for use and clinical experience with alpha- and beta-adrenergic blocking drugs in the treatment of various cardiovascular disorders are also discussed.

Adrenergic Receptors: Hormonal and Drug Receptors

The effects of an endogenous hormone or exogenous drug depend ultimately on physiochemical interactions with macromolecular structures of cells called receptors. Agonists interact with a receptor and elicit a response; antagonists interact with receptors and prevent the action of agonists.

In the case of catecholamine action, the circulating hormone or drug (“first messenger”) interacts with its specific receptor on the external surface of the target cells. The drug hormone-receptor complex, mediated by a G protein called Gs, activates the enzyme adenyl cyclase on the internal surface of the plasma membrane of the target cell, which accelerates the intracellular formation of cyclic adenosine monophosphate (cAMP). cAMP-dependent protein kinase (“second messenger”) then stimulates or inhibits various metabolic or physiologic processes. Catecholamine-induced increases in intracellular cAMP are usually associated with stimulation of beta-adrenergic receptors, whereas the stimulation of alpha-adrenergic receptors is mediated by a G protein known as Gi and is associated with lower concentrations of cAMP and possibly increased amounts of guanosine-3’5’-monophosphate in the cell. These changes may result in the production of opposite physiologic effects from those of catecholamines, depending on which adrenergic receptor system is activated.

Until recently, most research on receptor action bypassed the initial binding step and the intermediate steps and examined either the accumulation of cAMP or the end step, the physiologic effect. Currently, radioactive agonists or antagonists (radioligands) that attach to and label the receptors have been used to study binding and hormone action. The cloning of adrenergic receptors has also revealed important clues about receptor function.

Alpha-Adrenergic Blockers

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When an adrenergic nerve is stimulated, catecholamines are released from their storage granules in the adrenergic neuron, enter the synaptic cleft, and bind to alpha receptors on the effector cell. A feedback loop exists that regulates the amount of neurotransmitter that is released; accumulation of catecholamines in the synaptic cleft leads
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Physiology</th>
<th>Pharmacology</th>
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<tbody>
<tr>
<td></td>
<td>Tissue</td>
<td>Response</td>
</tr>
<tr>
<td>α₁</td>
<td>Smooth muscle: vascular, iris radial ureter, pilomotor, uterus, sphincters (gut, bladder)</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
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<td>Heart</td>
<td>Positive inotropic (β₁ &gt; α₁), cell growth, hypertrophy</td>
</tr>
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<td></td>
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<td>Secretion</td>
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<tr>
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<td>Adipose tissue</td>
<td>Glycogenolysis</td>
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<tr>
<td></td>
<td>Sweat glands</td>
<td>Secretion</td>
</tr>
<tr>
<td></td>
<td>Kidney (proximal tubule)</td>
<td>Gluconeogenesis, Na+ reabsorption</td>
</tr>
<tr>
<td>α₂</td>
<td>Presynaptic autoreceptor on sympathetic nerve endings</td>
<td>Inhibition of norepinephrine release</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Aggregation, granule release</td>
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<tr>
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<td>Endocrine pancreas</td>
<td>Inhibition of insulin release</td>
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<td>Adipose tissue</td>
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<td></td>
<td>Vascular smooth tissue</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>Inhibition of renin release (?)</td>
</tr>
<tr>
<td>β₁</td>
<td>Heart</td>
<td>Positive inotropic effect, positive chronotropic effect, cell growth, hypertrophy</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>Kidney</td>
<td>Renin release</td>
</tr>
<tr>
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<td>Smooth muscle: bronchi, uterus, gut, vascular (skeletal muscle), detrusor</td>
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<tr>
<td></td>
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<td>Glycogenolysis; Gluconeogenesis</td>
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<td>Skeletal muscle</td>
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<td>Endocrine pancreas</td>
<td>Insulin secretion (?)</td>
</tr>
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<td></td>
<td>Salivary gland</td>
<td>Amylase secretion</td>
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<tr>
<td>β₃⁺</td>
<td>Adipose tissue</td>
<td>Lipolysis</td>
</tr>
<tr>
<td></td>
<td>Striated muscle</td>
<td>Thermogenesis</td>
</tr>
</tbody>
</table>

? = possible action.

to stimulation of alpha receptors in the neuronal surface and inhibition of further catecholamine release. Catecholamines from the systemic circulation can also enter the synaptic cleft and bind to presynaptic or postsynaptic receptors.

Initially, it was believed that alpha1 receptors were limited to postsynaptic sites, where they mediated vasoconstriction, whereas the alpha2 receptors existed only at the prejunctional nerve terminals and mediated the negative feedback control of norepinephrine release. The availability of compounds with high specificity for either alpha1 or alpha2 receptors demonstrated that while presynaptic alpha receptors are almost exclusively of the alpha2 subtype, the postsynaptic receptors are made up of comparable numbers of alpha1 and alpha2 receptors. Stimulation of the postsynaptic alpha2 receptors causes vasoconstriction. A functional difference does, however, exist between the 2 types of postsynaptic receptors. The alpha receptors appear to exist primarily within the region of the synapse and respond preferentially to neuronally released catecholamine, whereas alpha2 receptors are located extrasynaptically and respond preferentially to circulating catecholamines in the plasma.

Drugs having alpha-adrenergic blocking properties are of several types (Figure 5-1). Nonselective alpha blockers having prominent effects on both the alpha1 and alpha2 receptors (eg, the older drugs such as phenoxybenzamine and phentolamine). Although virtually all of the clinical effects of phenoxybenzamine are explicable in terms of alpha blockade, this is not the case with phentolamine, which also possesses several other properties, including a direct vasodilator action and sympathomimetic and parasympathomimetic effects.

Selective alpha1 blockers having little affinity for alpha2 receptors (eg, prazosin, terazosin, doxazosin, and other quinazoline derivatives). It is now clear that these drugs, originally introduced as direct-acting vasodilators, exert their major effect by reversible blockade of postsynaptic alpha1 receptors. Other selective alpha blockers include indoramin, trimazosin, and urapadil (see also Table 5-2). Urapadil is of interest because of its other actions, which include stimulation of presynaptic alpha2-adrenergic receptors and a central effect.

Selective alpha2 blockers (eg, yohimbine). The primary use of these drugs has been as tools in experimental pharmacology. Yohimbine is now marketed in the United States as an oral sympatholytic and mydriatic agent. Male patients with impotence of vascular, diabetic, or psychogenic origin have been treated successfully with yohimbine.

Blockers that inhibit both alpha- and beta-adrenergic receptors (eg, carvedilol, labetalol). Carvedilol and labetalol are selective alpha blockers. Since these agents are much more potent as beta blockers than alpha blockers, they are discussed in greater detail in the section on beta blockers.

Agents having alpha-adrenergic blocking properties but whose major clinical use appears unrelated to these properties (eg, chlorpromazine, haloperidol, quinidine, bromocriptine, amiodarone and ketanserin, a selective blocking agent of serotonin1 receptors). It has been demonstrated that verapamil, a calcium-channel blocker, also has alpha-adrenergic blocking properties. Whether this is a particular property of verapamil and its analogues or is common to all calcium-channel blockers is not clear. Also to be clarified is whether verapamil-induced alpha blockade occurs at physiologic plasma levels and helps to mediate the vasodilator properties of the drug.

All the alpha blockers in clinical use inhibit the postsynaptic alpha1 receptor and result in relaxation of vascular smooth muscle and vasodilation. However, the nonselective alpha blockers also antagonize the presynaptic alpha2 receptors, allowing for increased release of neuronal norepinephrine. This results in attenuation of the desired postsynaptic blockade and spillover stimulation of the beta receptors and, consequently, produces adverse effects such as tachycardia, tremulousness, and increased renin release. The alpha1-selective agents that preserve the alpha2-mediated presynaptic feedback loop prevent excessive norepinephrine release and thus avoid these adverse cardiac and systemic effects.

Because of these potent peripheral vasodilatory properties, one would anticipate, however, that even the selective alpha blockers would induce reflex stimulation of the sympathetic and renin-angiotensin system similar to that seen with other vasodilators such as hydralazine and minoxidil. The explanation for the relative lack of tachycardia and renin release observed after prazosin, terazosin,
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and doxazosin may in part be due to the drugs’ combined action of reducing vascular tone in both resistance (arteries) and capacitance (veins) beds. Such a dual action may prevent the marked increases in venous return and cardiac output observed with agents that act more selectively to reduce vascular tone only in the resistance vessels. The lack of tachycardia with prazosin, terazosin, and doxazosin use has also been attributed by some investigators to a significant negative chronotropic action of the drugs independent of their peripheral vascular effects.15

Use in Cardiovascular Disorders

Hypertension

Increased peripheral vascular resistance is present in the majority of patients with long-standing hypertension. Since dilation of constricted arterioles should result in lowering of elevated blood pressure, interest has focused on the use of alpha-adrenergic blockers in the medical treatment of systemic hypertension. Except for pheochromocytoma, the experience with nonselective alpha blockers in the treatment of hypertension was disappointing because of accompanying reflex stimulation of the sympathetic and renin-angiotensin system, resulting in frequent side effects and limited long-term antihypertensive efficacy. However, the selective alpha, blockers prazosin, doxazosin, and terazosin have been shown to be effective antihypertensive agents.12,13

Prazosin, doxazosin, and terazosin decrease blood pressure in both the standing and supine positions, although blood pressure decrements tend to be somewhat greater in the upright position. Because their antihypertensive effect is accompanied by little or no increase in heart rate, plasma renin activity, or circulating catecholamines, prazosin, doxazosin, and terazosin have been found to be useful as first-step agents in hypertension. Monotherapy with these agents, however, promotes sodium and water retention in some patients, although it is less pronounced than with other vasodilators. The concomitant use of a diuretic prevents fluid retention and in many cases markedly enhances the antihypertensive effect of the drugs. In clinical practice, prazosin, doxazosin, and terazosin have their widest application as adjuncts to one or more established antihypertensive drugs in treating moderate to severe hypertension. Their effects are additive to those of diuretics, beta blockers, alpha methyl-dopa, and the direct-acting vasodilators. The drugs cause little change in glomerular filtration rate or renal plasma flow and can be used safely in patients with severe renal hypertension. There is no evidence for attenuation of the antihypertensive effect of prazosin, doxazosin, or terazosin during chronic therapy.

In large comparative clinical trials, the efficacy and safety of alpha1 blockers have been well documented. In the TOMHS (Treatment of Mild Hypertension Study), 2 mg/day of doxazosin given over 4 years reduced blood pressure as much as agents from other drug classes.16 In a large Veterans Administration Study where patients with severe hypertension were studied, prazosin 20 mg daily given over one year had a treatment effect that was significantly greater than placebo.17 Doxazosin 2 mg to 8 mg daily was one of the drugs used in the ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial), which was designed to compare various antihypertensive agents and their effect on coronary morbidity and mortality in high-risk antihypertensives aged 55 years and older.18 Doxazosin was withdrawn from this trial after an interim analysis showed a 25% greater rate of a secondary endpoint, combined cardiovascular disease, in patients taking doxazosin than in those on chlorthalidone, largely driven by congestive heart failure.19-21 Based on this study, alpha1 blockers should not be considered as first-line monotherapy treatment for hypertension but as part of a combination regimen to provide maximal blood pressure control.13

Selective alpha blockers appear to have neutral or even favorable effects on plasma lipids and lipoproteins when administered to hypertensive patients. Investigators have reported mild reductions in levels of total cholesterol; low-density lipoprotein; and very-low-density lipoprotein cholesterol, and triglycerides and elevations in levels of high-density lipoprotein cholesterol and insulin sensitivity with prazosin, doxazosin, and terazosin.13,22 With long-term use, selective alpha blockers also appear to decrease left ventricular mass in patients with hypertension and left ventricular hypertrophy.23

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<thead>
<tr>
<th>Selective Alpha, Blocker</th>
<th>Daily Dose mg</th>
<th>Frequency per Day</th>
<th>Bioavailability (% of oral dose)</th>
<th>Plasma Half Life (h)</th>
<th>Urinary Excretion (% of oral dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxazosin</td>
<td>1–16</td>
<td>1</td>
<td>65</td>
<td>10–12</td>
<td>NA</td>
</tr>
<tr>
<td>Prazosin</td>
<td>2–20</td>
<td>2–3</td>
<td>44–69</td>
<td>2.5–4</td>
<td>10</td>
</tr>
<tr>
<td>Terazosin</td>
<td>1–20</td>
<td>1</td>
<td>90</td>
<td>12</td>
<td>39</td>
</tr>
</tbody>
</table>

Table 5-2. Pharmacokinetics of Selective Alpha1-Adrenergic Blocking Drugs
Doxazosin and terazosin have a longer duration of action than prazosin and have been shown to produce sustained blood pressure reductions with single daily administration. Prazosin, doxazosin, and terazosin are available for clinical use in the United States. A controlled-release formulation of doxazosin has been evaluated but it is not yet available.24

**Congestive Heart Failure**

Alpha-adrenergic blocking drugs appear particularly attractive for use in the treatment of heart failure (HF) because they hold the possibility of reproducing balanced reductions in resistance and capacitance beds. In fact, phentolamine was one of the earlier vasodilators shown to be effective in the treatment of heart failure.25 The drug was infused into normotensive patients with persistent left ventricular (LV) dysfunction after a myocardial infarction (MI) and found to induce a significant fall in systemic vascular resistance accompanied by considerable elevation in cardiac output and a reduction in pulmonary artery pressure.26 Because of the frequent adverse effects that it produces, especially tachycardia, phentolamine is no longer used in the treatment of HF. Oral phenoxybenzamine has also been used as vasodilator therapy in HF; like phentolamine, it has been replaced by newer vasodilator agents.

Studies evaluating the acute hemodynamic effects of prazosin in patients with congestive HF (CHF) consistently find significant reductions in systemic and pulmonary vascular resistances and left ventricular filling pressures associated with increases in stroke volume.15,27 In most studies, there is no change or a decrease in heart rate. The response pattern seen with prazosin is similar to that observed with nitroprusside with the exception that the heart rate tends to be higher with the use of nitroprusside; therefore, the observed increases in cardiac output are also higher with the latter agent.

Controversy still exists as to whether the initial clinical and hemodynamic improvements seen with prazosin are sustained during long-term therapy.28 Although some studies have demonstrated continued efficacy of prazosin therapy after chronic use, others have found little hemodynamic difference between prazosin- and placebo-treated patients. Some investigators believe that whatever tolerance to the drug does develop is most likely secondary to activation of counterposing neurohumoral forces; if the dose is raised and the tendency toward sodium and water retention is countered by appropriate increases in diuretic dose, prazosin is likely to remain effective. Others argue that sustained increases in plasma renin activity or plasma catecholamines are not seen during long-term therapy and that tolerance is not prevented or reversed by a diuretic. Some clinical studies suggest that patients with initially high plasma renin activity experience attenuation of beneficial hemodynamic effects more frequently. What appears clear is the need to evaluate patients individually as to the continued efficacy of their prazosin therapy. Whether there are subgroups of patients with HF (eg, those with highly activated sympathetic nervous systems) who are more likely to respond to prazosin or other alpha blockers remains to be determined.

A multicenter study conducted in Veterans Administration hospitals has shown that prazosin, when compared with placebo therapy, did not reduce mortality with long-term use in patients with advanced forms of CHF.19 However, favorable results were found in a retrospective analysis of the Vasodilator Heart Failure Trial 2, in which alpha-blockers were combined with nitrates.30

Doxazosin and metoprolol were combined and compared to metoprolol alone in the treatment of patients with chronic HF.31 After 3 months of continuous therapy, both treatment groups showed similar and significant reductions in systemic vascular resistance and heart rate, with significant increases in cardiac index, ejection fraction, and exercise capacity. It was concluded that the combination of doxazosin and metoprolol was no better than metoprolol used alone.

There is increasing evidence that alpha, adrenergic receptors also exist in the myocardium and that an increase in the force of contraction may be produced by stimulation of these sites.32 The mechanism of alpha-adrenergic positive inotropic response is unknown. Also unknown is the biologic significance of alpha-adrenergic receptors in cardiac muscle and whether these receptors play a role in the response to alpha-blocker therapy in CHF.

**Angina Pectoris**

Alpha-adrenergic receptors help mediate coronary vasoconstriction.33,34 It has been suggested that a pathologic alteration of the alpha-adrenergic system may be the mechanism of coronary spasm in some patients with variant angina pectoris.35 In uncontrolled studies, the administration of alpha-adrenergic blockers, both acutely and chronically, has been shown effective in reversing and preventing coronary spasm. However, in a long-term, randomized, double-blind trial, prazosin was found to exert no obvious beneficial effect in patients with variant angina.36 The demonstration of an important role for the postsynaptic alpha, receptors in determining coronary vascular tone may help explain prazosin’s lack of efficacy. Additional studies in this area are anticipated.

**Arrhythmias**

It has been postulated that enhanced alpha-adrenergic responsiveness occurs during myocardial ischemia and that it is a primary mediator of the electrophysiologic derangements and resulting malignant arrhythmias induced by catecholamines during myocardial ischemia and reperfusion.37 In humans, there have been favorable
reports of the use of an alpha blocker in the treatment of supraventricular and ventricular ectopy. Whether there is a significant role for alpha-adrenergic blockers in the treatment of cardiac arrhythmias will be determined through further clinical study.

Use in Other Disorders

Pheochromocytoma
Alpha blockers have been used in the treatment of pheochromocytoma to control the peripheral effects of excess catecholamines.38 In fact, intravenous phentolamine was used as a test for this disorder, but the test is now rarely done because of reported cases of cardiovascular collapse and death in patients who exhibited exaggerated sensitivity to the drug. It is still rarely used in cases of pheochromocytoma-related hypertensive crisis. However, for long-term therapy, oral phenoxybenzamine is the preferred agent. Beta-blocking agents are needed in pheochromocytoma for control of tachycardia and arrhythmias. A beta blocker of any kind, but primarily the nonselective agents, should not be initiated prior to adequate alpha blockade, since severe hypertension may occur as a result of the unopposed alpha-stimulating activity of the circulating catecholamines.38

Shock
In shock, hyperactivity of the sympathetic nervous system occurs as a compensatory reflex response to reduced blood pressure. Use of alpha blockers in shock has been advocated as a means of lowering peripheral vascular resistance and increasing vascular capacitance while not antagonizing the cardiotonic effects of the sympathomimetic amines. Although investigated for many years for the treatment of shock, alpha-adrenergic blockers are still not approved for this purpose.39 A prime concern about the use of alpha blockers in shock is that the rapid drug-induced increase in vascular capacitance may lead to inadequate cardiac filling and profound hypotension, especially in the hypovolemic patient. Adequate amounts of fluid replacement prior to use of an alpha blocker can minimize this concern.

Pulmonary Disease

Pulmonary Hypertension: The part played by endogenous circulating catecholamines in the maintenance of pulmonary vascular tone appears to be minimal. Studies evaluating the effects of norepinephrine administration on pulmonary vascular resistance have found the drug to have little or no effect. The beneficial effects on the pulmonary circulation that phentolamine and other alpha blockers have demonstrated in some studies is most likely primarily due to their direct vasodilator actions rather than to alpha blockade.40 As with other vasodilators in patients with pulmonary hypertension due to fixed anatomic changes (see Chapter 25, Prostacyclins, Endothelin Inhibitors, and Phosphodiesterase-5 Inhibitors in Pulmonary Hypertension), alpha blockers can produce hemodynamic deterioration secondary to their systemic vasodilatory properties.41

Bronchospasm: Bronchoconstriction is mediated in part through catecholamine stimulation of alpha receptors in the lung. It has been suggested that in patients with allergic asthma, a deficient beta-adrenergic system or enhanced alpha-adrenergic responsiveness could result in alpha-adrenergic activity being the main mechanism of bronchoconstriction.42 Several studies have shown bronchodilation or inhibition of histamine and allergen- or exercise-induced bronchospasm with a variety of alpha blockers.43 Additional studies are needed to define more fully the role of alpha blockers for use as bronchodilators.

Clinical Use and Adverse Effects

Oral phenoxybenzamine has a rapid onset of action, with the maximal effect from a single dose seen in 1 to 2 hours. The gastrointestinal absorption is incomplete, and only 20%-30% of an oral dose reaches the systemic circulation in active form. The half-life of the drug is 24 hours, with the usual dose varying between 20 mg and 200 mg daily in 1 or 2 doses. Intravenous phentolamine is initially started at 0.1 mg/minute and is then increased at increments of 0.1 mg/minute every 5 to 10 minutes until the desired hemodynamic effect is reached. The drug has a
short duration of action of 3 minutes to 10 minutes. Little is known about the pharmacokinetics of long-term oral use of phentolamine. The main adverse effects of the drug include postural hypotension, tachycardia, gastrointestinal disturbances, and sexual dysfunction. Intravenous infusion of norepinephrine can be used to combat severe hypertensive reactions. Oral phenoxybenzamine is approved for use in pheochromocytoma.

Prazosin is almost completely absorbed following oral administration, with peak plasma levels achieved at 2 to 3 hours. The drug is 90% protein-bound. Prazosin is extensively metabolized by the liver. The usual half-life of the drug is 2½ hours to 4 hours; in patients with HF, the half-life increases to the range of 5 hours to 7 hours.

The major adverse effect of prazosin is the first-dose phenomenon—severe postural hypotension occasionally associated with syncope, seen after the initial dose or after a rapid dose increment. The reason for this phenomenon has not been clearly established but may involve the rapid induction of venous and arteriolar dilatation by a drug that elicits little reflex sympathetic stimulation. It is reported more often when the drug is administered as a tablet rather than as a capsule, possibly related to the variable bioavailability or rates of absorption of the 2 formulations. (In the United States, the drug is available in capsule form.) The postural hypotension can be minimized if the initial dose of prazosin is not higher than 1 mg and if it is given at bedtime. In treating hypertension, a dose of 2 to 3 mg/day should be maintained for 1 to 2 weeks, followed by a gradual increase in dosage titrated to achieve the desired reductions in pressures, usually up to 20 to 30 mg/day, given in 2 or 3 doses. In treating HF, larger doses (2 to 7 mg) may be used to initiate therapy in recumbent patients, but the maintenance dose is also usually not more than 30 mg. Higher doses do not seem to produce additional clinical improvement.

Other adverse effects of prazosin include dizziness, headache, and drowsiness. The drug produces no deleterious effects on the clinical course of diabetes mellitus, chronic obstructive pulmonary disease, renal failure, or gout. It does not adversely affect the lipid profile.

Terazosin, which is approved for once-daily use in hypertension, may be associated with a lesser incidence of first-dose postural hypotension than prazosin. The usual recommended dose range is 1 to 5 mg administered once a day; some patients may benefit from doses as high as 20 mg daily or from divided doses.

Doxazosin is also approved as a once-daily therapy for systemic hypertension. The initial dosage of doxazosin is 1 mg once daily. Depending on the patient's standing blood pressure response, the dosage may then be increased to 2 mg and, if necessary, to 4, 8, or 16 mg to achieve the desired reduction in blood pressure. Doses beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, and postural hypotension.

The alpha2 blocker yohimbine, 5.4 mg orally, is used 4 times daily to treat male impotence. Urologists have used yohimbine for the diagnostic classification of certain cases of male erectile dysfunction. Increases in heart rate and blood pressure, piloerection, and rhinorrhea are the most common adverse reactions. Yohimbine should not be used with antidepressant drugs.

**Beta-Adrenergic Blocking Drugs**

Beta-adrenergic blocking drugs, which constitute a major pharmacotherapeutic advance, were conceived initially for the treatment of patients with angina and arrhythmias; however, they also have therapeutic effects in many other clinical disorders including systemic hypertension, hypertrophic cardiomyopathy, mitral valve prolapse, silent myocardial ischemia, migraine, glaucoma, essential tremor, and thyrotoxicosis. Beta blockers have been effective in treating unstable angina and for reducing the risk of cardiovascular mortality and nonfatal reinfarction in patients who have survived an acute MI. Beta blockade is a potential treatment modality, with or without thrombolytic therapy, for reducing the extent of myocardial injury and mortality during the hyperacute phase of MI.

Various beta blockers have been approved for use in patients with New York Heart Association (NYHA) class II-IV HF who are receiving angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digoxin to reduce the progression of disease and mortality.

**Beta-Adrenergic Receptor**

The concept of adrenergic receptor stimulation for mediating catecholamine actions had been recognized throughout the twentieth century, and during the past 35 years, scientists began to study the molecular steps that lay between the putative receptors and agonists and the response elements within the cell. It was found that adrenergic receptors, when stimulated, can trigger the production of second messengers (eg, adenyl cyclase) via an interaction with the coupling proteins attached to the beta receptor. The beta- and alpha-receptors are part of a major class of G protein-coupled receptors or seven-transmembrane receptors—the most important targets of clinically used drugs—that also zero in on serotonin receptors, histamine receptors, and angiotensin-II receptors.

Using radioligand labeling techniques and purification methods, Lefkowitz helped to identify the structures of the adrenergic receptors as membrane-bound polypeptide chains with a molecular weight of about 67,000 Da. The beta receptors consist of seven-transmembrane
alpha-helices of 20-28 amino acids joined by alternating extracellular and cytoplasmic loops (Figure 5-2). Lefkowitz and colleagues were successful in reconstituting the beta receptors and demonstrated that the receptors could convey catecholamine responsiveness when transplanted to previously unresponsive organic systems. Subsequently, the receptor genes and cDNAs for beta receptors were cloned in 1986, and the 3-dimensional crystalline structure of the beta 2 receptor was recently described in 2007.

A major contribution to our understanding of beta-receptor functioning came with the fundamental description of receptor desensitization. In contrast to the older concepts of adrenergic receptors as static entities on cell membranes that simply serve to initiate a chain of events, newer concepts suggest that adrenergic receptors are subject to a wide variety of controlling influences, resulting in the dynamic regulation of receptor sites and/or their sensitivity to catecholamine agonists. Changes in tissue concentration or sensitivity of receptors are important in drug activity and in the pathophysiology of disease. This desensitization phenomenon has been shown to be caused not by a change in receptor function or degradation, but rather by catecholamine-induced changes in the conformation of the receptor sites that renders them ineffective. Rapid desensitization of beta receptors was proved to be mediated by agonist stimulation of beta-adrenergic receptor kinases (BARK) or GRK2 that phosphorylate receptors and decrease the coupling of G proteins to adenyl cyclase.

However, it was also found that phosphorylation of the receptor itself was not sufficient to fully desensitize receptor function. A second reaction must occur that involves an arresting protein known as beta-arrestin. Through this desensitization process, internalization of receptors on the cell membrane also occurs. In contrast to adrenergic agonists, beta-adrenergic blocking drugs by themselves do not induce desensitization or changes in the conformation of receptors. They can also block the ability of catecholamines to desensitize receptors. Work is currently being carried out with beta-arrestin agonists to form “super” beta blockers that can turn off G protein-mediated signaling of the beta receptor but still maintain the benefits of continued beta-arrestin-mediated signaling on cell survival systems.

### Basic Pharmacologic Differences among Beta-Adrenoceptor Blocking Drugs

More than 100 beta-adrenoceptor blockers have been synthesized during the past 35 years, and over 30 are available worldwide for clinical use. Selectivity for 2 subgroups of the beta-adrenoceptor population has also been useful: beta, receptors in the heart and beta, receptors in the peripheral circulation and bronchi. More controversial has been the introduction of beta-blocking drugs with alpha-adrenergic blocking actions, varying amounts of selective and nonselective intrinsic sympathomimetic activity (partial agonist activity), calcium-channel blocker activity, antioxidant actions, effects on nitric oxide production, and nonspecific membrane-stabilizing effects. There are also pharmacokinetic differences between beta-blocking drugs that may be of clinical importance.

Sixteen beta-adrenoceptor blockers are now marketed in the United States for cardiovascular disorders: propranolol for angina, arrhythmias, systemic hypertension, migraine prophylaxis, essential tremor, and hypertrophic MI infarction; nadolol for hypertension and angina; timolol for hypertension and for reducing the risk of cardiovascular mortality and nonfatal reinfarction in survivors of MI and in topical form for glaucoma; atenolol for hypertension and angina and in intravenous and oral formulations for reducing the risk of cardiovascular mortality in survivors of MI; metoprolol for hypertension, angina, moderate CHF, and in intravenous and oral formulations for reducing the risk of cardiovascular mortality in survivors of acute MI; penbutolol, bisoprolol, pindolol, and nebivolol for treat-
ing hypertension; betaxolol and carteolol for hypertension and in a topical form for glaucoma; acebutolol for hypertension and ventricular arrhythmias; intravenous esmolol for supraventricular arrhythmias; oral and intravenous sotalol for ventricular and atrial arrhythmias; labetalol for hypertension and in intravenous form for hypertensive emergencies; and carvedilol for hypertension and moderate to severe CHF. In addition, oxprenolol has been approved for use in hypertension but is not marketed in the United States.

Despite extensive experience with beta blockers in clinical practice, there have been no studies suggesting that any of these agents have major advantages or disadvantages in relation to the others for treatment of most cardiovascular diseases. When any available blocker is titrated properly, it can be effective in patients with arrhythmia, hypertension, or angina. However, 1 agent may be more effective than other agents in reducing adverse reactions in some patients and for managing specific situations.

Potency
Beta-adrenergic-receptor blocking drugs are competitive inhibitors of catecholamine binding at beta-adrenergic-receptor sites. The dose-response curve of the catecholamine is shifted to the right; that is, a given tissue response requires a higher concentration of agonist in the presence of beta-blocking drugs. Beta-blocking potency can be assessed by the inhibition of tachycardia produced by isoproterenol or exercise (the more reliable method in the intact organism); the potency varies from compound to compound (Table 5-3). These differences in potency are of no therapeutic relevance; however, they do explain the different drug doses needed to achieve effective beta-adrenergic blockade in initiating therapy in patients or in switching from 1 agent to another.

Structure-Activity Relationships
The chemical structures of most beta-adrenergic blockers have several features in common with the agonist isoproterenol (Figure 5-3), an aromatic ring with a substituted ethanolamine side chain linked to it by an -OCH₂ group. The beta blocker timolol has a catecholamine-mimicking side chain but a more complex ring than seen with most other beta blockers.

Most beta-blocking drugs exist as pairs of optical isomers and are marketed as racemic mixtures. Almost all the beta-blocking activity is found in the negative (–) levorotatory stereoisomer. The 2 stereoisomers of beta-adrenergic blockers are useful for differentiating between the pharmacologic effects of beta blockade and membrane-stabilizing activity (possessed by both optical forms). The positive (+) dextrorotatory stereoisomers of beta-blocking agents have no apparent clinical value except for d-nebivolol, which has beta-blocking activity.

### Table 5-3. Pharmacodynamic Properties of Beta-Adrenergic Blocking Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>β₁ Blockade Potency Ratio (propranolol = 1.0)</th>
<th>Relative β₁ Selectivity</th>
<th>ISA</th>
<th>MSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>0.3</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1.0</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>1.0</td>
<td>++</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>10.0</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carteolol</td>
<td>10.0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>10.0</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Esmolol</td>
<td>0.02</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Labetalol</td>
<td>0.3</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1.0</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nadolol</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>10.0</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>1.0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Pindolol</td>
<td>6.0</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Sotalol</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Timolol</td>
<td>6.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isomer-D-propranolol</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>++</td>
</tr>
</tbody>
</table>

ISA = intrinsic sympathomimetic activity; MSA = membrane-stabilizing activity; ++ = strong effect; + = modest effect; 0 = absent effect.

'bisoprolol is also approved as a first-line antihypertensive therapy in combination with a very low-dose diuretic.

Carvedilol has peripheral vasodilating activity and additional alpha₁-adrenergic blocking activity.

Labetalol has additional alpha₁-adrenergic blocking activity and direct vasodilatory activity.

Nebivolol can augment vascular nitric oxide release.

Sotalol has an additional type of antiarrhythmic activity.

Adapted with permission from the McGraw-Hill Companies from Frishman WH. Clinical Pharmacology of the β-Adrenoceptor Blocking Drugs. 2nd ed. Norwalk, CT: Appleton-Century-Crofts; 1984.
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and d-sotalol, which appears to have type III antiarrhythmic properties. Penbutolol and timolol are marketed only in the l-form. As a result of asymmetric carbon atoms, labetalol and nebivolol have 4 stereoisomers and carvedilol has 2. With carvedilol, beta-blocking effects are seen in the (−) levorotatory stereoisomer and alpha-blocking effects in both the (−) levorotatory and (+) dextrorotary stereoisomers.

Membrane Stabilizing Activity
At concentrations well above therapeutic levels, certain beta blockers have a quinidine-like or local anesthetic membrane-stabilizing effect on the cardiac action potential. This property is exhibited equally by the 2 stereoisomers of the drug and is unrelated to beta-adrenergic blockade and major therapeutic antiarrhythmic actions. There is no evidence that membrane-stabilizing activity is responsible for any direct negative inotropic effect of the beta blockers, since drugs with and without this property equally depress LV function. However, membrane-stabilizing activity can manifest itself clinically with massive beta-blocker intoxications.

Beta-Selectivity
In 1967, Lands et al described 2 types of beta-adrenergic receptors, beta₁ and beta₂. Beta-adrenergic blockers are now classified as being beta₁-selective or nonselective, according to their relative abilities to antagonize the actions of sympathomimetic amines at lower doses in some tissues than what is required in other tissues. When used in low doses, beta₁-selective blocking drugs inhibit cardiac beta₁-receptors but have less influence on beta₂-receptors in bronchial and vascular locations, however, given in higher doses, beta₁-selective agents also block beta₂-receptors. Accordingly, beta₁-selective agents may be safer than nonselective ones in patients with bronchospastic disease, since beta₂-receptors are still able to be stimulated and in the process mediate adrenergic bronchodilation. Nevertheless, even selective beta blockers need to be used with caution in patients with reversible bronchospasm.

A second theoretical advantage is that unlike nonselective beta blockers, beta₁-selective blockers in low doses may not block the beta₂ receptors that mediate dilation of arterioles. During the infusion of epinephrine, nonselective blockers can cause a pressure response by blocking beta₁ receptor–mediated vasodilation, since α-adrenergic vasoconstrictor responses are still operative. Selective beta₂-antagonists may not induce the pressor effect in the presence of epinephrine and may lessen the risk of peripheral blood flow being reduced. It is possible that leaving beta₂-receptors unblocked (and responsive to epinephrine) may be functionally important in a subset of patients with asthma, drug-induced hypoglycemia, and/or peripheral vascular disease who need to be treated with beta-blocking drugs.

Practolol was introduced in 1970 as the first β₁-selective blocker, but after 4 years of clinical use it was found to cause a unique toxicity (the oculomucocutaneous syndrome) manifested by keratoconjunctivitis, sclerosing peritonitis, and pleurisy and was ultimately removed from the market. Subsequently, other beta₁-selective blockers without this toxicity were introduced, including metoprolol, atenolol, betaxolol, bisoprolol, esmolol, acebutolol and nebivolol.

Intrinsic Sympathomimetic Activity (ISA, partial agonist activity)
The 2 earliest β-blocking drugs that were synthesized, dichloroisoproterenol and pronethalol, were found to inhibit the effects of catecholamines while at the same time
stimulating adrenergic receptors, although with less potency (partial agonist activity). This concept did not become popular, and these drugs were quickly abandoned as clinical agents. Subsequently, other agents that had much less ISA (pindolol, carteolol, and penbutolol) were synthesized and then approved for clinical use. The level of ISA with these particular beta blockers caused a minor stimulation of the receptor (in the absence of catecholamines), which could be blocked by propranolol (Figure 5-4). In the presence of catecholamines, beta blockers with ISA remain effective antihypertensive agents; however, it is still debated whether a beta blocker with the potential for ISA constitutes an overall advantage or disadvantage in cardiac therapy.66,77 Drugs with ISA cause less slowing of the heart rate at rest than do propranolol and metoprolol, although the increases in heart rate with exercise are similarly blunted.66 These beta-blocking agents directly reduce peripheral vascular resistance, and may also cause less depression of atrioventricular conduction than drugs lacking this action.66,80

Some investigators have made claims that ISA in a beta blocker protects against myocardial depression, adverse lipid changes, bronchial asthma, and peripheral vascular complications seen in some patients on a compound without ISA, such as propranolol.66 The evidence to support this claim still remains unconvincing. The ISA beta blocker xamoterol was investigated in patients with CHF, but the studies were terminated because of an increased morbidity and mortality rate.41

### Alpha-Adrenergic Activity

Labetalol and carvedilol are 2 beta-blocking agents that have antagonistic effects at both alpha- and beta-adrenergic receptors; both have direct vasodilator effects.77 Labetalol has been shown to be 6 to 10 times less potent than phenotolamine on α-adrenergic receptors and 1.5 to 4 times less potent than propranolol at beta-adrenergic receptors.77,82 Labetalol is itself much less potent at alpha receptors than at beta receptors. However, the additional alpha-blocking property does lead to a reduction in peripheral vascular resistance in patients and better preservation of cardiac output than what is observed with propranolol. The drug is useful as a parenteral agent for treating hypertensive urgencies or emergencies and as an oral drug for chronic hypertension management in the patient receiving multiple antihypertensive agents.83

Although carvedilol has somewhat less alpha-adrenergic blocking potency than labetalol (the ratio of alpha, to beta-adrenergic blockade for carvedilol is 1:10, as compared to 1:4 for labetalol), it is useful as a treatment for systemic hypertension and for patients with symptomatic CHF related to ischemic and nonischemic causes.74 Unlike labetalol, carvedilol also has been shown to have antioxidant and antiproliferative properties.54 In addition, carvedilol was recently shown to stimulate beta-arrestin signaling.84

### Direct Vasodilator Activity

Nebivolol is a β1-selective adrenergic receptor antagonist with additional nitric oxide-mediated vasodilatory action on arteries and veins. In addition, the drug has similar antioxidant effects to those observed with carvedilol. Nebivolol was approved for clinical use in patients with systemic hypertension66 and has been studied in patients with CHF.

### Pharmacokinetics

Although the beta-adrenergic blocking drugs as a group have similar therapeutic effects, their pharmacokinetic properties are markedly different (Table 5-4).48,74,85-87 Their varied aromatic ring structures lead to differences in completeness or gastrointestinal absorption, amount of first-pass hepatic metabolism, lipid-solubility, protein binding, extent of distribution in the body, penetration into the brain, concentration in the heart, rate of hepatic biotransformation, pharmacologic activity of metabolites, and renal clearance of a drug and its metabolites, which may influence the clinical usefulness of these drugs in some patients.47,49,70,74,86 The desirable pharmacokinetic characteristics in this group of compounds are a lack of major individual differences in bioavailability and in

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**Figure 5-4. Physiologic effects of beta-adrenergic blocking drugs with and without partial agonist activity in the presence of circulating catecholamines.** When circulating catecholamines (●) combine with beta-adrenergic receptors, they produce a full physiologic response. When these receptors are occupied by a beta blocker lacking partial agonist activity (○), no physiologic effects from catecholamine stimulation can occur. A beta-blocking drug with partial agonist activity (✚) also blocks the binding of catecholamines to beta-adrenergic receptors, but, in addition, the drug causes a relatively weak stimulation of the receptor.

metabolic clearance of the drug and a rate of removal from active tissue sites that is slow enough to allow longer dosing intervals.47,49,88

The beta blockers can be divided by their pharmacokinetic properties into 2 broad categories: those eliminated by hepatic metabolism, which tend to have relatively short plasma half-lives, and those eliminated unchanged by the kidney, which tend to have longer half-lives.47 Propranolol and metoprolol are both lipid-soluble, are almost completely absorbed by the small intestine, and are largely metabolized by the liver. They tend to have highly variable bioavailability and relatively short plasma half-lives.49,63,70,86 A lack of correlation between the duration of clinical pharmacologic effect and plasma half-life may allow these drugs to be administered once or twice daily.47

In contrast, agents such as atenolol and nadolol are more water-soluble, are incompletely absorbed through

<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Extent of Absorption (% of dose)</strong></th>
<th><strong>Extent of Bioavailability (% of dose)</strong></th>
<th><strong>Dose-Dependent Bioavailability (major first-pass hepatic metabolism)</strong></th>
<th><strong>Interpatient Variations in Plasma Levels</strong></th>
<th><strong>Beta-blocking Plasma Concentrations (%)</strong></th>
<th><strong>Protein Binding</strong></th>
<th><strong>Lipid Solubility</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>&gt;90</td>
<td>~40</td>
<td>Yes</td>
<td>7-fold</td>
<td>0.2–2.0 µg/mL</td>
<td>25</td>
<td>Low</td>
</tr>
<tr>
<td>Atenolol</td>
<td>~50</td>
<td>~40</td>
<td>No</td>
<td>4-fold</td>
<td>0.2–5.0 µg/mL</td>
<td>&lt;5</td>
<td>Low</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>&gt;90</td>
<td>~80</td>
<td>No</td>
<td>2-fold</td>
<td>0.005–0.05 µg/mL</td>
<td>50</td>
<td>Low</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>~90</td>
<td>~88</td>
<td>No</td>
<td>—</td>
<td>0.005–0.02 µg/mL</td>
<td>~33</td>
<td>Low</td>
</tr>
<tr>
<td>Carteolol</td>
<td>~90</td>
<td>~90</td>
<td>No</td>
<td>2-fold</td>
<td>40–160 ng/mL</td>
<td>23–30</td>
<td>Low</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>90</td>
<td>~30</td>
<td>Yes</td>
<td>5-fold</td>
<td>10–100 ng/mL</td>
<td>98</td>
<td>Moderate</td>
</tr>
<tr>
<td>Carvedilol LA 90</td>
<td>~30</td>
<td>Yes</td>
<td>5-fold</td>
<td>10-100 ng/mL</td>
<td>98</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Esmolol†</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5-fold</td>
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</tr>
<tr>
<td>Labetalol</td>
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<td>~33</td>
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<td>10-fold</td>
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<tr>
<td>Metoprolol</td>
<td>90</td>
<td>~50</td>
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<td>10-fold</td>
<td>50–100 ng/mL</td>
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<tr>
<td>Metoprolol LA</td>
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<td>65-70</td>
<td>Yes</td>
<td>10-fold</td>
<td>35–323 ng/mL</td>
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</tr>
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<td>Nadolol</td>
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<td>~30</td>
<td>No</td>
<td>7-fold</td>
<td>50–100 ng/mL</td>
<td>~30</td>
<td>Low</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>90</td>
<td>12-96</td>
<td>Yes</td>
<td>7-fold</td>
<td>1.5 mg/mL</td>
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<tr>
<td>Penbutolol</td>
<td>90</td>
<td>~100</td>
<td>No</td>
<td>4-fold</td>
<td>5–15 mg/mL</td>
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<td>High</td>
</tr>
<tr>
<td>Pindolol</td>
<td>90</td>
<td>~90</td>
<td>No</td>
<td>4-fold</td>
<td>50–100 ng/mL</td>
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<tr>
<td>Propranolol</td>
<td>90</td>
<td>30–70</td>
<td>Yes</td>
<td>20-fold</td>
<td>50–100 ng/mL</td>
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<td>High</td>
</tr>
<tr>
<td>Propranolol LA</td>
<td>90</td>
<td>30–40</td>
<td>Yes</td>
<td>20-30-fold</td>
<td>20–100 ng/mL</td>
<td>93</td>
<td>High</td>
</tr>
<tr>
<td>Sotalol</td>
<td>~70</td>
<td>~90</td>
<td>No</td>
<td>4-fold</td>
<td>1–3.2 µg/mL</td>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>Timolol</td>
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<td>~75</td>
<td>Yes</td>
<td>7-fold</td>
<td>5–10 ng/mL</td>
<td>~10</td>
<td>Low-moderate</td>
</tr>
</tbody>
</table>

NA = not applicable or no data; LA = long-acting.
† Ultra-short-acting beta blocker available only in intravenous form.

Adapted with permission of the McGraw-Hill Companies from Frishman WH. Clinical Pharmacology of the β-Adrenoceptor Blocking Drugs. 2nd ed. Norwalk, CT: Appleton-Century-Crofts; 1984.

Determined by the distribution ratio between octanol and water.
tachycardias. The short half-life (approximately 15 minutes) of perioperative hypertension and supraventricular tachycardias has been shown to be useful in the treatment of these conditions. Studies have shown that long-acting propranolol, metoprolol, and carvedilol can provide a much smoother curve of daily plasma levels than do comparable divided doses of conventional immediate-release formulations.

Ultra-short-acting beta blockers are also available and may be useful where a short duration of action is desired (eg, in patients with questionable CHF). One of these compounds, esmolol, a beta1-selective drug (see Tables 5-3 and 5-4) has been shown to be useful in the treatment of perioperative hypertension and supraventricular tachycardias. The short half-life (approximately 15 minutes) relates to the rapid metabolism of the drug by blood and hepatic esterases. Metabolism does not seem to be altered by disease states. A propranolol nasal spray that can provide immediate beta blockade has been tested in clinical trials, as has a new sublingual immediate-release formulation (esprolol). Bisoprolol is being evaluated in a transcutaneous patch.

The specific pharmacokinetic properties of individual beta-adrenergic blockers (first-pass metabolism, active metabolites, lipid solubility, and protein binding) may be clinically important. When drugs with extensive first-pass metabolism are taken by mouth, they undergo so much hepatic biotransformation that relatively little drug reaches the systemic circulation. Depending on the extent of first-pass effect, an oral dose of beta blocker must be larger than an intravenous dose to produce the same clinical effects. Some beta-adrenergic blockers are transformed into pharmacologically active compounds (acebutolol, nebivolol) rather than inactive metabolites. The total pharmacologic effect, therefore, depends on the amount of the drug administered and its active metabolites.

Characteristics of lipid solubility in a beta blocker have been associated with the ability of the drug to concentrate in the brain and many adverse effects of these drugs, which have not been clearly related to beta blockade, may result from their actions on the central nervous system (CNS) (lethargy, mental depression, and hallucinations). It is still not certain, however, whether drugs that are less lipid-soluble cause fewer of these adverse reactions.

There are genetic polymorphisms that can influence the metabolism of various beta-blocking drugs, which include propranolol, metoprolol, timolol, and carvedilol. A single codon difference of CYP2D6 may explain a significant proportion of interindividual variation of propranolol’s pharmacokinetics in Chinese subjects. There is no effect of exercise on propranolol’s pharmacokinetics. Relationships between Dose, Plasma Level, and Efficacy

Attempts have been made to establish a relation between the oral dose, the plasma level measured by gas chromatography, and the pharmacologic effect of each beta-blocking drug. After administration of a certain oral dose, beta-blocking drugs that are largely metabolized in the liver show large interindividual variation in circulating plasma levels. Many explanations have been proposed to explain wide individual differences in the relation between plasma concentrations of beta blockers and any associated therapeutic effect. First, patients may have different levels of “sympathetic tone” (circuiting catecholamines and active beta-adrenoceptor binding sites) and may thus require different drug concentrations to achieve adequate beta blockade. Second, many beta blockers have flat plasma–drug level response curves. Third, active drug isomers and active metabolites are not specifically measured in many plasma assays. Fourth, the clinical effect of a drug may last longer than the period suggested by the drug’s half-life in plasma, since recycling of the beta blocker between receptor site and neuronal nerve endings may occur.

Despite the lack of correlation between plasma levels and therapeutic effect, there is some evidence that a relation does exist between the logarithm of the plasma level and the beta-blocking effect (blockade of exercise- or isoproterenol-induced tachycardia). Plasma levels have little to offer as therapeutic guides except for ensuring adherence and diagnosis of overdose. Pharmacodynamic characteristics and clinical response should be used as guides in determining efficacy. For instance, the magnitude of heart rate reduction is statistically associated with the survival benefit of beta blockers in HF, whereas the dose of beta blocker is not.

Clinical Effects and Therapeutic Applications

The therapeutic efficacy and safety of beta-adrenoceptor blocking drugs has been well established in patients with angina, cardiac arrhythmias, congestive cardiomyopathy, and hypertension; these drugs also are recognized for reducing the risk of mortality and possibly nonfatal reinfarction in survivors of acute MI. Beta-adrenoceptor blocking drugs may be useful as a primary protection against cardiovascular morbidity and mortality in hypertensive patients. The drugs are also used for a multitude of other cardiac (Table 5-5) and noncardiac (Table 5-6) uses.
Cardiovascular Effects

Effects on Elevated Systemic Blood Pressure

Beta-adrenergic blockers are effective drugs for reducing elevated blood pressure (Tables 5-7 and 5-8), including in elderly patients with isolated systolic hypertension.63,124-126 Sixteen beta blockers are approved for clinical use in the United States and appear to be equally efficacious in controlling blood pressure. Sustained-release formulations of carvedilol, metoprolol, and propranolol have allowed these shorter-acting beta blockers to be used once daily in hypertention. In its intravenous form, labetalol is approved for parenteral use in hypertensive emergencies, and oral carvedilol and labetalol are useful for hypertensive urgencies.49

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has recommended that beta blockers be considered an alternative first-line treatment for hypertension.127 However, a meta-analysis revealed that the beneficial effects on clinical outcomes with diuretic treatment use was more favorable than those observed with beta blockers, especially atenolol, and that this is a class effect of all beta blockers.128-131 Most recently it was shown that losartan had a more favorable effect than atenolol on cardiovascular morbidity and mortality and a similar reduction in blood pressure in hypertensive patients with left ventricular hypertrophy.131 In a prospective cohort study, it was found that antihypertensive therapy with beta blockers was associated with a greater incidence of type 2 diabetes mellitus than treatment with ACE inhibitors, diuretics, and calcium blockers.132 However, this increased risk of diabetes mellitus must be weighed against the proven benefit of beta blockers in reducing the risk of cardiovascular events.133

Atenolol is probably not an effective antihypertensive drug when used once daily (the dose used in clinical trials); more frequent oral dosing may be necessary to achieve the blood pressure control seen with other beta blockers, appropriately dosed, and other antihypertensive drug classes.134

The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial135 compared the effects of beta blockers with different pharmacological profiles on glycemic and metabolic control in participants with hypertension and diabetes mellitus already receiving renin-angiotensin system blockade in the context of cardiovascular risk factors. This trial compared the effects of carvedilol and metoprolol tartrate on glycemic control after equivalent blood pressure lowering; the mean HbA1c increased significantly with metoprolol but not with carvedilol. Insulin sensitivity significantly improved with carvedilol but not with metoprolol. Progression to microalbuminuria was less frequent

<table>
<thead>
<tr>
<th>Table 5-5. Reported Cardiovascular Indications for Beta-Adrenoceptor Blocking Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension’ (systolic and diastolic)</td>
</tr>
<tr>
<td>Isolated systolic hypertension in the elderly</td>
</tr>
<tr>
<td>Angina’</td>
</tr>
<tr>
<td>“Silent” myocardial ischemia</td>
</tr>
<tr>
<td>Supraventricular arrhythmias’</td>
</tr>
<tr>
<td>Ventricular arrhythmias’</td>
</tr>
<tr>
<td>Reducing the risk of mortality and reinfarction in survivors of acute myocardial infarction’</td>
</tr>
<tr>
<td>Reducing the risk of mortality following percutaneous coronary’ revascularization</td>
</tr>
<tr>
<td>Hyperacute phase of myocardial infarction’</td>
</tr>
<tr>
<td>Dissection of aorta</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy’</td>
</tr>
<tr>
<td>Reversing left ventricular hypertrophy</td>
</tr>
<tr>
<td>Digitalis intoxication (tachyarrhythmias)’</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>QT interval prolongation syndrome</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Congestive cardiomyopathy’</td>
</tr>
<tr>
<td>Fetal tachycardia</td>
</tr>
<tr>
<td>Neurocirculatory asthenia</td>
</tr>
<tr>
<td>Prevention of aortic rupture in Ehlers-Danlos syndrome</td>
</tr>
</tbody>
</table>

*Indications formally approved by the U.S. FDA.

<table>
<thead>
<tr>
<th>Table 5-6. Some Reported Noncardiovascular Indications for Beta-Adrenoceptor Blocking Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric</td>
</tr>
<tr>
<td>Migraine prophylaxis’</td>
</tr>
<tr>
<td>Essential tremor’</td>
</tr>
<tr>
<td>Situational anxiety</td>
</tr>
<tr>
<td>Alcohol withdrawal (delirium tremens)</td>
</tr>
<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>Thyrotoxicosis’</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Pheochromocytoma (after β blockers)’</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Glaucoma’</td>
</tr>
<tr>
<td>Portal hypertension and gastrointestinal bleeding</td>
</tr>
<tr>
<td>Severe burns</td>
</tr>
</tbody>
</table>

*Indications formally approved by the U.S. FDA.
Table 5-7. Proposed Mechanisms to Explain the Antihypertensive Actions of Beta-Blockers

<table>
<thead>
<tr>
<th>Reduction in cardiac output</th>
<th>Inhibition of renin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS effects</td>
<td>Effects on prejunctional beta receptors:</td>
</tr>
<tr>
<td>reductions in norepinephrine release</td>
<td>Reduction in peripheral vascular resistance</td>
</tr>
<tr>
<td>Improvement in vascular adherence</td>
<td>Reduction in vasomotor tone</td>
</tr>
<tr>
<td>Reduction in plasma volume</td>
<td>Resetting of baroreceptor levels</td>
</tr>
<tr>
<td>Attenuation of pressor response to catecholamines with exercise and stress</td>
<td></td>
</tr>
</tbody>
</table>


with carvedilol than with metoprolol. Based on this study, it appears that the pharmacological differences among the beta blockers can affect the utility of these agents in hypertensive patients with diabetes mellitus.

In patients with angina and hypertension, CHF and hypertension, arrhythmias and hypertension, and in those who are post-MI with hypertension, beta blockers remain important first-line treatments. In addition, beta blockers are effective in hyperkinetic forms of hypertension (sinus tachycardia with blood pressure elevation) and in hypertensive individuals with a high "cardiac awareness" profile (somatic manifestations of anxiety such as tremor, sweating, and palpitations). When compared with other antihypertensive agents, there is a similar but no incremental benefit from beta blockers for the prevention of HF. When compared to other antihypertensive agents for primary prevention, however, they may be less effective for preventing strokes.

There is no consensus as to the mechanism(s) by which these drugs lower blood pressure. It is probable that some or all of the following proposed mechanisms play a part. Beta blockers without vasodilatory activity appear to be more efficacious in white patients and younger patients than they are in the elderly and in black patients.

Negative Chronotropic and Inotropic Effects
Slowing of the heart rate and some decrease in myocardial contractility with beta blockers lead to a decrease in cardiac output, which in both the short and the long term may lead to a reduction in blood pressure. It might be expected that these factors would be of particular importance in the treatment of hypertension related to high cardiac output and increased sympathetic tone.

Differences in Effects on Plasma Renin
The relation between the hypotensive action of beta-blocking drugs and their ability to reduce plasma renin activity remains controversial. Some beta-blocking drugs can antagonize sympathetically mediated renin release, although adrenergic activity is not the only mechanism by which renin release is mediated. Other major determinants are sodium balance, posture, and renal perfusion pressure.

The important question remains whether there is a clinical correlation between the beta blockers effect on the plasma renin activity and the lowering of blood pressure. Investigators have found that "high renin" patients do not respond or may even show a rise in blood pressure, and that "normal renin" patients have less predictable responses. In high-renin hypertensive patients, it has been suggested that renin may not be the only factor maintaining the high blood pressure state. At present, the exact role of renin reduction in blood pressure control is not well defined.

Central Nervous System Effect
There is now good clinical and experimental evidence to suggest that beta blockers cross the blood–brain barrier and enter the CNS. Although there is little doubt that beta blockers with high lipophilicity (eg, metoprolol, propranolol) enter the CNS in high concentrations, a direct antihypertensive effect mediated by their presence appears to be as effective as propranolol in lowering blood pressure.

Peripheral Resistance
Nonselective beta blockers have no primary action in lowering peripheral resistance and indeed may cause it to rise by leaving the alpha-stimulatory mechanisms unopposed. The vasodilating effect of catecholamines on skeletal muscle blood vessels is beta₂-mediated, suggesting possible therapeutic advantages in using beta₂-selective blockers, agents with partial agonist activity, and drugs with alpha-blocking activity and direct vasodilator effects. Since beta₂-selectivity diminishes as the drug dosage is raised, and since hypertensive patients generally have to be given far larger doses than are required simply to block the beta₁-receptors alone, beta₂-selectivity offers the clinician little if any real specific advantage in the treatment of hypertension.

Effects on Prejunctional Receptors
Apart from their effects on postjunctional tissue beta receptors, it is believed that blockade of prejunctional beta receptors may be involved in the hemodynamic actions of beta-blocking drugs. The stimulation of prejunctional
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alpha2 receptors leads to a reduction in the quantity of norepinephrine released by the postganglionic sympathetic fibers. Conversely, stimulation of prejunctinal beta receptors is followed by an increase in the quantity of norepinephrine released by the postganglionic sympathetic fibers. Blockade of prejunctional beta receptors should therefore diminish the amount of norepinephrine released, leading to a weaker stimulation of postjunctional alpha receptors—an effect that would produce less vasoconstriction. Opinions differ, however, on the contributions of presynaptic beta blockade to both a reduction in the peripheral vascular resistance and the antihypertensive effects on beta-blocking drugs.

Other Proposed Mechanisms
Less well-documented effects of beta blockers that may contribute to their antihypertensive actions include favorable effects on arterial adherence, venous tone and plasma volume, membrane-stabilizing activity, and resetting of baroreceptors. Genetic polymorphisms of the beta1 and beta2 receptor and other genetic markers have been implicated as a cause for systemic hypertension and the responsiveness of patients to treatment with beta blockers.

Effects in Angina
Ahlquist demonstrated that sympathetic innervation of the heart causes the release of norepinephrine, activating beta adrenoceptors in myocardial cells (Table 5-8). This adrenergic stimulation causes an increment in heart rate, isometric contractile force, and maximal velocity of muscle fiber shortening, all of which lead to an increase in cardiac work and myocardial oxygen consumption. The decrease in intraventricular pressure and volume caused

<table>
<thead>
<tr>
<th>Relative β1 Selectivity</th>
<th>ISA</th>
<th>MSA</th>
<th>HR Rest/Exer</th>
<th>MC Rest</th>
<th>BP Rest/Exer</th>
<th>AV Conduction</th>
<th>Antiarrhythmic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atenolol</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Carvedilol†</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Esmolol</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Labetalol†</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nadolol</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nebivolol§</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pindolol</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sotalol</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Timolol</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Isomer-d-propranolol</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

ISA = intrinsic sympathomimetic activity; MSA = membrane stabilizing activity; HR = heart rate; MC = myocardial contractility; BP = blood pressure; AV = atrioventricular; rest/exer = resting and exercise; ++ = strong effect; += modest effect; 0 = absent effect; ↑ = elevation; ↓ = reduction; ↔ = no change.
† β1 selectivity is seen only with low therapeutic drug concentrations. With higher concentrations, β2 selectivity is not seen.
‡ Carvedilol has peripheral vasodilating activity and additional alpha1-adrenergic blocking activity.
§ Labetalol has additional alpha1-adrenergic blocking activity and direct beta2 vasodilatory activity.
¶ Nebivolol can augment vascular nitric oxide release.
|| Effects of D-propranolol with doses in human beings well above the therapeutic level. The isomer also lacks β blocking activity.
by the sympathetic-mediated enhancement of cardiac contractility tends, on the other hand, to reduce myocardial oxygen consumption by reducing myocardial wall tension (LaPlace’s law).158 Although there is a net increase in myocardial oxygen demand, this is normally balanced by an increase in coronary blood flow. Angina is believed to occur when oxygen demand exceeds supply, i.e., when coronary blood flow is restricted by coronary atherosclerosis. Since the conditions that precipitate anginal attacks (exercise, emotional stress, food, etc.) cause an increase in cardiac sympathetic activity, it might be expected that blockade of cardiac beta adrenoreceptors would relieve anginal symptoms. It is on this basis that the early clinical studies with beta-blocking drugs in patients with angina were initiated.159

Three main factors—heart rate, ventricular systolic pressure, and the size of the LV—contribute to the myocardial oxygen requirements of the LV. Of these, heart rate and systolic pressure appear to be important (the product of heart rate multiplied by the systolic blood pressure is a reliable index to predict the precipitation of angina in a given patient).160,161 However, myocardial contractility may be even more important.162

The reduction in heart rate effected by beta blockade has 2 favorable consequences: (1) a decrease in blood pressure, thus reducing myocardial oxygen needs, and (2) a longer diastolic filling time associated with a slower heart rate, allowing for increased coronary perfusion.163 Beta blockade also reduces exercise-induced blood pressure increments, the velocity of cardiac contraction, and oxygen consumption at any patient workload.160,161 Pre-treatment heart rate variability or low exercise tolerance may predict which patients will respond best to treatment with beta blockade.162,164 Despite the favorable effects on heart rate, the blunting of myocardial contractility with beta blockers may also be the primary mechanism of their antianginal benefit.162,165

Studies in dogs have shown that propranolol causes a decrease in coronary blood flow.166 However, subsequent experimental animal studies have demonstrated that beta-blocking-induced shunting occurs in the coronary circulation, thus maintaining blood flow to ischemic areas, especially in the subendocardial region.167 In human beings, concomitantly with the decrease in myocardial oxygen consumption, beta blockers can cause a reduction in coronary blood flow and a rise in coronary vascular resistance.168 On the basis of coronary autoregulation, the overall reduction in myocardial oxygen needs with beta blockers may be sufficient cause for this decrease in coronary blood flow.160,161

Virtually all beta blockers—whether or not they have partial agonist activity, alpha-blocking effects, membrane-stabilizing activity, and general or selective beta-blocking properties—produce some degree of increased work capacity without pain in patients with angina. Therefore it must be concluded that this results from their common property: blockade of cardiac beta receptors.160 Both D- and L-propranolol have membrane-stabilizing activity, but only L-propranolol has significant beta-blocking activity. The racemic mixture (D- and L-propranolol) causes a decrease in both heart rate and force of contraction in dogs, while the D-isomer has hardly any effect.169 In human beings, D-propranolol, which has “membrane” activity but no beta-blocking properties, has been found to be ineffective in relieving angina even at very high doses.170

Beta blockers are recommended as the initial therapy for long-term management of angina.171-176 The orally active beta blockers that have been approved for use in angina include propranolol, metoprolol, atenolol, and nadolol.

Although exercise tolerance improves with beta blockade, the increments in heart rate and blood pressure with exercise are blunted, and the rate-pressure product (systolic blood pressure x heart rate) achieved when pain occurs is lower than that reached during a control run.117,178 The depressed pressure-rate product at the onset of pain (about 20% reduction from control) is reported to occur with various beta-blocking drugs, probably related to decreased cardiac output. Thus, although there is increased exercise tolerance with beta blockade, patients exercise less than might be expected. This may also relate to the action of beta blockers in increasing LV size, causing increased LV wall tension and an increase in oxygen consumption at a given blood pressure.179

Combined Use of Beta Blockers with Other Antianginal Therapies in Angina

Nitrates

Combined therapy with nitrates and beta blockers (see Chapter 14, The Organic Nitrates and Nitroprusside) may be more efficacious for the treatment of angina than the use of either drug alone.150,171,178,180 The primary effects of beta blockers are to cause a reduction in both resting heart rate and the response of heart rate to exercise. Since nitrates produce a reflex increase in heart rate and contractility owing to a reduction in arterial pressure, concomitant beta-blocker therapy is extremely effective because it blocks this reflex increment in the heart rate. Similarly, the preservation of diastolic coronary flow with a reduced heart rate will also be beneficial.160 In patients with a propensity for myocardial failure who may have a slight increase in heart size with the beta blockers, the nitrates will counteract this tendency by reducing heart size as a result of its peripheral venodilator effects. During the administration of nitrates, the reflex increase in contractility that is mediated through the sympathetic nervous system will be checked by the presence of beta blockers.
Similarly, the increase in coronary resistance associated with beta-blocker administration can be ameliorated by the administration of nitrates.160

**Calcium-Entry Blockers**

Calcium-entry blockers are a group of drugs that block transmembrane calcium currents in vascular smooth muscle to cause arterial vasodilatation (see Chapter 8, Calcium Channel Blockers). Some calcium-entry blockers (diltiazem, verapamil) also slow the heart rate and reduce atrioventricular (AV) conduction. Combined therapy with beta-adrenergic and calcium-entry blockers can provide clinical benefits for patients with angina who still remain symptomatic with either agent used alone.171,176,181–183 Because adverse cardiovascular effects, especially bradycardia and heart block, can occur, patients being considered for such treatment must be carefully selected and observed.181,182

**Ranolazine**

Beta-adrenergic blockers can be combined with ranolazine in patients with stable angina who remain symptomatic with monotherapy. (See Chapter 15, Ranolazine: A Piperazine Derivative.)

**Angina at Rest and Vasospastic Angina**

Angina can be caused by multiple mechanisms, including coronary vasospasm, myocardial bridging, and thrombosis, which appear to be responsible for ischemia in a significant proportion of patients with unstable angina and angina at rest.184,185 Therefore, beta blockers that primarily reduce myocardial oxygen consumption but fail to exert vasodilating effects on coronary vasculature may not be totally effective in patients in whom angina is caused or increased by dynamic alterations in coronary luminal diameter.160,182 Despite potential dangers in angina at rest and vasospastic angina, beta blockers have been used successfully both as monotherapy and in combination with vasodilating agents in many patients.186,186a The drugs have also been shown to favorably affect C-reactive protein concentrations in the blood, an important disease marker for active coronary artery disease.187

**Electrophysiologic and Antiarrhythmic Effects**

Adrenoceptor-blocking drugs have 2 main effects on the electrophysiologic properties of specialized cardiac tissue (Table 5-9).188 The first effect results from specific blockade of adrenergic stimulation of cardiac pacemaker potentials. In concentrations causing significant inhibition of adrenergic receptors, beta blockers produce little change in the transmembrane potentials of cardiac muscle. By competitively inhibiting adrenergic stimulation, however, beta blockers decrease the slope of phase 4 depolarization and the spontaneous firing rate of sinus or ectopic pacemakers and thus decrease automaticity. Arrhythmias occurring in the setting of enhanced automaticity—as seen in MI, digitalis toxicity, hyperthyroidism, and pheochromocytoma—would therefore be expected to respond well to beta blockade.160,188–190

The second electrophysiologic effect of beta blockers involves membrane-stabilizing action, also known as “quinidine-like” or “local anesthetic” action, which is observed only at very high dose levels. This property is unrelated to inhibition of catecholamine action and is possessed equally by both the D- and L-isomers of the drugs (D-isomers have almost no beta-blocking activity).188 Characteristic of this effect is a reduction in the rate of rise of the intracardiac action potential without an effect on the spike duration of the resting potential.188 Associated features include an elevated electrical threshold of excitability, a delay in conduction velocity, and a significant increase in the effective refractory period. This effect and its attendant changes have been explained by inhibition of the depolarizing inward sodium current.188 There is a greater antifibrillatory effect when beta blockers are combined with some other antiarrhythmics.191

Sotalol is unique among the beta blockers in that it possesses class III antiarrhythmic properties, causing prolongation of the action potential period and thus delaying repolarization.192 Clinical studies have verified the efficacy of sotalol in the control and prevention of both atrial and ventricular arrhythmias,193–204 but additional investigation will be required to determine whether its class III antiarrhythmic properties contribute significantly to its efficacy as an antiarrhythmic agent. A clinical study

**Table 5-9. Antiarrhythmic Properties of Beta Blockers**

<table>
<thead>
<tr>
<th><strong>β Blockade</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrophysiology: depress excitability and conduction</td>
</tr>
<tr>
<td>Prevention of ischemia: decreased automaticity, inhibit reentrant mechanisms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Membrane-stabilizing effects</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthetic “quinidine-like” properties: depress excitability, prolong refractory period, delay conduction</td>
</tr>
<tr>
<td>Clinically: probably not significant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Special pharmacologic properties</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>β, selectivity, intrinsic sympathomimetic activity (do not appear to contribute to antiarrhythmic effectiveness)</td>
</tr>
</tbody>
</table>

demonstrated an increased mortality risk with D-sotalol, the stereoisomer with class III antiarrhythmic activity and no beta-blocking effect.\(^{205,206}\)

There is a quantitative gender difference between men and women in response to D, L sotalol, which may explain the greater propensity of women to drug-induced torsades de pointes.\(^{207}\) To ensure patient safety with sotalol use, it has been suggested that patients be admitted to the hospital for initiation of treatment.\(^{208,209}\)

The most important mechanism underlying the antiarrhythmic effect of beta blockers, with the possible exclusion of sotalol, is believed to be beta blockade with resultant inhibition of pacemaker potentials. The contribution of membrane-stabilizing action does not appear to be clinically significant. In vitro experiments with human ventricular muscle have shown that the concentration of propranolol required for membrane stabilizing is 50 to 100 times the concentration that is usually associated with inhibition of exercise-induced tachycardia and at which only beta-blocking effects occur.\(^{270}\) Moreover, D-propranolol, which possesses membrane-stabilizing properties but no beta-blocking action, is a weak antiarrhythmic even at high doses, while beta blockers devoid of membrane stabilizing action (atenolol, esmolol, metoprolol, nadolol, pindolol, etc.) have been shown to be effective antiarrhythmic drugs.\(^{48,49,92}\) Differences in the overall clinical usefulness of beta blockers for arrhythmia are related to their other associated pharmacologic properties.\(^{48,49}\)

### Therapeutic Uses in Cardiac Arrhythmias

Beta-adrenergic blocking drugs have become an important treatment modality for various cardiac arrhythmias (Table 5-10), used alone and in combination with other antiarrhythmic drugs.\(^{48,49,188,210-214}\) While it has long been believed that beta blockers are more effective in treating supraventricular arrhythmias than ventricular arrhythmias, this may not be the case.\(^{215-218}\) These agents can be quite useful in the treatment of ventricular tachyarrhythmias in the setting of myocardial ischemia, mitral valve prolapse, and other cardiovascular conditions (see Chapter 17, Antiarrhythmic Drugs).\(^{218-225}\) A high prevalence of antibodies against beta, and beta, adrenoceptors has been observed in patients with atrial arrhythmias, ventricular arrhythmias, and conduction disturbances.\(^{226,227}\)

### Effects in Survivors of Acute MI

Beta-adrenergic blockers have beneficial effects on many determinants of myocardial ischemia (Table 5-11).\(^{58,161,228,229}\) The results of placebo-controlled, long-term treatment trials with some beta-adrenergic blocking drugs in survivors of acute MI have demonstrated a favorable effect on total mortality; cardiovascular mortality, including sudden and nonsudden cardiac deaths; and the incidence of nonfatal infarction.\(^{52,230-231}\) These beneficial results with beta-blocker therapy can be explained by both the antiarrhythmic (Table 5-11) and the anti-ischemic effects of these drugs.\(^{231,232,234-236}\) It has also been proposed that beta-adrenergic blockers could reduce the risk of atherosclerotic plaque fissure and subsequent thrombosis.\(^{240,242}\) Two nonselective beta blockers, propranolol and timolol, have been approved for reducing the risk of mortality in infarct survivors when started 5 to 28 days after an MI. Metoprolol and atenolol, 2 beta, -selective blockers, are approved for the same indication and can

---

**Table 5-10. Effects of Beta Blockers in Various Arrhythmias**

<table>
<thead>
<tr>
<th>Supraventricular</th>
<th>Ventricular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia: treat underlying disorder; excellent response to beta blocker if need to control rate (eg, ischemia, heart failure).</td>
<td>Premature ventricular contractions: good response to beta blockers, especially digitalis-induced, exercise (ischemia-induced, mitral valve prolapse, or hypertrophic cardiomyopathy).</td>
</tr>
<tr>
<td>Atrial fibrillation: Beta blockers reduce rate, rarely restore sinus rhythm, may be useful in combination with digoxin and/or verapamil and diltiazem.</td>
<td>Ventricular tachycardia: effective as quinidine, most effective in digitalis toxicity or exercise (ischemia)-induced.</td>
</tr>
<tr>
<td>Atrial flutter: Beta blockers reduce rate, sometimes restore sinus rhythm.</td>
<td>Ventricular fibrillation: electrical defibrillation is treatment of choice. Beta blockers can be used to prevent recurrence in cases of excess digitalis or sympathomimetic amines; appear to be effective in reducing the incidence of ventricular fibrillation and sudden death post–myocardial infarction.</td>
</tr>
</tbody>
</table>

both be used intravenously in the hyperacute phase of a MI. Oral carvedilol given twice daily was approved for use in survivors of acute MI with clinical evidence of LV dysfunction with or without symptoms of HF who are also on standard treatments and are receiving ACE inhibition and other contemporary post-MI treatments.243 Carvedilol is now available as a once-daily sustained-release formulation.244

Beta blockers have also been suggested as a treatment for reducing the extent of myocardial injury,245,246 and mortality during the hyperacute phase of MI,247,248 but their exact role in this situation remains unclear.249 Intravenous and oral atenolol has been shown to be effective in causing a modest reduction in early mortality when given during the hyperacute phase of acute MI.248 Atenolol and metoprolol reduce early infarct mortality by 15%,247,248 an effect that may be improved upon when beta-adrenergic blockade is combined with acute thrombolytic therapy.250 Metoprolol and atenolol combined with acute thrombolysis has been evaluated in the TIMI-II and GUSTO studies.250 Immediate beta-blocker therapy given to patients with acute MI who have received tissue transminogen activator (t-PA) is associated with a significant reduction in the frequency of intracranial hemorrhage.251 Despite all the evidence showing that beta blockers are beneficial in patients surviving MI,252–255 they are considerably underused in clinical practice. Beta blocker use post-infarction is part of the national quality indicators for hospitals in the United States.

Recent studies have shown the cost-effectiveness of using beta blockers in a larger percentage of the postinfarction population,256 including the elderly, diabetics, and patients with mild to moderate chronic obstructive pulmonary disease.257–265 Beta blockers have also been shown to be effective in patients following coronary revascularization and in those with diminished ejection fraction post–MI.266,267 Attempts should be made to increase beta-blocker use in clinical practice.268–270 Treatment with lower doses of beta blockers than those used in large clinical trials is associated with at least as great a reduction in mortality as treatment with higher doses. In patients surviving an MI in whom larger doses of beta blockers might be contraindicated, the use of smaller doses should be encouraged.271 Studies have examined the use of beta blockade by paramedics, before hospital admission, with some benefit observed.272

*Silent* Myocardial Ischemia

In recent years, investigators have observed that not all myocardial ischemic episodes detected by electrocardiography (ECG) are associated with detectable symptoms.273 Positron emission tomography imaging techniques have validated the theory that these silent ischemic episodes are indicative of true myocardial ischemia.274 Compared to symptomatic ischemia, the prognostic importance of silent myocardial ischemia occurring at rest and/or during exercise has not been determined. Beta blockers are as successful in reducing the frequency of silent ischemic episodes detected by ambulatory ECG monitoring as they are in reducing the frequency of painful ischemic events.273–279

**Congestive Cardiomyopathy**

The ability of intravenous sympathomimetic amines to affect an acute increase in myocardial contractility through stimulation of the beta-adrenergic receptor had prompted the hope that the use of oral catecholamine analogues could provide long-term benefit for patients with severe HF. However, recent observations concerning the regulation of the myocardial adrenergic receptor and abnormalities of beta-receptor–mediated stimulation of the failing myocardium have caused a critical reappraisal of the scientific validity of sustained beta-adrenergic-receptor stimulation.270–273 Evidence suggests that beta-receptor blockade may, when tolerated, have a favorable effect on the underlying cardiomyopathic process,286,287 perhaps by upregulation and preservation of beta-receptor signaling.288

It has been shown that excess catecholamine stimulation of beta receptors can result in receptor desensitization by the phosphorylation of inhibitory beta-adrenergic-receptor kinases with beta-receptor uncoupling from

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**Table 5-11. Possible Mechanisms by Which Beta Blockers Protect the Ischemic Myocardium**

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in myocardial consumption, heart rate, blood pressure, and myocardial contractility.</td>
</tr>
<tr>
<td>Augmentation of coronary blood flow; increase in diastolic perfusion time by reducing heart rate, augmentation of collateral blood flow, and coronary flow reserve, and redistribution of blood flow to ischemic areas.</td>
</tr>
<tr>
<td>Prevention of attenuation of atherosclerotic plaque, rupture, and subsequent coronary thrombosis.</td>
</tr>
<tr>
<td>Alterations in myocardial substrate utilization.</td>
</tr>
<tr>
<td>Decrease in microvascular damage.</td>
</tr>
<tr>
<td>Stabilization of cell and lysosomal membranes.</td>
</tr>
<tr>
<td>Shift of oxyhemoglobin dissociation curve to the right.</td>
</tr>
<tr>
<td>Inhibition of platelet aggregation.</td>
</tr>
<tr>
<td>Inhibition of myocardial apoptosis, allowing natural cell regeneration to occur.</td>
</tr>
</tbody>
</table>

---

“Silent” Myocardial Ischemia

In recent years, investigators have observed that not all myocardial ischemic episodes detected by electrocardiography (ECG) are associated with detectable symptoms.273 Positron emission tomography imaging techniques have validated the theory that these silent ischemic episodes are indicative of true myocardial ischemia.274 Compared to symptomatic ischemia, the prognostic importance of silent myocardial ischemia occurring at rest and/or during exercise has not been determined. Beta blockers are as successful in reducing the frequency of silent ischemic episodes detected by ambulatory ECG monitoring as they are in reducing the frequency of painful ischemic events.273–279

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It has been shown that excess catecholamine stimulation of beta receptors can result in receptor desensitization by the phosphorylation of inhibitory beta-adrenergic-receptor kinases with beta-receptor uncoupling from
Gs due to beta-arrestin activity. In addition, agonist anti-beta-adrenergic-receptor autoantibodies have been described in patients with HF, which can also cause receptor desensitization.

Enhanced sympathetic activation is seen consistently in patients with CHF and is associated with decreased exercise tolerance, hemodynamic abnormalities, and increased mortality. Increases in sympathetic tone can potentiate the patient's renin-angiotensin system, leading to increased salt and water retention, arterial and venous constriction, and increments in ventricular preload and afterload. Catecholamines in excess can increase heart rate and cause coronary vasoconstriction. They can adversely influence myocardial contractility while causing myocyte hypertrophy and vascular remodeling. Catecholamines can stimulate growth and provoke oxidative stress in terminally differentiated cardiac cells; these 2 factors can trigger the process of programmed cell death known as apoptosis. Finally, they can increase the risk of sudden death in patients with CHF by adversely influencing the electrophysiologic properties of the failing heart.

Controlled trials over the last 25 years with several different beta blockers in patients with both ischemic and nonischemic cardiomyopathy have shown that these drugs can improve symptoms, ventricular function, and functional capacity while reducing the need for hospitalization (Table 5-12). A series of placebo-controlled clinical trials with the alpha-beta blocker carvedilol showed a morbidity and mortality benefit in patients with NYHA class II-IV HF when the drug was used in addition to diuretics, ACE inhibitors, and digoxin. Carvedilol has also been studied in symptomatic patients with low ejection fraction after an acute MI, with a benefit shown on

Table 5-12. Beta-Blocker Therapy in Randomized Placebo-Controlled Clinical Trials in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo (% of events)</th>
<th>β-Blocker Therapy (% of events)</th>
<th>Risk Reduction (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol HF Program</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>7.5</td>
<td>2.6</td>
<td>65</td>
<td>.0001</td>
</tr>
<tr>
<td>Sudden death</td>
<td>3.8</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to HF</td>
<td>3.3</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for CV Causes</td>
<td>19.6</td>
<td>14.1</td>
<td>27</td>
<td>.036</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>17.3</td>
<td>11.8</td>
<td>34</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CV mortality</td>
<td>12</td>
<td>9</td>
<td>29</td>
<td>.0049</td>
</tr>
<tr>
<td>Sudden death</td>
<td>6.3</td>
<td>3.6</td>
<td>44</td>
<td>.0011</td>
</tr>
<tr>
<td>All-cause hospital admission</td>
<td>39</td>
<td>33</td>
<td>20</td>
<td>.0006</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>11</td>
<td>7.2</td>
<td>34</td>
<td>0.0062</td>
</tr>
<tr>
<td>CV mortality</td>
<td>6.4</td>
<td>10.1</td>
<td>38</td>
<td>0.0063</td>
</tr>
<tr>
<td>Sudden death</td>
<td>3.9</td>
<td>6.6</td>
<td>41</td>
<td>0.0002</td>
</tr>
<tr>
<td>Death due to worsening HF</td>
<td>1.5</td>
<td>2.9</td>
<td>49</td>
<td>0.0023</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>16.8</td>
<td>11.2</td>
<td>35</td>
<td>.0014</td>
</tr>
<tr>
<td>SENIORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality or CV hospitalization</td>
<td>35.3</td>
<td>31.1</td>
<td>14</td>
<td>.039</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>18.1</td>
<td>15.8</td>
<td>12</td>
<td>.21</td>
</tr>
<tr>
<td>CV mortality</td>
<td>13.7</td>
<td>11.5</td>
<td>16</td>
<td>.17</td>
</tr>
<tr>
<td>Sudden death</td>
<td>6.6</td>
<td>4.1</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Trial; SENIORS = Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure

all-cause and cardiovascular mortality and recurrent non-
fatal MI. Both the short-acting (twice daily) and sus-
tained-release formulations are approved for clinical use
in patients with NYHA class II-IV HF having had MI. It
has been shown that patients treated with inotropic ther-
apy (milrinone) can be titrated on carvedilol after reaching
a stable state, with subsequent weaning of the inotrope.

Placebo-controlled studies have also been done show-
ing the benefit of using the beta-1-selective blockers, meto-
prolol (sustained-release) and bisoprolol, in patients with
NYHA class II-III HF. Sustained-release metoprolol is
approved as a once-daily treatment for patients with con-
gestive cardiomyopathy. A trial with the beta blocker-
vasodilator bucindolol showed less benefit than that seen
with other beta blockers used to treat CHF; demonstrating that all beta blockers may not be interchangeable
for this indication.

The Carvedilol or Metoprolol European Trial (COM-
ET) was the only head-to-head comparison of the effects
of 2 beta blockers in patients with congestive cardiomy-
opathy. This study compared carvedilol to metoprol-
ol in patients with mild to severe heart failure (NYHA
class II or greater). The overall mortality was significantly
higher with metoprolol. However, there were no signifi-
cant differences in the co-primary endpoints of death or
hospitalization. The results of the study have been chal-
lenged since metoprolol tartrate was used in the study
and not sustained-release metoprolol succinate, which
was approved for clinical use.

The SENIORS (Study of the Effects of Nebivolol In-
tervention on Outcome and Rehospitalization in Seniors
with Heart Failure) trial was designed to evaluate the
effects of nebivolol, a beta 1-selective-vasodilator blocker
in elderly patients (age 70 years). There was a significant
14% relative risk reduction in all-cause mortality and hos-
pitalizations with nebivolol. However, for all-cause mor-
tality alone, there was no significant difference observed
between placebo and nebivolol. In patients with HF and
normal ejection fraction, there were similar findings as in
between placebo and nebivolol. In patients with HF and
preserved LV function. It has been shown by invasive and
noninvasive methods that propranolol can improve left
ventricular function in this condition. The drug also
proves effective in the therapy of patients with hypertro-
phic cardiomyopathy and idiopathic hypertrophic sub-
aortic stenosis. These drugs are useful in controlling
the symptoms of dyspnea, angina, and syncope. Beta
blockers have also been shown to lower the intraventricu-
lar pressure gradient both at rest and with exercise.

The outflow pressure gradient is not the only abnor-
mality in hypertrophic cardiomyopathy; more impor-
tant is the loss of ventricular adherence, which impedes
normal LV function. It has been shown by invasive and
noninvasive methods that propranolol can improve left
ventricular function in this condition. The drug also
produces favorable changes in ventricular adherence
while it relieves symptoms. Propranolol has been ap-
proved for this condition and may be combined with the
calcium-entry blocker verapamil in patients who do not
respond to the beta blocker alone.

The salutary hemodynamic and symptomatic effects
produced by propranolol derive from its inhibition of sym-
pathetic stimulation of the heart. There is no evidence
that the drug alters the primary cardiomyopathic process;
many patients remain in or return to their severely symp-
tomatic state, and some die despite its administration.

Mitra Valve Prolapse

This auscultatory clinical complex, characterized on
physical exam by a nonejection systolic click, a late sys-
tolic murmur, or a midsystolic click followed by a late sys-
tolic murmur, has been studied extensively over the past
35 years. Atypical chest pain, malignant arrhythmias,
and nonspecific ST- and T-wave abnormalities have been
observed with this condition. By decreasing sympathetic
tone, beta-adrenergic blockers have been shown to be
useful for relieving the chest pains and palpitations that
many of these patients experience and for reducing the
incidence of life-threatening arrhythmias and other asso-
ciated ECG abnormalities.
Dissecting Aneurysms

Beta-adrenergic blockers play a major role in the treatment of patients with acute dissection of the aorta. During the hyperacute phase of dissection, beta blockers such as propranolol reduce the force and velocity of myocardial contraction (dP/dt) and hence the progression of the dissecting hematoma. Propranolol is often used with other antihypertensive vasodilator drugs, which may cause reflex tachycardia and increases in cardiac output, factors that can aggravate the dissection process. Initially, propranolol is administered intravenously to reduce the heart rate to < 60 beats per minute. Once a patient is stabilized and long-term medical management is contemplated, the patient should be maintained on an oral beta blocker to prevent recurrence. The oral beta blocker labetalol in intravenous form has been used as a monotherapy to treat acute aortic dissection.

Beta blockers with and without ACE inhibitors may also reduce the incidence of dissection and rupture in high-risk individuals prone to this complication (eg, Marfan’s syndrome, Ehlers-Danlos syndrome).

Tetralogy of Fallot

By reducing the effects of increased adrenergic tone on the right ventricular infundibulum in tetralogy of Fallot, beta blockers have been shown to be useful for the treatment of severe hypoxic spells and hypercyanotic attacks. With chronic use, these drugs have also been shown to prevent prolonged hypoxic spells. These drugs should be looked upon as palliative only, as definitive surgical repair of this condition is usually required.

QT Interval–Prolongation Syndrome

The syndrome of ECG QT-interval prolongation is usually a congenital condition associated with deafness, syncope, and sudden death. Abnormalities in sympathetic nervous system functioning in the heart have been proposed as explanations for the electrophysiologic aberrations seen in these patients. Propranolol and other beta blockers appear to be the most effective drugs for the treatment of this syndrome. They reduce the frequency of syncopal episodes in most patients and may prevent sudden death. These drugs will reduce the ECG QT interval. Patients not responding to beta blockers should be candidates for implantable defibrillators.

Regression of Left Ventricular Hypertrophy

LV hypertrophy induced by systemic hypertension is an independent risk factor for cardiovascular mortality and morbidity. Regression of LV hypertrophy with drug therapy is feasible and may improve patient outcome. Beta-adrenergic blockers can cause regression of LV hypertrophy, as determined by echocardiography, with or without an associated reduction in blood pressure.
Atherogenesis
Beta blockers may have a direct antiatherosclerotic effect at a dose well below commonly prescribed regimens.\textsuperscript{350,351} The mechanisms underlying this beta-blocker benefit is not known. An effect on reactive oxygen species has been proposed.\textsuperscript{352} Recently it was shown that chronic propranolol treatment did not influence the course of patients having abdominal aortic aneurysms.\textsuperscript{353}

Syncope
Vasovagal syncope is the most common form of syncope observed. Upright tilt-table testing with isoproterenol can help differentiate vasovagal syncope from other forms.\textsuperscript{354} Beta blockers, including those with partial agonism, have been shown to be useful for both relieving symptoms and normalizing abnormal tilt-table tests in patients with syncope; however, some studies have shown no benefit with this treatment.\textsuperscript{354–356} The mechanism for benefit with beta blockers may be an interruption of the Bezold-Jarisch reflex or an enhancement of peripheral vasoconstriction by blockade of beta,\textsubscript{2}-adrenergic receptors.\textsuperscript{357}

Myocardial Protection during Surgery
Beta-adrenergic blockers will reduce perioperative ischemia, and studies published in the 1990s suggested that their routine administration before surgery could provide protection against perioperative cardiovascular complications.\textsuperscript{358–360} Based on these early studies, several national organizations endorsed the perioperative use of beta blockers as a best practice in certain patients.\textsuperscript{361,362} However, more recent evidence has been accumulating to suggest that routine use of beta blockers may not benefit as many patients as was once hoped and may actually cause harm in some individuals.\textsuperscript{358,363–365} The benefit of beta blockers may be only in high-risk patients undergoing high-risk surgery. Currently the best evidence supports their use in 2 patient groups: patients undergoing vascular surgery who have known ischemic heart disease or multiple risk factors for it, and patients who are already receiving beta blockers for cardiovascular conditions.\textsuperscript{358}

The results of the Perioperative Ischemic Evaluation (POISE) Trial suggested that beta blockers should only be administered in the immediate preoperative period with great caution, after ensuring that the patient is clinically stable, and without evidence of infection, hypovolemia, anemia, or other conditions that would make heart rate titration misleading or use of the drugs harmful.\textsuperscript{363} The criticism of POISE was the fact that a high metoprolol extended-release dose was used in many patients who had never received beta blockers.\textsuperscript{363} When feasible, beta,\textsubscript{1}-selective blockers should be started a month before noncardiac surgery, titrated to a heart rate of 60 bpm, and continued for 1 month. If the drug is then to be discontinued, it should be withdrawn gradually.\textsuperscript{363,366}

Noncardiovascular Applications
Since the introduction of beta blockers over 50 years ago, their therapeutic use has extended well beyond cardiovascular disorders. The drugs have been approved for the prevention and treatment of migraine headache (propranolol),\textsuperscript{317} essential tremor (propranolol),\textsuperscript{318} reducing intraocular pressure (topical timolol, betaxolol, carteolol),\textsuperscript{367} thyrotoxicosis (propranolol),\textsuperscript{219} and pheochromocytoma (propranolol).\textsuperscript{219} These drugs have also been used to treat alcohol withdrawal,\textsuperscript{118} to prevent bleeding and mortality in patients with esophageal varices,\textsuperscript{368} and to relieve the symptoms of situational anxiety (stage fright).\textsuperscript{119} The drugs are ineffective in preventing varices\textsuperscript{368} and can worsen exercise tolerance and pulmonary hemodynamics in patients with portopulmonary hypertension.\textsuperscript{356} Beta blockers may reduce the risk of exacerbation and improve survival in patients with COPD.\textsuperscript{370a} Recently, beta blockers have been used for reducing aberrant behaviors in children with autism.\textsuperscript{371} In combination with diuretics, they reduce the risk of fractures in elderly patients.\textsuperscript{372} In experimental studies, they have been shown to have anti-inflammatory actions and survival benefits in sepsis.\textsuperscript{372a}

Adverse Effects of Beta Blockers
Evaluation of adverse effects is complex because of the use of different definitions of adverse effects, the kinds of patients studied, study design features, and different methods of ascertaining and reporting adverse effects from study to study.\textsuperscript{373–375} Overall, the types and frequencies of adverse effects attributed to various beta-blocker compounds appear to be similar.\textsuperscript{373,375} The adverse-effect profiles resemble those seen with concurrent placebo treatments, attesting to the remarkable safety margin of the beta blockers.\textsuperscript{373}

Adverse effects fall into 2 categories: (1) those from known pharmacologic consequences of beta-adrenoceptor blockade, and (2) other reactions apart from beta-adrenoceptor blockade.

The first type includes asthma, fatigue, heart failure, hypoglycemia, bradycardia and heart block, intermittent claudication, and Raynaud’s phenomenon. The incidence of these adverse effects varies with the beta blocker used.\textsuperscript{38,374,375}

Adverse effects of the second category are rare. They include an unusual oculomucocutaneous reaction and the possibility of carcinogenesis.\textsuperscript{46,374,375}

Adverse Cardiac Effects Related to Beta-Adrenoceptor Blockade

Congestive Heart Failure
Despite benefit in many patients with congestive cardiomyopathy related to systolic dysfunction, the blockade of beta receptors may cause CHF in an enlarged heart with impaired myocardial function where excessive sympa-
thetatic drive is essential to maintain the myocardium on a compensated Starling curve and where LV stroke volume is restricted and tachycardia is needed to maintain cardiac output.

Thus, any beta-blocking drug may be associated with the development or worsening of HF. Furthermore, HF may also be augmented by increases in peripheral vascular resistance produced by nonselective agents (eg, propranolol, timolol, sotalol). It has been claimed that beta blockers with ISA, alpha-blocking activity, and direct vasodilatory activity are better in preserving LV function and less likely to precipitate HF. In patients with impaired myocardial function who require beta-blocking agents, physicians may prescribe digoxin, ACE inhibitors, and diuretics.

The results of a recent study (Beta Blocker Continuation Versus Interruption in Patients with Congestive Heart Failure Hospitalized for Decompensated Episode [B-CONVINCED]) found that patients with acute HF exacerbation should have their beta blocker maintained.377

**Sinus Node Dysfunction and Atrioventricular Conduction Delay**

Slowing of the resting heart rate is a normal response to treatment with beta-blocking drugs with and without ISA. Healthy persons can sustain a heart rate of 40 to 50 beats per minute without disability unless there is clinical evidence of HF. Drugs with ISA, alpha-blocking activity, and direct vasodilatory activity do not lower the resting heart rate to the same degree as propranolol, but all beta-blocking drugs are contraindicated (unless an artificial pacemaker is present) in patients with sick sinus syndrome.375

If there is a partial or complete AV conduction defect, the use of a beta-blocking drug may lead to a serious bradyarrhythmia. The risk of AV impairment may be less with beta blockers that have ISA.379

**Overdosage**

Suicide attempts and accidental overdosing with beta blockers are being described with increasing frequency. Since beta-adrenergic blockers are competitive pharmacologic antagonists, their life-threatening effects (bradycardia and myocardial and ventilatory failure) can be overcome with an immediate infusion of beta-agonist agents such as isoproterenol and dobutamine. In situations where catecholamines are not effective, intravenous glucagon, amrinone, or milrinone have been used.

Close monitoring of cardiorespiratory function is necessary for at least 24 hours after the patient responds to therapy. Patients who recover usually have no long-term sequelae; however, they should be observed for the cardiac signs of sudden beta-blocker withdrawal.375

**Beta-Adrenergic Blocker Withdrawal**

After abrupt cessation of chronic beta-blocker therapy, exacerbation of angina and, in some cases, acute MI and death have been reported. Observations made in multiple double-blind randomized trials have confirmed the reality of a propranolol withdrawal reaction. The mechanism for this reaction is unclear. There is some evidence that the withdrawal phenomenon may be due to the generation of increased beta adrenoceptor sensitivity during the period of beta-adrenoceptor blockade. When the beta-adrenoceptor blocker is then withdrawn, the sensitized beta-receptor population readily results in excessive beta-receptor stimulation from catecholamines, which is clinically important when the delivery and use of oxygen are finely balanced, as occurs in ischemic heart disease. Other suggested mechanisms for the withdrawal phenomenon include heightened platelet aggregability, an elevation in thyroid hormone activity, and an increase in circulating catecholamines. A beta-blocker withdrawal phenomenon with an increased risk for death has also been described in patients with HF who are withdrawn from beta blockers.

**Noncardiac Adverse Effects Related to Beta-Adrenergic Blockade**

**Effect on Ventilatory Function**

The bronchodilatory effects of catecholamines on the bronchial beta1-adrenoceptors are inhibited by nonselective beta blockers (eg, propranolol, nadolol). Beta-blocking compounds with partial agonist activity, beta1-selectivity, and alpha-adrenergic blocking actions are less likely to increase airways resistance in asthmatics. Beta1-selectivity, however, is not absolute and may be lost with high therapeutic doses, as shown with atenolol and metoprolol. It is possible in treating asthma to use a beta2-selective agonist (such as albuterol) in certain patients with concomitant low-dose beta1-selective blocker treatment. In general, all beta blockers should be avoided in patients with active bronchospastic disease. However, benefit has been shown with these drugs in patients with COPD.

**Peripheral Vascular Effects (Raynaud’s Phenomenon)**

Cold extremities and absent pulses have been reported more frequently in patients receiving beta blockers for hypertension than in those receiving methyldopa. Among the beta blockers, the incidence was highest with propranolol and lower with drugs having beta1-selectivity or ISA. In some instances, vascular compromise has been severe enough to cause cyanosis and impending gangrene. This is probably due to the reduction in cardiac output and blockade of beta1-adrenoceptor-mediated skeletal muscle vasodilation, resulting in unopposed beta-adrenoceptor vasoconstriction. Beta-blocking drugs with beta2-selectivity, partial agonist activity or direct vasodilatory activity will not affect peripheral vessels to the same degree as does propranolol.

Raynaud’s phenomenon is one of the more common adverse effects of propranolol treatment. It is more
troublesome with propranolol than with metoprolol, atenolol, or pindolol, probably because of the beta₂-blocking properties of propranolol. Patients with peripheral vascular disease who suffer from intermittent claudication occasionally report worsening of the claudication when treated with beta-blocking drugs.\textsuperscript{389,390} Whether drugs with beta₁-selectivity, partial agonist activity, or vasodilatory activity can protect against this adverse reaction has not been determined.\textsuperscript{391}

Hypoglycemia and Hyperglycemia

Several authors have described severe hypoglycemic reactions during therapy with beta-adrenergic blocking drugs.\textsuperscript{392} Some of the patients affected were insulin-dependent diabetics while others were nondiabetic. Studies of resting normal volunteers have demonstrated that propranolol produces no alteration in blood glucose values,\textsuperscript{393} although the hyperglycemic response to exercise is blunted. Beta blockers can increase the incidence of type 2 diabetes mellitus.\textsuperscript{113} Weight gain (average 1.2 kg) and insulin resistance have been reported with chronic beta-blocker use.\textsuperscript{394} The effects of beta blockers on hyperglycemia appear to be less with those drugs having partial agonist and alpha-adrenergic blocking activity.

The enhancement of insulin-induced hypoglycemia and its hemodynamic consequences may be less with beta₁-selective agents (where there is no blocking effect on beta₂ receptors) and agents with ISA (which may stimulate beta₂ receptors).\textsuperscript{395}

There is also marked diminution in the clinical manifestations of the catecholamine discharge induced by hypoglycemia (tachycardia).\textsuperscript{396} These findings suggest that beta blockers interfere with compensatory responses to hypoglycemia and can mask certain “warning signs” of this condition. Other hypoglycemic reactions, such as diaphoresis, are not affected by beta-adrenergic blockade.

Hyperlipidemia

Nonselective beta-blocking agents can raise triglycerides and reduce high-density lipoprotein cholesterol.\textsuperscript{397} This effect may not be seen with agents having partial agonism or alpha-blocking activity.\textsuperscript{398}

Central Nervous System Effects

Dreams, hallucinations, insomnia, and depression can occur during therapy with beta blockers.\textsuperscript{119} These symptoms provide evidence of drug entry into the CNS and may be more common with the highly lipid-soluble beta blockers (propranolol, metoprolol), which presumably penetrate the CNS better. It has been claimed that beta blockers with less lipid-solubility (atenolol, nadolol) cause fewer CNS adverse effects.\textsuperscript{54,65} This claim is intriguing, but its validity has not been corroborated by other extensive clinical experiences.\textsuperscript{39,100,399}

Miscellaneous Adverse Effects

Diarrhea, nausea, gastric pain, constipation, and flatulence have been noted occasionally with all beta blockers (2%-11% of patients).\textsuperscript{400} Hematologic reactions are rare. Rare cases of purpura and agranulocytosis have been described with propranolol.\textsuperscript{401} Beta blocker use early in pregnancy has been associated with fetal growth retardation (see Appendix 3).\textsuperscript{402}

A devastating blood pressure rebound effect has been described in patients who discontinued clonidine while being treated with nonselective beta-blocking agents. The mechanism for this may be related to an increase in circulating catecholamines and an increase in peripheral vascular resistance.\textsuperscript{403} Whether beta₁-selective or partial agonist beta blockers have similar effects following clonidine withdrawal has not been determined. This has not been a problem with labetalol.\textsuperscript{404}

Adverse Effects Unrelated to Beta-Adrenoceptor Blockade

Oculomucocutaneous Syndrome

A characteristic immune reaction, the oculomucocutaneous syndrome—affecting one or both eyes, mucous and serous membranes, and the skin, often in association with a positive antinuclear factor—had been reported in patients treated with practolol, and has led to the curtailment of its clinical use.\textsuperscript{364,405} Close attention has been focused on this syndrome because of fears that other beta-adrenoceptor blocking drugs may be associated with this syndrome.

Drug–Drug Interactions

Beta blockers are commonly employed, and the list of commonly used drugs with which they can interact is extensive (Table 5-14; see Chapter 31, Cardiovascular Drug–Drug Interactions).\textsuperscript{406,407} The majority of the reported interactions have been associated with propranolol, the best-studied beta blocker, and may not necessarily apply to other drugs in this class.

How to Choose a Beta Blocker

The various beta-blocking compounds given in adequate dosage appear to have comparable antihypertensive, antiarrhythmic, and antianginal effects. Therefore, the beta-blocking drug of choice in an individual patient is determined by the pharmacodynamic and pharmacokinetic differences between the drugs, in conjunction with the patient’s concomitant medical conditions.\textsuperscript{48,49,66}

Note: References for this chapter can be found here: www.cvpcct3.com
Table 5-14. Drug Interactions That May Occur with Beta-Adrenoceptor–Blocking Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetic Interactions</th>
<th>Pharmacodynamic Interactions</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>None</td>
<td>Enhanced blood pressure effects and bronchospasm</td>
<td>Monitor response.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Enhanced first-pass hepatic degradation</td>
<td>None</td>
<td>May need increased doses of lipid-soluble agents.</td>
</tr>
<tr>
<td>α-Adrenergic blockers</td>
<td>Increased risk for first-dose hypotension</td>
<td></td>
<td>Use with caution.</td>
</tr>
<tr>
<td>Aluminum hydroxide gel</td>
<td>Decreased β-blocker absorption</td>
<td>None</td>
<td>Clinical efficacy rarely altered.</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Mutual inhibition</td>
<td>Enhanced negative chronotropic activity</td>
<td>Observe patient’s response.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>None</td>
<td></td>
<td>Monitor response.</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Impaired GI absorption leading to decreased β-blocker bioavailability</td>
<td></td>
<td>May need to increase β-blocker dose.</td>
</tr>
<tr>
<td>Angiotensin II–receptor blockers (losartan)</td>
<td>None</td>
<td>Enhanced blood pressure effects and bronchospasm</td>
<td>Monitor response.</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>Both enhanced and blunted responses seen</td>
<td>None</td>
<td>Monitor for altered diabetic response.</td>
</tr>
<tr>
<td>Calcium</td>
<td>Decreases β-blocker absorption</td>
<td></td>
<td>May need to increase β-blocker dose.</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>Decreased hepatic clearance of lipid-soluble and water soluble β blockers; Decreased clearance of calcium blockers</td>
<td>Potentiation of AV nodal negative inotropic and hypotensive responses</td>
<td>Avoid use if possible, although few patients show ill effects.</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Decreased hepatic clearance of lipid soluble β blockers</td>
<td>None</td>
<td>Combination should be used with caution.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>None</td>
<td>Nonselective agents exacerbate clonidine withdrawal phenomenon</td>
<td>Use only β₁-selective agents or labetalol.</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Diazepam metabolism reduced</td>
<td></td>
<td>Observe patient’s response.</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
<td>None</td>
<td>Potentiation of bradycardic and AV blocks</td>
<td>Observe patient’s response; interactions may benefit angina patients with abnormal ventricular function.</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>None</td>
<td>Severe hypertension and bradycardia</td>
<td>Administer epinephrine cautiously; cardioselective β blocker may be safer.</td>
</tr>
</tbody>
</table>

(Table 5-14 continued next page)
Table 5-14. Drug Interactions That May Occur with Beta-Adrenoceptor–Blocking Drugs (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetic Interactions</th>
<th>Pharmacodynamic Interactions</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergot alkaloids</td>
<td>None</td>
<td>Severe hypertension and peripheral artery hyperperfusion have been seen, though β blockers are commonly coadministered.</td>
<td>Observe patient’s response; few patients show ill effects.</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Decreased hepatic clearance of propranolol</td>
<td></td>
<td>Use with caution.</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Enhanced clearance of lipid-soluble β-blockers</td>
<td>None</td>
<td>Monitor for reduced soluble β-blockers response.</td>
</tr>
<tr>
<td>Halofenate</td>
<td></td>
<td></td>
<td>Observe for impaired response to β blockade.</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Decreased hepatic clearance of lipid-soluble β blockers</td>
<td>Enhanced hypotensive response</td>
<td>Cautious coadministration.</td>
</tr>
<tr>
<td>Indomethacin and Ibuprofen</td>
<td>None</td>
<td>Reduced efficacy in treatment of hypertension</td>
<td>Observe patient’s response.</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>None</td>
<td>Cancels pharmacologic effect</td>
<td>Avoid concurrent use or choose selective β₁ blocker.</td>
</tr>
<tr>
<td>Levodopa</td>
<td></td>
<td>Antagonism of hypotensive and positive inotropic effects of levodopa</td>
<td>Monitor for altered response; interaction may have favorable results.</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Decreased hepatic clearance of lidocaine by lipid-soluble β blockers</td>
<td>Enhanced lidocaine toxicity</td>
<td>Combination should be used with caution; use lower doses of lidocaine.</td>
</tr>
<tr>
<td>Methyldopa</td>
<td></td>
<td>Hypertension during stress</td>
<td>Monitor for hypertensive episodes.</td>
</tr>
<tr>
<td>Monoamine</td>
<td>Uncertain</td>
<td>Enhanced hypotension</td>
<td>Manufacturer of propranol oxidase inhibitors considers concurrent use contraindicated.</td>
</tr>
<tr>
<td>Nitrites</td>
<td>None</td>
<td>Enhanced hypotension</td>
<td>Monitor response.</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>None</td>
<td>None</td>
<td>None.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Increased hepatic metabolism of β blockers</td>
<td></td>
<td>May need to increase lipid soluble β-blocker dose.</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Increased phenothiazine and β-blocker blood levels</td>
<td>Additive hypotensive response</td>
<td>Monitor for altered response; especially with high doses of phenothiazine.</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td></td>
<td>Severe hypertensive reaction</td>
<td>Avoid use, especially in hypertension controlled by both methyldopa and β blockers.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td>Additive ventricular depressive effects</td>
<td>Use with caution.</td>
</tr>
<tr>
<td>Drug</td>
<td>Pharmacokinetic Interactions</td>
<td>Pharmacodynamic Interactions</td>
<td>Precautions</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Reserpine</td>
<td></td>
<td>Depression, possible enhanced sensitivity to β-adrenergic blockade</td>
<td>Monitor closely.</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Not marked</td>
<td>None</td>
<td>Observe response.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Enhanced first-pass metabolism</td>
<td>None</td>
<td>May need to increase dose of lipid-soluble β blockers.</td>
</tr>
<tr>
<td>Sulindac and Naproxen</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td></td>
<td>Inhibits negative inotropic and chronotropic effects; enhanced hypotension</td>
<td>Use with caution with sotalol because of additive effects on ECG QT interval.</td>
</tr>
<tr>
<td>Tubucuraine</td>
<td></td>
<td>Enhanced neuromuscular blockade</td>
<td>Observe response in surgical patients, especially after high doses of propranolol.</td>
</tr>
<tr>
<td>Type I Anti-Arrhythmics</td>
<td>Propafenone and quinidine decrease clearance of lipid-soluble β blockers</td>
<td>Disopyramide is a potent negative inotropic and chronotropic agent.</td>
<td>Cautious coprescription; use with sotalol can be dangerous because of additive effects on ECG QT interval.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Decreased clearance of warfarin</td>
<td>None</td>
<td>Monitor response.</td>
</tr>
</tbody>
</table>

The sympathetic nervous system is a major control mechanism for blood pressure and cardiac function. The system is composed of reflex feedback loops linking the carotid baroreceptors and low-pressure cardiopulmonary receptors to integrative sites in the hind brain. Efferent pathways emerge from the brain becoming spinal cord pathways of preganglionic fibers. These fibers end in the cholinergic synapses of paraspinal ganglia from which emanate postganglionic fibers that terminate in vascular or cardiac synapses. Postganglionic sympathetic neurons release norepinephrine from intraneuronal storage sites to alpha- or beta-adrenergic receptors. The adrenal medulla is a ganglion-like organ receiving preganglionic cholinergic fibers and releasing epinephrine directly to the circulation.

The exact role of the sympathetic nervous system in causing human hypertension remains to be fully characterized. However, drugs that diminish sympathetic function at virtually any level of its organization lower blood pressure. Some of these drugs are only of historic interest and are no longer used (such as the ganglionic blocking agents). However, other drug classes whose primary action is to reduce sympathetic function remain useful for the treatment of cardiovascular disease.1-3 This chapter focuses primarily on two groups of antiadrenergic drugs and one “orphan” drug: (1) those whose action lies primarily within the central nervous system, (2) methyl-meta-tyrosine, whose use is confined to treatment of pheochromocytoma, and (3) peripheral adrenergic neuron depletors. These drugs have been used to treat hypertension, but some have been studied in congestive heart failure or have properties useful in cardiac arrhythmia management. The use of these agents for noncardiovascular indications (mainly anesthesia and pain management) is not included in this chapter.

Reserpine is a distinct antihypertensive drug that has both central and peripheral actions. This drug was isolated from an herbal source, Rauwolfia serpentine4,5 and is orally absorbed, but can be given by intramuscular injection. Reserpine enters central and peripheral adrenergic and serotonergic neurons, where it specifically eliminates amine storage granules. This action causes irreversible depletion of neurotransmitters through intraneuronal metabolism by monoamine oxidase. Blood pressure falls due to the sustained deficit in catecholamine release. Reserpine is rapidly eliminated from the circulation; its metabolism is poorly characterized. However, because of the time necessary for regeneration of new intraneuronal amine storage granules, there is a prolonged pharmacologic effect. After administration of reserpine is stopped, it may take weeks or even months for full adrenergic neuronal functional recovery.

Reserpine is an effective antihypertensive agent but has many adverse effects. Fatigue, depression, nasal
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...congestion, and gastric hyperacidity have often been observed. Depression may occur insidiously months after initiation of treatment and can be severe, even leading to suicide. Reserpine causes salt/water retention, offsetting its antihypertensive effect (pseudotolerance), which then requires the addition of a diuretic for control of pressure. Early retrospective studies suggested that reserpine use was associated with breast cancer, but data from prospective studies have not substantiated this relationship.6

At present, reserpine is rarely used as monotherapy for hypertension. In combination with a thiazide-type diuretic, low-dose reserpine (0.1 mg daily) is highly effective for the reduction of pressure with an acceptable adverse effect experience and low cost.7 Reserpine was employed as additional therapy to low-dose chlorthalidone by some clinics in the SHEP trial,8 which demonstrated the benefit of antihypertensive drug treatment for prevention of both fatal and nonfatal cardiovascular diseases and stroke in elderly patients with isolated systolic hypertension.

**Table 6-1. Major Features of the Centrally Acting Antiadrenergic Drugs Used for Treatment of Hypertension**

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism of Action</th>
<th>Usual Dose Range, Frequency</th>
<th>More Frequent Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>Aminergic neuron depletor</td>
<td>0.05–0.1 mg</td>
<td>Sedation, fatigue, nasal congestion, depression</td>
<td>Effective at low doses with diuretic</td>
</tr>
<tr>
<td>Alpha Methyldopa</td>
<td>Mixed action: inhibits dopa decarboxylase</td>
<td>250–500 mg twice or three times daily</td>
<td>Fatigue, dizziness, positive Coombs test, hepatitis (rare)</td>
<td>Use generally limited to hypertension of pregnancy</td>
</tr>
</tbody>
</table>
| Alpha Methyldopa
erester | Same as above                        | IV: 250-500 mg q 6–8 h           | Sedation                                 | Same as above                  |
| Clonidine oral    | Alpha₂ agonist                       | 0.1–0.3 mg two to three times daily | Fatigue, dry mouth                        | Withdrawal overshoot hypertension |
| Clonidine TTS* skin patch | Alpha₂ agonist                      | One patch each week              | Skin reactions                           | May be useful for less adherent patients |
| Guanabenz         | Alpha₂ agonist                       | 4–16 mg once or twice daily      | Fatigue, dry mouth                        | Withdrawal overshoot hypertension |
| Guanfacine        | Alpha₂ agonist                       | 1–3 mg daily                     | Fatigue, dry mouth                        | Withdrawal overshoot hypertension |

*Transdermal Delivery System


...Alpha Methyldopa

Alpha methyldopa is an antiadrenergic antihypertensive agent with multiple actions at central and peripheral sites. Originally developed as an inhibitor of dopa decarboxylase, alpha methyldopa was conceived as a drug that would inhibit catecholamine synthesis (preventing the enzymatic conversion of dihydroxyphenylalanine, dopa, to dopamine by dopa decarboxylase). However, this effect was far too small to account for methyldopa’s antihypertensive effect, as dopa decarboxylase is not a rate-limiting enzyme but is present in excess in a variety of tissues. Later studies led to the recognition that alpha methyldopa could be converted to alpha methyldopamine, a false neurotransmitter but also an alpha₂ agonist, with the central and peripheral actions characteristic of the other members of this group. More recently, it has been proposed that conversion of alpha methyldopa to alpha methyl epinephrine (by N-methylation) may also participate in this drug’s hypotensive action. A single dose of alpha methyldopa is effective for only 6-8 hours, so it is usually prescribed as a twice-a-day agent.

Alpha methyldopa is an effective antihypertensive agent when given by mouth or intravenously. Prolonged treatment with alpha methyldopa is often associated with salt and water retention, reversing the antihypertensive effect (pseudotolerance), which then requires the addition of a diuretic agent. The intravenous formulation is an ester of the parent drug and has been used for hypertensive emergencies, including toxemia of pregnancy.

Adverse effects related to alpha methyldopa are fatigue, somnolence, possible memory impairment, and diminished sexual function (reduced libido and impotence). Several of these are common to other centrally...
active agents. Unique to alpha methyldopa, however, are (1) a positive Coombs test (owing to appearance of an antibody directed against red cell Rh determinants), which occasionally causes significant hemolysis, (2) a drug-induced hepatitis with fever, eosinophilia, and increased serum levels of hepatic enzymes, and (3) drug-induced lupus. The acute drug-induced hepatitis is self-limited, once alpha methyldopa is discontinued. There have been several case reports and a small series of patients with chronic hepatitis and even cirrhosis found after many years of exposure to alpha methyldopa. Whether these cases were truly drug-induced or the consequence of undetected viral hepatitis (eg, prior to the discovery of hepatitis C virus) is not certain. One drug surveillance study has reported an association of alpha methyldopa with acute pancreatitis.9

At present, alpha methyldopa is a “niche drug” as it is used as monotherapy or with hydralazine for pregnancy-related hypertension.10 In the United States, treatment of systemic hypertension with alpha methyldopa as monotherapy or in combination with a thiazide diuretic is infrequent. Beta blockers or ACEI inhibitors have virtually replaced methyldopa for management of essential hypertension. However, it should be recalled that a thiazide plus methyldopa was often used in the special clinics of the HDFP trial, a landmark outcome study that established the benefit of antihypertensive therapy for mild to moderate hypertension.21

**Alpha2-Receptor Agonists: Clonidine and Related Drugs**

The classic alpha2-receptor agonists have been well studied for their various effects. They reduce sympathetic tone within the brainstem by stimulating alpha2 receptors on neurons of vasomotor centers that inhibit outflow of impulses to spinal preganglionic neurons. In addition, they may also achieve their effect by stimulating the imidazole receptors found in the rostral ventrolateral medulla. In peripheral postganglionic noradrenergic neurons, stimulation of presynaptic alpha2 receptors diminishes release of transmitter—a feedback system for control of intrasynaptic norepinephrine concentration. Thus, alpha2 agonists reduce arterial pressure by both central and peripheral effects.12 However, at post- or nonsynaptic sites on cardiac or smooth muscle cells, alpha2 receptors may be stimulated by alpha2 agonists, causing an increase in pressure. Thus a transient rise in pressure may occur within the first hour after a single dose of clonidine is given. Thereafter, blood pressure falls to well below pretreatment levels in parallel with a demonstrable decrement in sympathetic neural function. Clonidine has been used to increase pressure in patients with severe symptomatic orthostatic hypotension during the day and hypertension at night (when supine).13 Clonidine’s pressor effect accounts for occasional reports of hypertensive crises due to massive overdose of the drug when used in anesthesia.14

The reduction of sympathetic (noradrenergic) function due to administration of alpha2-receptor agonists has been the basis of a clinically useful assessment, the clonidine suppression test. In this test, normal subjects and those with essential hypertension have a > 40% reduction in plasma norepinephrine, 2 to 3 hours after clonidine is given.15,16 Patients with pheochromocytoma have little change in plasma norepinephrine concentration after clonidine is given, providing the rationale for the clonidine suppression test as a diagnostic assessment for these tumors.17–19 Several forms of suspected neurogenic hypertension have been evaluated by the clonidine suppression test. Those with hypertension and neurovascular compression of the ventrolateral medulla oblongata (by magnetic resonance imaging) tend to have high baseline plasma norepinephrine, compared to those without vascular compression, but responses to clonidine are similar.20 In a small series of four patients with hypertension associated with lumbar sacral paraplegia, clonidine suppression of norepinephrine was > 35% in three but < 5% in one.21

Clonidine is the prototype alpha2 agonist. Guanabenz and guanfacine are similar to clonidine but have longer durations of action. Guanfacine is approved in an extended-release formulation for attention deficit disorder in adolescents.21a All the alpha2 agonists are effective antihypertensive drugs when used as monotherapy or in combination with a thiazide-type diuretic.22 Clonidine is also considered to be a treatment of choice for hypertensive urgencies because of its ease of use and relative safety.24 Both resting and exercise-induced blood pressure are decreased by these agents.25

The available alpha2 agonists have a similar pattern of adverse effects: sedation, dry mouth, and a tendency to overshoot or produce rebound hypertension on withdrawal. In sleep studies, clonidine has been found to reduce rapid-eye-movement (REM) sleep, presumably a detrimental effect, when compared with the beta blocker atenolol.26 Clonidine has also been studied in patients having sleep apnea, with inconsistent effects.27 However, a case report describes severe somnolence with respiratory acidosis associated with clonidine treatment of a patient with known sleep apnea syndrome. Yohimbine, the alpha2-receptor antagonist, was given and was thought to be beneficial in reversing the coma.28

Clonidine is the only antihypertensive drug that is available in an effective transdermal delivery system (TTS), which releases medication at a relatively constant rate over 7 days. Some studies suggest that clonidine TTS is associated with fewer adverse effects, compared with the tablets. This preparation may be useful for selected
nonadherent patients who do not like to take pills. In patients already taking clonidine tablets and who must have surgery with general anesthesia, the TTS formulation can be used to maintain control of blood pressure and avoid rebound hypertension during the perioperative period, when medications cannot be given by mouth. The TTS delivery of clonidine has demonstrated usefulness in controlling blood pressure when oral drugs could not be absorbed due to severe malabsorption. Prolonged use of the TTS patch can cause a skin reaction severe enough that a change to alternative therapy becomes necessary.

Oral clonidine has been used for rapid (2- to 4-hour) reduction of elevated pressure in emergency departments for patients with very high pressure without the full picture of a hypertensive emergency. The term “hypertensive urgency” has been applied to such patients who may present with headache or dizziness without evidence of a more severe emergency. A significant fall in pressure usually follows within a few hours of a single dose of clonidine 0.1 to 0.3 mg. Such patients are often stable and can be discharged shortly thereafter for follow-up as outpatients. Whether treatment of “hypertensive urgencies” has any benefit with regard to cardiovascular outcome remains unknown, as no relevant follow-up studies have been conducted.

Clonidine has been studied in congestive heart failure as a strategy to reduce the sympathetic activation often found in this disorder. Short-term studies suggest that reduction of sympathetic activity by clonidine may be beneficial in congestive heart failure. There is, however, evidence that presynaptic downregulation of norepinephrine release by alpha agonists is impaired in congestive heart failure, which may limit the effectiveness of clonidine as treatment. Outcome studies evaluating alpha agonists in congestive heart failure have not been reported as of this writing.

In addition, oral clonidine has been shown to be effective in controlling rapid ventricular rates in patients with new-onset atrial fibrillation with an efficacy comparable to that of standard agents.

**Imidazole Receptor Agonists, Variants of \( \alpha_2 \) Agonists**

Part of clonidine’s antihypertensive effect is due to agonism of imidazole receptors at brain-stem sympathetic control sites where imidazole receptors may be abundant. Two other antihypertensive drugs, moxonidine, and rilmenidine, are effective imidazole agonists, but also have alpha, agonism. Moxonidine and rilmenidine are then classified as imidazole agonists, somewhat distinct from clonidine, guanabenz, and guanfacine. Both moxonidine and rilmenidine are available for the treatment of hypertension in Europe but not approved for use in the United States. Moxonidine has been studied in patients with congestive heart failure, where no benefit of treatment was observed. An anti-inflammatory effect of moxonidine has been described, but its significance in outcome studies has not been established. The pattern of adverse effects reported for moxonidine and rilmenidine is similar to that reported for clonidine and the other alpha, agonists, implying that they share most relevant pharmacologic properties.

**Alpha-methyl-meta-tyrosine**

The vasoactive catecholamines are synthesis products of L-tyrosine in a sequence beginning with hydroxylation by tyrosine hydroxylase, the rate limiting enzyme for this pathway. Alpha-methyl-meta-tyrosine was developed to inhibit tyrosine hydroxylase, and thereby reduce synthesis and secretion of norepinephrine and epinephrine. Alpha-methyl-meta-tyrosine reduces catecholamine production in the central nervous system and peripheral tissues as well; its only indicated use is for inhibition of tyrosine hydroxylase in malignant or inoperable pheochromocytoma. The rarity of its use for a single indication qualifies it as an “orphan drug.” Adverse effects of alpha-methyl-meta-tyrosine are (1) significant crystalluria, as the drug is poorly soluble in urine, and (2) a pseudoparkinsonian neurologic syndrome due to depletion of central norepinephrine and dopamine.

**Peripheral Neuron Depleters**

Guanethidine, bethanidine, and guanadrel enter peripheral noradrenergic nerve terminals via amine uptake channels, where these drugs bind to norepinephrine storage vesicles, inhibiting the trans-synaptic release of transmitter. In addition, norepinephrine stores are depleted by displacement from vesicles and intraneuronal metabolism by monoamine oxidase. Both cardiac and vascular postganglionic sympathetic neurons are depleted by these drugs. Unlike reserpine, the peripheral neuron depleters do not damage or eliminate storage vesicles. Consequently, sympathetic neurotransmission returns to normal as drug concentration falls with dissociation of the drug-vesicle complex. Duration of action is longest for guanethidine, about 24 hours, and shorter for bethanidine and guanadrel, 6 to 10 hours.

The reduction of sympathetic transmitter release during treatment with the neuron depleters affects basal or resting blood pressure but is much more prominent during standing or exercise, when sympathetic activity is normally increased. Orthostatic hypotension and/or exercise weakness, even syncope, have often been observed during treatment. It is therefore necessary to monitor both
supine and standing blood pressures when these agents are used as antihypertensive therapy. Bradycardia and possibly heart block may occur as a result of diminished cardiac adrenergic transmission. Other effects of reduced peripheral sympathetic function that may be observed during treatment with these agents are (1) retrograde ejaculation, (2) loose and diarrheal like stools, and (3) loss of normal adrenergic pupillary responses. Because the peripheral neuron depletors enter the nerve terminal via norepinephrine uptake, their actions are interfered with by drugs such as cocaine or tricyclic antidepressants (eg, imipramine). This unique drug interaction accounts for the reversal of blood pressure control in patients receiving the peripheral neuron depletors when tricyclies are given concurrently.

The peripheral neuron depletors may be effective for treatment of hypertension as monotherapy or together with low-dose diuretics. This drug class has not been studied in congestive heart failure. In general, because of their prominent adverse effects and the development of far more acceptable antihypertensive drug classes, the peripheral neuron depletors have nearly disappeared from clinical use in the United States.

**Effectiveness of Central-Acting Drugs and Peripheral Neuron Depletors**

Reserpine, alpha-methyl dopa, and guanethidine were used in clinical trials of antihypertensive therapy that helped establish the "proof of principle" that such treatment could reduce cardiovascular morbidity and mortality. Most often these drugs were given together with a thiazide diuretic and other available drugs (usually hydralazine). For the historian, these reports were land-marks in the progress of cardiovascular therapeutics. For the past 30 years, the new drug classes have nearly completely replaced the centrally active drugs and peripheral neuron depletors in clinical trials and evidence-based guidelines. There are a few situations, however, that justify use of the central acting agents as described below.

**Special Considerations**

**Pregnancy**

Few antihypertensive drugs have been thoroughly studied in pregnancy. The cumulative observations with alpha methyldopa over the past decades suggest that it is a safe and effective agent for use in pregnancy-induced hypertension or for treatment of hypertensive women who become pregnant. In these settings, alpha methyldopa has the legitimacy of an extensive but largely uncontrolled clinical experience. However, the value of drug treatment for mild to moderate hypertension in pregnancy has never been fully established by randomized clinical trials. Recent systematic reviews focusing on this issue imply that the issue remains unresolved.

**Alcohol and Tobacco Withdrawal**

The cessation of alcohol intake in those who drink to excess, known as alcohol withdrawal syndrome, is a hyperadrenergic state in which tachycardia, cardiac arrhythmias, and hypertensive episodes may accompany the agitation and other signs and symptoms of the disorder. The cardiovascular features of the alcohol withdrawal syndrome are due to centrally mediated activation of the sympathetic nervous system. Alpha₂ receptors may be downregulated, since the hypotensive response to clonidine during early alcohol withdrawal is less than that of age-matched controls. Nonetheless, clonidine may be effective for reducing blood pressure and heart rate, if needed, during treatment of alcohol withdrawal. The sedative effect of clonidine is also beneficial in this situation but of lesser magnitude than that of the benzodiazepines.

Clonidine has also been used as a therapy for patients undergoing tobacco withdrawal. (See also Chapter 22, Pharmacotherapy for Smoking Cessation.)

**Patients Undergoing Surgery**

Alpha₂-adrenergic agonists have been shown to reduce mortality, myocardial infarction, and ischemia following vascular surgery. They may also have beneficial effects after cardiac surgery. Beta-adrenergic blockers should still be used as first-line drugs to minimize perioperative risk in high-risk patients with cardiovascular disease. The TTS patch for perioperative care may be useful when oral medications aren't appropriate.

**Summary of Current and Recommended Use**

Most of the approved antihypertensive drugs reviewed in this chapter will have little or no role to play in the management of the majority of patients with systemic hypertension, having been largely replaced by more recently developed drug classes. However, the long-term safety record for these drugs cannot be discounted. If hypertensive patients are well controlled on these older agents and have no related adverse effects, there is no compelling rationale for changing medication.

*Note: References for this chapter can be found here: www.cvpct3.com*
The term parasympathetic nervous system refers to those portions of the peripheral autonomic nervous system that begin as preganglionic fibers in 1 of 3 distinct regions of the central nervous system (CNS), exit the CNS in either the cranial or the sacral regions, and have their postganglionic fibers distributed in a variety of organs throughout the body. One of the 3 sites of origin for parasympathetic fibers is the midbrain. Fibers originating here join the third cranial nerve and course to the ciliary ganglion. At this ganglion they synapse, and postganglionic fibers innervate the iris and ciliary body

The second site of origin for the parasympathetic system is in the medulla. Fibers originating here join the seventh, ninth, and tenth cranial nerves to exit the CNS. These preganglionic fibers distribute in the pattern of each of these nerves. Fibers in the tenth nerve (the vagus) are distributed to ganglia associated with various visceral organs, including the heart and gastrointestinal tract.

The third and final source of parasympathetic outflow is in the sacral portion of the spinal cord. Preganglionic fibers from this site lead to connections with the bladder, bowel, and pelvic organs.

The anatomic organization of the parasympathetic system differs from that of the sympathetic system. The preganglionic fibers of the parasympathetic system extend from their sites of origin in the CNS to the end organ they are innervating. Ganglia of the parasympathetic system are relatively smaller than those of the sympathetic system, and the ganglionic fibers that emerge from these ganglia are short and localized to a specific organ. The sympathetic system has preganglionic fibers that synapse in large paravertebral ganglia and has an extensive and diffuse postganglionic network that distributes to multiple organs of the body.

Inherent in the structural organization of the parasympathetic system is the ability to act on specific organs to cause very specific responses via localized discharges. In general, where the sympathetic system tends to diffusely stimulate activity through its widespread postganglionic network, the effects of the parasympathetic system are to act on specific organs to accommodate periods of rest and recovery. The system lowers heart rate, increases gastrointestinal motility, stimulates bladder emptying, increases biliary contraction, and lowers blood pressure. The parasympathetic nervous system is exclusively cholinergic in character (using acetylcholine as a transmitter), whereas in the sympathetic system the postganglionic fibers are almost exclusively adrenergic.

Acetylcholine receptors were first recognized as being of two basic types in 1914, when Dale noted that while acetylcholine could stimulate all types of cholinergic receptors, certain effects could be blocked by the administration of atropine. Effects that are blocked by atropine are termed muscarinic effects, named after a substance isolated from the poisonous mushroom Amanita muscaria, which produces these pharmacologic properties. These effects correspond almost directly to the actions of the parasympathetic system. After atropine blockade, higher doses of acetylcholine can elicit another constellation of effects that appear to be very similar to the properties of nicotine. Dale called these nicotinic effects.

Modern investigation into the muscarinic receptors that constitute the parasympathetic system has demonstrated that there are at least 5 major subtypes of muscarinic receptors (Table 7-1). All muscarinic receptors act via G proteins. Types 1, 3, and 5 activate a G protein that in turn stimulates phospholipase C, which then hydrolyzes phosphatidyl inositol. Ultimately activation of these receptors leads to increased intracellular calcium concentration. Type 2 and 4 receptors activate a different G protein that inhibits adenylate cyclase, activates K+ channels, and may also suppress voltage controlled Ca2+ channels.
The most important subgroup of muscarinic receptors for the cardiovascular system are the M2 or cardiac receptors. Activation of these receptors and alteration of potassium transport produces the negative chronotropic and inotropic effects noted in Table 7-1. Most muscarinic receptors are located in the specialized conduction tissue of the heart, and direct innervation of the myocardium itself is sparse. Effects of muscarinic stimulation lead to a decreased rate of spontaneous depolarization of the sinoatrial (SA) node, a consequent delay in the achievement of threshold potential, and a slowing of spontaneous firing. The rate of conduction in the atrioventricular (AV) node is also decreased, and the refractory period to repetitive stimulation is prolonged. The effects of muscarinic receptors on the contractility of the ventricle are substantially less intense than on the conduction system. Blockade of cholinergic receptors produces positive inotropic effects; negative inotropic effects with cholinergic stimulation can be demonstrated in experimental situations. The clinical relevance of the aforementioned effects remains unknown. All effects of muscarinic stimulation are enhanced in the context of activation of the sympathetic nervous system. M3 receptors have vasodilatory properties. Since direct muscarinic innervation of the vasculature has not been demonstrated and acetylcholine is a local neurotransmitter, the exact role of these receptors as part of the parasympathetic nervous system is debatable. It appears that the pharmacologic effect of M3

### Table 7-1. Types of Muscarinic Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Effect</th>
<th>Mechanism</th>
<th>Agonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 (neural)</td>
<td>Cortex, hippocampus, Gastric parietal cells, Enteric ganglia</td>
<td>Memory? Gastric acid secretion GI motility</td>
<td>Stimulates phospholipase C Increased intracellular Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>Acetylcholine, Oxotremorine</td>
<td>Atropine, Pirenzepine</td>
</tr>
<tr>
<td>M2 (cardiac)</td>
<td>SA node</td>
<td>Slowed spontaneous depolarization Shortened action potential duration, decreased contractile force Decreased speed of conduction Decreased contractile force</td>
<td>Inhibition of adenylate cyclase Activation of K&lt;sup&gt;+&lt;/sup&gt; channels</td>
<td>Acetylcholine</td>
<td>Atropine, Gallamine, AF-DX116</td>
</tr>
<tr>
<td>AV node</td>
<td>Ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>Smooth muscle, Vascular endothelium, Secretory glands</td>
<td>Contraction Vasodilation Increased secretions</td>
<td>Increased phospholipase C Vasodilation via nitric oxide</td>
<td>Acetylcholine Hexahydrosiladifenidol</td>
<td>Atropine</td>
</tr>
<tr>
<td>M4</td>
<td>CNS</td>
<td>?</td>
<td>Like M2 via adenylate cyclase</td>
<td>Acetylcholine</td>
<td>?Himbacine</td>
</tr>
<tr>
<td>M5</td>
<td>CNS</td>
<td>?</td>
<td>?Increased phos-pholipase C</td>
<td>Acetylcholine</td>
<td>?</td>
</tr>
</tbody>
</table>

AV, atrioventricular; CNS, central nervous system; GI, gastrointestinal; SA, sinoatrial; ?, unknown

receptors is mediated by receptor-mediated local release of nitric oxide.11,12

Drugs that act on muscarinic receptors can do so by a number of mechanisms to produce their effects. The most common mechanisms of action and the relevant drugs are shown in Table 7-2.

### Drugs That Enhance Muscarinic Activity

#### Choline Esters

Acetylcholine itself is not a useful drug. It has been used in heart failure patients in experimental studies to assess peripheral vascular function (endothelial release of nitric oxide). It has also been used in patients with coronary artery disease during angiography to assess endothelial function.13 Its pharmacologic properties are nonselective and include the stimulation of all muscarinic and nicotinic sites. Therefore, an attempt has been made to develop synthetic analogues of acetylcholine that would have greater selectivity for specific subpopulations of muscarinic receptors. The only clinically useful agents that have thus far emerged from this effort are bethanechol and methacholine. Bethanechol is relatively selective for the urinary bladder and gastrointestinal tract. It has very little activity at M2 receptors in the heart. Methacholine is potentially useful in the diagnosis of reactive airway disease and has some activity at cardiac receptors as well. Pilocarpine is a naturally occurring muscarinic agent that has agonist properties principally at muscarinic receptors in the eye and in the gastrointestinal tract.14,15 Selective M1 receptor agonists have been developed for use in patients with Alzheimer's disease with little evidence to date for their effectiveness.16

#### Anticholinesterase Agents

The effects of acetylcholine at postsynaptic sites are a function of the concentration of the transmitter at the postsynaptic receptor site. The compound is inactivated by the enzyme acetylcholinesterase, which is readily demonstrable at high concentrations at the postsynaptic sites. Some of the enzyme is bound to the membrane at the synaptic cleft itself, and some floats free in the medium. Acetylcholine effects can be enhanced and prolonged by the inhibition of the action of acetylcholinesterase. Clinically available anticholinesterases are listed in Table 7-2. These agents reversibly inhibit cholinesterase activity at all receptor sites; therefore, their pharmacologic effects reflect not only muscarinic but also nicotinic actions. All of these drugs also inhibit the activity of butyrylcholinesterase. This pseudocholinesterase is present in many sites of the body, including the liver and plasma. Anticholinesterase drug effects constitute an enhancement of the vagal stimulus on the heart. This leads to a shortening of the effective refractory period, a decrease in SA- and AV-nodal conduction time, and a diminution of cardiac

### Table 7-2. Mechanisms of Action of Drugs Active at Muscarinic Receptors

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Effect</th>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline esters</td>
<td>Mimic effect of acetylcholine at receptors</td>
<td>Bethanechol, Methacholine, Edrophonium</td>
<td>Moderate selectivity (see text)</td>
</tr>
<tr>
<td>Anticholinesterases</td>
<td>Enhance effect of acetylcholine at receptors</td>
<td>Physostigmine, Pyridostigmine, Neostigmine, Rivastigmine, Galantamine, Donepezil, Tacrine</td>
<td>Nicotinic and muscarinic effects are present</td>
</tr>
<tr>
<td>Muscarinic receptor antagonists</td>
<td>Compete for binding at synaptic receptor</td>
<td>Atropine, Scopolamine</td>
<td>Minimal structural selectivity for different muscarinic receptor; selectivity reflects distribution/density of receptors; selectivity may be enhanced by route of administration</td>
</tr>
</tbody>
</table>

output. This is modified somewhat by effects at nicotinic receptors. In addition, with persistent stimulation, a paradoxical decrease in effect will occur. Therefore, with high doses and longer duration of action, a paradoxical decrease in acetylcholine effect can be seen. All of these agents have significant potential for noncardiac effects, including gastrointestinal (increased contraction, acidity, propulsion); skeletal muscle (enhanced activity); and pulmonary effects (enhanced bronchoconstriction).17

Edrophonium is an anticholinesterase with the shortest duration of action.14,15 When given intravenously, it has an onset of effect within 30 to 60 seconds and a duration of effect that is generally less than 10 minutes, although longer durations of action may be seen in some susceptible individuals. Given this pharmacodynamic profile, edrophonium has been used for the acute diagnosis of myasthenia gravis and for the diagnosis and acute termination of paroxysmal supraventricular tachycardia. Cardiac disease is listed by the manufacturer of edrophonium as a reason for caution in its use, and the US Food and Drug Administration (FDA) has not approved the drug for use in the management of cardiac disease. However, many clinicians have used the drug’s capacity to produce acute and intense muscarinic effects as a way of diagnosing atrial arrhythmias after other routine measures have failed. Occasionally, edrophonium is used for the acute control of heart rate; for example, slowing heart rate in the context of an evaluation of demand pacemaker functioning. As a single dose, edrophonium should not exceed 10 mg. In older or sicker patients, the maximal dose may need to be reduced to 5 to 7 mg. When the goal of therapy is to gradually decrease heart rate, the drug may be administered in 2-mg boluses up to a total dosage of 10 mg. Significantly higher doses of the drug have been used safely in other clinical contexts.20-22

Recent articles have suggested that the diagnostic use of edrophonium in cardiovascular disease may be extended to include its administration during tilt-table testing as part of the evaluation for possible vasovagal syncope.23,24 It is also used in the diagnostic evaluation of patients with atypical chest pain syndromes, where response to acid infusion and edrophonium administration may identify those with esophageal sources of pain.25 Edrophonium is a quaternary drug whose affinity is limited to peripheral nervous system synapses.

Other anticholinesterases include physostigmine, pyridostigmine, and neostigmine. These drugs have generally not been found to have any significant role in the management of cardiovascular disease. However, they are used in other areas of medicine;26 therefore, it is important to be familiar with the indications for their use and their potential cardiac adverse effects. Perhaps the most important use for some of these drugs is in the immediate reversal of neuromuscular blockade during general anesthesia. They will reverse the effects of nondepolarizing muscular blocking agents such as tubocurarine, metocurine, gallamine, vecuronium, atracurium, and pancuronium. When titrated appropriately with close monitoring of their effects on neuromuscular blockade, the cardiac effects of these drugs are generally not a problem. On occasion, however, they may produce the syndrome of excessive parasympathetic effect. Since they have no effect on the muscle blockade produced by depolarizing agents such as succinylcholine or decamethonium, these drugs should not be used in that context.18,19

Pyridostigmine, and neostigmine are commonly used for the management of myasthenia gravis.27 They may also be used to improve bladder function postoperatively.

Physostigmine is used in topical ophthalmic medications for the treatment of glaucoma. Since this drug is a tertiary amine and penetrates into the CNS more than other agents in this class, similar drugs were developed to enhance cholinergic transmission in the CNS for patients with Alzheimer’s disease.28

The oral cholinesterase inhibitors donepezil hydrochloride, galantamine hydrobromide, and rivastigmine are currently approved to treat the symptoms of Alzheimer’s disease and related dementias. Their use in patients has been associated with increased rates of syncope, heart blocks, bradycardia, hypotension, and pacemaker insertions when compared to the rates of their complications in patients not receiving the drugs.29 The risk of these events must be weighed carefully when prescribing these agents to older patients with Alzheimer’s disease.

Drugs That Diminish Muscarinic Activity

Muscarinic Receptor Antagonists

Atropine is the best known of the muscarinic receptor antagonists. Atropine has a dose-related effect upon muscarinic receptors. At its lowest doses, a relatively selective effect on salivary secretion and sweating is demonstrated; at higher doses, it exhibits cardiac effects and more diffuse anticholinergic effects that include nicotinic as well as muscarinic blockade. Atropine’s dose-response curve is described in Table 7-3.30 It has been reported that Chinese individuals show an increased sensitivity to atropine that is independent of resting vagal and sympathetic tone.31 At low doses (< 0.5 mg), it may produce a paradoxical and usually mild slowing of heart rate. The mechanism for this mild bradycardia has been debated. It has been attributed by some authors to a central stimulation of vagal afferents. At higher doses, atropine causes a progressive vagolytic effect on the heart, with increased heart rate, decreased refractory period of the AV node, and increased...
AV conduction velocity. Atropine is indicated for use in the acute treatment of severe symptomatic bradycardia, particularly in the context of acute myocardial infarction. On rare occasions, where it may be hypothesized that endogenous sympathetic activity is suppressed by parasympathetic effects of vagal stimulation, atropine has been thought to precipitate ventricular arrhythmias.32 For this reason, it is clear that the drug should not be used casually; its use should be restricted to cases of severe symptomatic bradycardias.30,33

Since atropine will counteract bradycardia or heart block produced by acetylcholine or its analogues, it can be used to counteract the cardiac effects of any syndromes in which vagal nerve stimulation plays an important role. The drug can therefore block the bradycardia and hypotension seen in vasovagal syndromes. Since atropine is available only as a parenteral injection and because its effects are relatively brief, it is useful only for acute reversal of bradyarrhythmias and has no role in chronic management of these conditions.

A selective muscarinic antagonist for the M2 receptor is available (tryptamine), which has the potential to be used to treat cholinergic bradycardia.

Atropine has also been investigated recently for its potential utility as an adjunct to dobutamine-stress echocardiography. Atropine has been given as a secondary medication for the enhancement of cardiac response where dobutamine infusion has limited success in producing the desired tachycardia, particularly for patients receiving beta-blockers.34-38

There are other drugs with muscarinic blocking effects like those of atropine, but they have not had a significant role in cardiovascular therapy. Instead, their use has been largely confined to delivery systems designed to provide therapeutic benefit without cardiac effects. Ipratropium bromide and tiotropium are quaternary ammonium compounds with atropine-like effects that are commonly used as inhalational agents for the reversal of cholinergically mediated bronchoconstriction. Ipratropium bromide has had its greatest clinical utility in the management of patients with chronic obstructive pulmonary disease.39 As a quaternary ammonium compound, ipratropium is very inefficiently absorbed from the pulmonary vascular bed. Approximately 1% of a dose is absorbed systemically. Most of this is probably secondary to oral absorption of swallowed drug. It is possible that, on rare occasions, systemic effects from this drug might be seen.40,41 Recently it was shown there is an increased risk of adverse cardiovascular effects with the use of inhaled ipratropium in patients with COPD.42 This adverse reaction may not be seen with the inhaled anticholinergic tiotropium.43,44

Scopolamine continues to be available as a parenteral drug but is very rarely used. Its most common use at this time is in a transdermal patch preparation that delivers a low, continuous dose of drug over a 2- to 3-day period for the treatment of motion sickness. On occasion—either due to changes in the permeability of skin, excessive dosing (several patches at once), or from careless handling of the patches—a significant systemic effect from this drug can be seen.40,41 Transdermal scopolamine has been investigated as an antiarrhythmic drug in patients with acute myocardial infarction and congestive heart failure, but it is not indicated for these conditions.48

Note: References for this chapter can be found here:
www.cvpct3.com

### Table 7-3. Dose-Effect Relationship for Atropine

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pharmacologic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-0.5 mg</td>
<td>Mild bradycardia, dry mouth, decreased sweating.</td>
</tr>
<tr>
<td>0.5-1.0 mg</td>
<td>Cardioacceleration, very dry mouth, some pupillary dilation.</td>
</tr>
<tr>
<td>1.0-2.0 mg</td>
<td>Tachycardia (potentially symptomatic) very dry mouth, pupillary dilation, blurred vision.</td>
</tr>
<tr>
<td>&gt; 3.0 mg</td>
<td>All of the preceding, except more marked, and including erythematous, hot skin, increased intestinal tone, urinary retention. At highest doses excitement and agitation leading to delirium or ultimately to coma, accompanied by fevers and scarlet skin.</td>
</tr>
</tbody>
</table>

The calcium-channel blockers are a heterogeneous group of drugs with widely variable effects on heart muscle, sinus node function, atrioventricular (AV) conduction, peripheral blood vessels, and the coronary circulation.1–5 Ten of these drugs—nifedipine, nicardipine, nimodipine, nisoldipine, felodipine, isradipine, amlodipine, clevidipine, verapamil, and diltiazem—are approved in the United States for clinical use. Other agents that are available for clinical use outside the United States include barnidipine,6 benidipine,7 cilnidipine,8 lacidipine,9 ler- canidipine,10 manidipine,10 and efonidipine.11

Physiologic Background

Calcium ions play a fundamental role in the activation of cells. An influx of calcium ions into the cell through specific ion channels is required for myocardial contraction, for determining peripheral vascular resistance through calcium dependent-regulated tone of vascular smooth muscle, and for helping to initiate the pacemaker tissues of the heart, which are activated largely by the slow calcium current.2

The concept of calcium-channel inhibition originated in 1960, when it was noted that prenylamine, a newly developed coronary vasodilator, depressed cardiac performance in canine heart-lung preparations.12 Initial studies with verapamil showed that it also exerted negative inotropic effects on the isolated myocardium in addition to having vasodilator properties.13 These potent negative inotropic effects seemed to differentiate these drugs from the classic coronary vasodilators, such as nitroglycerin and papaverine, which have little if any myocardial depressant activity. Unlike beta-adrenergic antagonists, many of the calcium antagonists depress cardiac contractility without altering the height or contour of the monophasic action potential and thus can interfere with excitation-contraction coupling.14 Reversible closure of specific calcium ion channels in the membrane of the mammalian myocardial cell was suggested as the explanation of these observed effects.15

Subsequently, the effects of verapamil on atrial and ventricular intracellular potentials were studied.16 Antiarrhythmic compounds were classified into local anesthetics, which decreased the maximum rate of depolarization; beta blockers; and a third class, which prolonged the duration of the cardiac action potential.17 However, none of these electrophysiologic actions could explain the antiarrhythmic effect of verapamil.17 Thus, a fourth class of antiarrhythmic drug, typified by verapamil, was proposed, with effects separate from those of sodium channel inhibitors and beta blockers.18 It has been shown that the antiarrhythmic actions and negative inotropic effects of verapamil are mediated predominantly through interference with calcium conductance.19

Chemical Structure and Pharmacodynamics

Structure of the Calcium-Channel Blockers

The structures of some of the available calcium-channel blockers are shown in Figure 8-1. Diltiazem is a benzothiazepine derivative that is structurally unrelated to other vasodilators.1 Nifedipine is a dihydropyridine derivative unrelated to the nitrates, which is lipophilic and is inactivated by light.1 Nicardipine, amlodipine, felodipine, isradipine, nisoldipine, and nimodipine are also dihydropyridine derivatives similar in structure to nifedipine. Verapamil ([+] verapamil) has some structural similarity to papaverine.1
The most important characteristic of all calcium-channel blockers is their ability to selectively inhibit the inward flow of charge-bearing calcium ions when the calcium ion channels become permeable. Previously, the term slow channel was used, but it has recently been recognized that the calcium ion current develops faster than previously thought and that there are at least two types of calcium channels, the L and T. The conventional calcium channel, which has been known to exist for a long time, is called the L channel. It is blocked by all the available calcium-channel antagonists and has its permeability increased by catecholamines. The T-type channel appears at more negative potentials than the L-type and probably plays an important role in the initial depolarization of sinus and AV nodal tissue. The function of the L-type channel is to admit the substantial amount of calcium ions required for initiation of contraction via calcium-induced calcium release from the sarcoplasmic reticulum. Mibefradil, used in angina pectoris, was the first calcium-channel blocker shown to have selective blocking properties on the T-type channel in addition to its blocking effects on the L-type channel. Efondipine is also a combined L- and T-type calcium channel blocker, which is currently available in Japan for the treatment of hypertension. Specific blockers for the T-type channel are not yet available, but they could be expected to inhibit the sinus and AV nodes profoundly.

Bepridil, which also was used in angina, possesses all the characteristics of the traditional calcium antagonists. In addition, the drug appeared to affect the sodium channel (fast channel) and possibly the potassium channel, producing a quinidine-like effect. Bepridil specifically inhibited maximal upstroke velocity (dV/dt_max)—that is, the influx of sodium in appropriate load dosages. The effect of bepridil on the maximum rate of depolarization has been examined; the action potential height is not changed; however, the action potential duration is extended in a quinidine-like manner.20

Cardiovascular Effects

Effects on Coronary and Peripheral Arterial Blood Vessels

The contraction of vascular smooth muscle such as that found in the coronary arteries is slightly different from the contraction of cardiac and skeletal muscles (Table 8-1). Myosin must be phosphorylated, and calmodulin is the regulatory protein to which calcium binds. In addition, vascular smooth muscle cells have significantly less intracellular calcium stores than do myocardial cells and so rely more heavily on the influx of extracellular calcium. The observation that calcium-channel blockers are significantly more effective in inhibiting contraction in coronary and peripheral arterial smooth muscle than in cardiac and skeletal muscle is of great clinical importance. This differential effect is explained by the observation that arterial smooth muscle is more dependent on external calcium entry for contraction, whereas cardiac and skeletal muscle rely on a recirculating internal pool of calcium. Because calcium-entry blockers are membrane-active drugs, they reduce the entry of calcium into cells and therefore exert a much larger effect on vascular wall contraction. This preferential effect allows calcium-entry blockers to dilate coronary and peripheral arteries in doses that do not severely affect myocardial contractility or have little if any effect on skeletal muscle.
It has been shown that dihydropyridines can also induce the release of nitric oxide (NO) from the vascular endothelium of various blood vessels. In addition, in several preparations, including micro- and macrovasculature, the sensitivity of the vasorelaxing effects of the dihydropyridines to inhibitors of NO synthase, such as L-NG-nitroarginine or L-nitro-arginine-methyl-ester, has been shown. These findings on a dual mode of action of dihydropyridines—ie, the direct relaxing effect by inhibition of the smooth muscle L-type calcium ion channel and the indirect relaxing effect by the release of NO from vascular endothelium—may explain the highly potent vasodilatory actions of these drugs. In addition, an antiendothelin action of calcium-channel blockers has also been described, as well as an inhibitory effect on matrix metalloproteinase-1.

### Effects on Veins

The calcium-channel blockers seem to be less active in veins than in arteries and are ineffective at therapeutic doses (in contrast to nitrates) for increasing venous capacitance.

### Effects on Myocardial Contractility

Force generation during cardiac muscle contraction depends in part on calcium influx during membrane depolarization (Table 8-1). In isolated myocardial preparations, all calcium-channel antagonists have been demonstrated to exert potent negative inotropic effects. In guinea pig atria exposed to drug concentration of 1026 mol/L, the order of potency for depressing the maximal rate of force development during constant pacing was found to be nifedipine > verapamil-diltiazem. In dog papillary muscle, developed tension was also decreased most markedly by nifedipine; the relative potencies (on a weight basis) of verapamil and diltiazem were 1/15 and 1/40, respectively.

The negative inotropic effect of the calcium-channel antagonists are dose-dependent. The excitation-contraction coupling of vascular smooth muscle is 3 to 10 times more sensitive to the action of calcium-channel antagonists than is that of myocardial fibers. Hence the relatively low doses of these drugs used in vivo to produce vasodilatation or beneficial antiarrhythmic effects may not produce significant negative inotropic effects. Furthermore, in intact animals and human beings, the intrinsic negative inotropic properties of these compounds are greatly modified by a baroreceptor-mediated reflex augmentation of beta-adrenergic tone consequent to vasodilatation and a decrease in blood pressure. Nifedipine and other dihydropyridines, which exert the greatest vasodilator effects among these agents, accordingly produce the strongest reflex beta-adrenergic response and the one most likely to offset the negative inotropic activity of the drugs and lead to enhancement of ventricular performance. Although this mechanism plays an important

### Table 8-1. Pharmacologic Effects of Calcium-Channel Blockers

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate</th>
<th>Conduction</th>
<th>Myocardial</th>
<th>Peripheral</th>
<th>CO</th>
<th>Coronary</th>
<th>MVO2</th>
<th>Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Chronic</td>
<td>SA Node</td>
<td>AV Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>V</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Verapamil</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>V</td>
<td>↑</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>↑</td>
<td>↑ –</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>↓</td>
<td>↑ –</td>
<td>↓</td>
</tr>
<tr>
<td>Clevadine</td>
<td>↑</td>
<td>↑ –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>↑ –</td>
<td>↓</td>
</tr>
<tr>
<td>Felodipine</td>
<td>↑</td>
<td>↑ –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>↑ –</td>
<td>↓</td>
</tr>
<tr>
<td>Isradipine</td>
<td>↑</td>
<td>↑ –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>↑ –</td>
<td>↓</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>↑</td>
<td>↑ –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>↑ –</td>
<td>↓</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>↑</td>
<td>↑ –</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>↓</td>
<td>↑ –</td>
<td>↓</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>↑</td>
<td>↑ –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>V</td>
<td>↑ –</td>
<td>↓</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>↑</td>
<td>↑ –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>↑ –</td>
<td>↓</td>
</tr>
</tbody>
</table>

SA = sinoatrial; AV = atrioventricular; CO = cardiac output; MVO2 = myocardial oxygen; ↑ = increase; ↓ = decrease; – = no change; V = variable.

role in patients with normal or nearly normal left ventricular (LV) function, it is unlikely to play a similar role in patients with severe congestive heart failure (CHF), in whom the baroreceptor sensitivity is markedly attenuated. Regarding the newer calcium-channel blockers, the hemodynamic profile of amlodipine was compared with those of verapamil and diltiazem in conscious nor-motensive rats. Verapamil and diltiazem were negatively inotropic. Amlodipine decreased LV contractility only at the highest dose used.

Electrophysiologic Effects

While verapamil, nifedipine, and diltiazem all depress cardiac contractility with only quantitative differences (Table 8-1), their effects on the electrophysiology of the heart are different qualitatively. Local anesthetic actions of diltiazem and particularly verapamil may account for some of these differences. Nifedipine and other dihydropyridines have a more selective action at the slow channels, whereas verapamil and diltiazem, at least at higher doses, also inhibit currents in the fast channels in the manner of the local anesthetics. 

Verapamil and diltiazem prolong the conduction and refractoriness in the AV node; the A-H interval is lengthened more than is the H-V interval. In therapeutic concentrations, there are no demonstrable actions on the rate of depolarization or the repolarization phases of the action potentials in atrial, ventricular, and Purkinje fibers. 

The rate of discharge of the sinus node, which depends on the calcium ion current, is depressed by all calcium-channel blockers. In vivo, this effect can be compensated or overcompensated for by activation of baroreceptor reflexes, which increase sympathetic nervous activity. 

The antiarrhythmic actions of verapamil and diltiazem relate to their effects on nodal cardiac tissues. In sinoatrial (SA) and AV nodal cells, the drugs modify slow-channel electropotentials in 3 ways: (1) there is a decrease in the rate of rise and slope of diastolic slow depolarization and an increase in the membrane threshold potential, which reduces the rate of firing in the cell; (2) the action potential upstroke is decreased in amplitude, which slows conduction; and (3) the duration of the action potential is increased. These electrophysiologic effects are dose-related, and above the clinical range electrical standstill may occur in SA- and AV-nodal cells. These observations and others support the concept that slow-channel activity is important in the generation of pacemaker potential in the SA node.

Verapamil and diltiazem also exert a depressant effect on the AV node and in low concentrations prolong the effective refractory period. Unlike beta-adrenergic blocking drugs and vagomimetic interventions, which depress AV node transmission by altering autonomic im-

Effects on Nonvascular Tissues

Calcium ions are required for contraction in all smooth muscles, and these drugs can inhibit contractions in the gastrointestinal tract. Calcium is also important in excitation-secretion coupling. However, there is no evidence that, in clinical doses, these drugs have significant effects on the endocrine glands. Although antiadrenergic effects of some calcium-entry blockers have been suggested, further studies are needed. 

Some calcium-entry blockers may partially inhibit adenosine diphosphosphate (ADP)- and epinephrine-induced platelet aggregation and thromboxane release from platelets. There are good experimental data that verapamil and diltiazem and, to a lesser extent, nifedipine and amiodipine can inhibit platelet aggregation in vitro. The drugs appear to be more efficacious in attenuating aggregation when they are present in the reaction mixture before aggregation begins. This can, however, interrupt or slow the rate of aggregation if added after the beginning of the reaction. In addition, the effect of aspirin in attenuating platelet aggregation appears to be potentiated in vitro in the presence of diltiazem. This has led to considerable speculation as to how much this effect may contribute to the efficacy of calcium-channel blockers in the treatment of unstable angina. There has been at least one report of patients with unstable angina in which those treated with verapamil demonstrated decreased platelet aggregability and thromboxane A2 levels. If this is true in vivo, it would substantially support the use of some of these agents as first-line drugs for the treatment of unstable angina.

Pharmacokinetics

Although calcium-entry blockers are classified together, there are differences in their pharmacokinetic properties (Tables 8-2 and 8-3).
Table 8-2. Pharmacokinetics of Calcium-Channel Blockers and Sustained-Release Preparations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade Name</th>
<th>Absorption (%)</th>
<th>Bioavailability (%)</th>
<th>Protein Binding (%)</th>
<th>VOD (L/kg)</th>
<th>t₁/₂ (h)</th>
<th>Clearance (mL/min/kg)</th>
<th>Time to Peak Plasma Concentration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Cardizem</td>
<td>&gt; 90</td>
<td>35-60</td>
<td>78</td>
<td>5.0</td>
<td>4.1-5.6</td>
<td>15</td>
<td>2-3</td>
</tr>
<tr>
<td>Diltiazem SR</td>
<td>Cardizem SR</td>
<td>&gt; 90</td>
<td>35-60</td>
<td>78</td>
<td>5.0</td>
<td>5.7</td>
<td>15</td>
<td>6-11</td>
</tr>
<tr>
<td>Diltiazem IV</td>
<td>Cardizem</td>
<td>100</td>
<td>78</td>
<td>5.0</td>
<td>3.4</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem CD</td>
<td>Cardizem CD</td>
<td>&gt; 95</td>
<td>40</td>
<td>70-80</td>
<td>5.0</td>
<td>5-8</td>
<td>15</td>
<td>10-14</td>
</tr>
<tr>
<td>Diltiazem XR</td>
<td>Dilacor XR</td>
<td>&gt; 95</td>
<td>40</td>
<td>70-80</td>
<td>5.0</td>
<td>5-10</td>
<td>15</td>
<td>4-6</td>
</tr>
<tr>
<td>Diltiazem ER</td>
<td>Tiazac</td>
<td>&gt; 90</td>
<td>40</td>
<td>70-80</td>
<td>5.0</td>
<td>4-9.5</td>
<td>15</td>
<td>6-11</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Calan, Isoptin</td>
<td>&gt; 90</td>
<td>10-20</td>
<td>90</td>
<td>4.3</td>
<td>6 ± 4 IV</td>
<td>13 ± 7</td>
<td>1-2</td>
</tr>
<tr>
<td>Verapamil SR</td>
<td>Calan SR, Isoptin SR,</td>
<td>&gt; 90</td>
<td>10-20</td>
<td>90</td>
<td>4.3</td>
<td>4.5-12</td>
<td>13 ± 7</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>Verelan, Verelan PM</td>
<td>&gt; 90</td>
<td>20-35</td>
<td>90</td>
<td>162-380 L</td>
<td>12</td>
<td>—</td>
<td>7-9</td>
</tr>
<tr>
<td>Coer Verapamil</td>
<td>Covera</td>
<td>&gt; 90</td>
<td>20-30</td>
<td>90</td>
<td>—</td>
<td>6-12</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>Verapamil IV</td>
<td></td>
<td>100</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6-12</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Procardia, Adalat</td>
<td>&gt; 90</td>
<td>65</td>
<td>90</td>
<td>1.32</td>
<td>5</td>
<td>500-600</td>
<td>0.5</td>
</tr>
<tr>
<td>Nifedipine CC</td>
<td>Adalat CC</td>
<td>&gt; 90</td>
<td>84-89</td>
<td>92-98</td>
<td>.32</td>
<td>—</td>
<td>500-600</td>
<td>2-2.5</td>
</tr>
<tr>
<td>Nifedipine GITS</td>
<td>Procardia XL</td>
<td>&gt; 90</td>
<td>85</td>
<td>&gt; 95</td>
<td>1.32</td>
<td>3.8-16.9</td>
<td>500-600</td>
<td>6 to plateau</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Cardene</td>
<td>&gt; 90</td>
<td>30</td>
<td>&gt; 90</td>
<td>0.6</td>
<td>1 IV</td>
<td>14</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Nicardipine SR</td>
<td>Cardene SR</td>
<td>&gt; 90</td>
<td>35</td>
<td>&gt; 95</td>
<td>8.6</td>
<td>0.6</td>
<td>1-4 immediate</td>
<td></td>
</tr>
<tr>
<td>Nicardipine IV</td>
<td>Cardene</td>
<td>100</td>
<td>&gt; 90</td>
<td>9.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Norvasc</td>
<td>&gt; 90</td>
<td>60-65</td>
<td>&gt; 95</td>
<td>21</td>
<td>35-45</td>
<td>7</td>
<td>6-12</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Dynacirc</td>
<td>90-95</td>
<td>17</td>
<td>97</td>
<td>2.9</td>
<td>8.8</td>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>Felodipine ER</td>
<td>Plendil</td>
<td>&gt; 95</td>
<td>15-25</td>
<td>&gt; 99</td>
<td>10</td>
<td>15.1 ± 2.6</td>
<td>12</td>
<td>2.5-5</td>
</tr>
<tr>
<td>Clevidipine IV</td>
<td>Cleviprex</td>
<td>NA</td>
<td>NA</td>
<td>&gt; 99.5</td>
<td>0.17</td>
<td>15 min</td>
<td>50</td>
<td>.</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Nimotop</td>
<td>&gt; 90</td>
<td>13</td>
<td>&gt; 95</td>
<td>0.94</td>
<td>8-9</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Sular</td>
<td>87</td>
<td>5</td>
<td>&gt; 99</td>
<td>7-12</td>
<td>7-12</td>
<td>6-12</td>
<td></td>
</tr>
</tbody>
</table>

VOD = volume of distribution; SR = sustained-release; IV = intravenous; CD, XR, CC, XL = extended release; PO = oral; GITS = gastrointestinal therapeutic system.

* Extraction ratio.

### Table 8-3. Additional Pharmacokinetic Characteristics of Calcium-Channel Blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Onset of Action (min)</th>
<th>Therapeutic PC (ng/mL)</th>
<th>Site of Metabolism</th>
<th>Active Metabolites</th>
<th>Excretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Oral 30-90 q 6-8 h IV 75-150 μg/kg; 10-20 mg</td>
<td>Oral &lt; 30 IV &lt; 10</td>
<td>50-200</td>
<td>Deacetylation N-deacetylation O-demethylation; major hepatic first-pass effect</td>
<td>Yes</td>
<td>60 (fecal) 2-4 (unchanged in urine)</td>
</tr>
<tr>
<td>Diltiazem SR</td>
<td>60-120 mg q 12 h</td>
<td>30-60 50-200</td>
<td></td>
<td></td>
<td>Yes</td>
<td>60 (fecal) 2-4 (unchanged in urine)</td>
</tr>
<tr>
<td>Diltiazem IV</td>
<td>0.25 mg/kg (20 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem CD</td>
<td>180-360 mg q 24 h</td>
<td>30-60 50-200</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Diltiazem XR</td>
<td>180-540 mg q 24 h</td>
<td>30-60 40-200</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Diltiazem ER</td>
<td>120-540 mg q 24 h</td>
<td>40-200 40-200</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>80-120 mg q 6-12 h 150 μg/kg; 10-20 mg</td>
<td>&lt; 30 &lt; 5 &gt; 100</td>
<td></td>
<td>N-dealkylation O-demethylation Major hepatic first-pass effect</td>
<td>Yes</td>
<td>15 (fetal) 70 (renal) 3-4 (unchanged in urine)</td>
</tr>
<tr>
<td>Verapamil SR</td>
<td>240-480 mg q 12 or 24 h</td>
<td>&lt; 30 &gt; 50</td>
<td></td>
<td></td>
<td>Yes</td>
<td>15 (fetal) 70 (renal) 3-4 (unchanged in urine)</td>
</tr>
<tr>
<td>Verelan (Verapamil SR)</td>
<td>120-480 mg q 24 h</td>
<td>&gt; 50</td>
<td></td>
<td></td>
<td>Yes</td>
<td>16 (fetal) 70 (renal) 3-4 (unchanged in urine)</td>
</tr>
<tr>
<td>Verelan PM</td>
<td>200-400 mg q 24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coer Verapamil</td>
<td>180-540 mg q 24 h</td>
<td>4-5 h</td>
<td></td>
<td></td>
<td>Yes</td>
<td>16 (fetal) 70 (renal) 3-4 (unchanged in urine)</td>
</tr>
<tr>
<td>Verapamil IV</td>
<td>5-10 mg (0.075-0.15 mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>16 (fetal) 70 (renal) 3-4 (unchanged in urine)</td>
</tr>
<tr>
<td>Clevidipine IV</td>
<td>4-6 mg/hr</td>
<td>1</td>
<td>Blood esterases</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Nifedipine CC</td>
<td>30–90 mg/day</td>
<td>&lt; 60</td>
<td>25–100</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>------</td>
<td>--------</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Nifedipine GITS</td>
<td>30–180 mg q 24 h</td>
<td>2 h</td>
<td></td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>30–20 mg tid 1.15 mg/h</td>
<td>&lt; 20</td>
<td>&lt; 5</td>
<td>28–50</td>
<td>Major hepatic first-pass effect No</td>
<td></td>
</tr>
<tr>
<td>Nicardipine SR</td>
<td>30–60 mg bid</td>
<td>20</td>
<td></td>
<td>28–50</td>
<td>30 (fecal) 60 (renal) &lt; 1 (unchanged in urine)</td>
<td></td>
</tr>
<tr>
<td>Nicardipine IV</td>
<td>5–15 mg/h</td>
<td>&lt; 2–3</td>
<td>60–800</td>
<td>Hepatic</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td>60 mg q 4 h</td>
<td>&lt; 30</td>
<td>7</td>
<td>Major hepatic first-pass effect No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nisoldipine ER</td>
<td>20–40 mg q 24 h</td>
<td></td>
<td></td>
<td>Hepatic hydroxylation</td>
<td>Yes 80 (renal) &lt; 1 (unchanged in urine)</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5–10 mg q 24 h 90–120 in vitro</td>
<td>6–10</td>
<td>Oxidation; extensive but slow hepatic metabolism No 20–25 (fecal) 60 (renal) 10 (unchanged in urine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isradipine</td>
<td>2.5–10 mg q 12 h</td>
<td>120</td>
<td>Hepatic de-esterification and aromatization No 30 (fecal) 70 (renal) 0 (unchanged in urine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isradipine CR</td>
<td>5–20 mg q 24 h</td>
<td>2–3 h</td>
<td></td>
<td></td>
<td>25–30 (fecal) ll 60–65 (renal)</td>
<td></td>
</tr>
<tr>
<td>Felodipine ER</td>
<td>5–20 mg q 24 h</td>
<td>2–5 h</td>
<td>2–20 nmol/L</td>
<td>Hepatic microsomal P450 system oxidation Major hepatic first-pass effect No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PC = plasma concentrations; bid = twice daily; tid = thrice daily; SL = sublingual; nd = no data.

Differences in completeness of gastrointestinal absorption, amount of first-pass hepatic metabolism, protein binding, extent of distribution in the body, and the pharmacologic actions of different metabolites may influence the clinical usefulness of these drugs in different patients.1,48

Since many of the calcium-channel blockers are relatively short-acting, they are now available in various sustained-release delivery systems: diffusion type (diltiazem, verapamil); bioerosion (diltiazem, nifedipine, nicardipine); osmosis (verapamil, isradipine, nifedipine); and diffusion-erosion (felodipine).50 Nisoldipine was approved as a once-daily therapy in the coat-core formulation,51 and verapamil was approved in 2 different delayed-onset sustained-release drug delivery systems.52

After administration of a certain oral dose, the calcium-entry blocking drugs, which are largely metabolized in the liver, show larger interindividual variation in circulating plasma levels.53,54 In angina and hypertension, wide individual differences also exist in the relation between plasma concentrations of calcium-entry blockers and the associated therapeutic effect.53,54

Various dihydropyridine calcium-channel blockers (felodipine, nifedipine, nisoldipine) should not be administered with grapefruit juice or Seville orange juice, as it has been shown to interfere with the drug’s metabolism, resulting in about a threefold mean increase in $C_{\text{max}}$ and an almost twofold mean increase in area under the plasma concentration-time curve.55

The pharmacokinetics of calcium-channel blockers are minimally impacted by renal failure. Furthermore, the drugs are not dialyzable. The predictability of the kinetic profile of the calcium-channel blockers in renal failure simplifies their use in end-stage renal disease.56

### Clinical Applications

The calcium-channel blockers are available as monotherapies in the United States for the treatment of patients with angina (diltiazem, nifedipine, amlodipine, nicardipine, verapamil); for chronic treatment of systemic hypertension (verapamil, isradipine, diltiazem, amlodipine, nicardipine, nisoldipine, felodipine); for the management of hypertensive emergencies and perioperative hypertension.

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**Table 8-4. Hemodynamic Effects of Calcium-Entry Blockers on Myocardial Oxygen Supply and Demand**

<table>
<thead>
<tr>
<th></th>
<th>Verapamil</th>
<th>Nifedipine</th>
<th>Diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demand</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wall tension</td>
<td>$\uparrow$</td>
<td>$\leftrightarrow$</td>
<td>$\leftrightarrow$</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>Ventricular volume</td>
<td>$\uparrow$</td>
<td>$\leftrightarrow$</td>
<td>$\leftrightarrow$</td>
</tr>
<tr>
<td>Heart rate</td>
<td>$\downarrow$</td>
<td>$\leftrightarrow$</td>
<td>$\uparrow$ reflex</td>
</tr>
<tr>
<td>Contractility</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td><strong>Supply</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
</tr>
<tr>
<td>Coronary vascular resistance</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>Spasm</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>Diastolic perfusion time</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
<td>$\leftrightarrow$</td>
</tr>
<tr>
<td>Collateral blood flow</td>
<td>$\leftrightarrow$</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
</tr>
</tbody>
</table>

$\uparrow$ = increase; $\downarrow$ = decrease; $\leftrightarrow$ = no apparent effect.

* Heart rate may increase sharply but decreases with long-term use.

Calcium Channel Blockers

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Angina Pectoris

The antianginal mechanisms of calcium-entry blockers are complex (Table 8-4).1,2,57 The drugs exert vasodilator effects on the coronary and peripheral vessels as well as depressant effects on cardiac contractility, heart rate, and conduction; all these actions may be important in mediating the antianginal effects of the drugs.2,57,58 These drugs are not only mild dilators of epicardial vessels not in spasm, but they also markedly attenuate sympathetically mediated and ergonovine-induced coronary vasoconstriction; these actions provide a rational basis for effectiveness of the drugs in vasospastic ischemic syndromes. In patients with exertional angina, the peripheral vasodilator actions of diltiazem and verapamil and the inhibitory effects on the sinus node serve to attenuate the increases in double product that normally accompany and serve to limit exercise.2,59

Stable Angina

Multiple double-blind placebo-controlled studies have clearly confirmed the efficacy of diltiazem,54,58 nifedipine,54,58 amiodipine,54,58 nicardipine,58,59 and verapamil,58-60 in stable angina, with patients showing a reduction in chest pain attacks and nitroglycerin consumption and improved exercise tolerance.60 Calcium-entry blockers, for the most part, appear to be as safe and effective as beta blockers and nitrates when used as monotherapies.61,62 They can also be used as single-dose therapies in hypertensive patients with angina.61,63,64

In choosing between a calcium-channel antagonist and a beta-adrenergic blocking drug in the management of patients with effort-related symptoms, it is apparent that some patients do better with one drug than with the other, although beta blockers are considered the preferred first-line therapy.65 Unfortunately, little is known about how to predict with confidence the superior agent in a specific patient without a therapeutic trial. However, verapamil and diltiazem can be used as effective alternatives in patients who remain symptomatic despite therapy with beta blockers and as first-time antianginal drugs in patients with contraindications to beta blockade; the use of nifedipine as a first-line drug in its original formulation was limited by the reflex tachycardia and potential aggravation of angina that accompanied its use.54,66 However, this has not been shown to be a problem with the nifedipine gastrointestinal therapeutic system (GITS) formulation or with amiodipine.42

Diltiazem is also approved as a once-daily treatment for angina in a sustained-delivery formulation.67 A delayed-release, sustained-release formulation of verapamil has been compared to atenolol, amiodipine, and the combination of amiodipine plus atenolol in patients with angina, and has been shown to be as effective in improving exercise tolerance and markers of silent ischemia.68

The comparative effects of abrupt withdrawal of verapamil and propranolol in patients with angina have been studied.44 Ten percent of patients with stable effort-related symptoms experienced a severe clinical exacerbation of the anginal syndrome upon withdrawal of propranolol; no patient experienced rebound symptoms when verapamil was abruptly discontinued.45 There also appear to be no major withdrawal reactions with nifedipine and diltiazem.54

Angina at Rest

Patients with angina at rest have a wide spectrum of disorders, ranging from those with variant angina (ST-segment elevation) associated with angiographically normal coronary arteries to those with unstable angina with ST-segment depression or elevation associated with multi-vessel coronary artery disease.51,62 Studies suggest that the coronary vasospasm and or thrombosis plays a major role in the pathogenesis of ischemia in most patients with angina at rest, regardless of the coronary anatomy.65 In clinical trials, calcium-channel antagonists were effective in this syndrome because of their ability to block spontaneous and drug-induced spasm.69-72

The comparative efficacy of verapamil and propranolol was assessed in a randomized blind crossover trial in angina at rest. Only verapamil reduced symptomatic and asymptomatic episodes of ischemia. These findings are consistent with the concept that coronary vasospasm plays a crucial role in patients with angina at rest; in contrast, rather than providing any benefit, propranolol may exacerbate vasospastic phenomena.73

Another study assessed the comparative efficacy of verapamil and nifedipine. Both verapamil and nifedipine proved equally effective, and neither drug depressed ventricular function at rest or during exercise.74 Accordingly, in the management of patients with variant angina, the choice of a calcium antagonist is likely to be determined not so much by which drug is more effective but by which agent is better tolerated by an individual patient.

The usefulness of calcium-channel antagonists as an adjunctive therapy in the long-term management of unstable angina was demonstrated in a double-blind, placebo-controlled, randomized clinical trial showing that the addition of nifedipine to patients receiving nitrates and propranolol can reduce the number of patients with
unstable anginal syndromes requiring surgery for relief of pain; the incidence of sudden death and myocardial infarction (MI) was similar in the 2 groups. However, clinical benefits were largely confined to patients whose pain was accompanied by ST-segment elevation. Current guidelines suggest that calcium-channel blockers be used as adjunctive therapy in patients with unstable angina.

Combination Therapy in Angina Pectoris
Combination therapy with nitrates and/or beta blockers may be more efficacious for the treatment of angina than one drug used alone. The hemodynamic effects of a calcium blocker/beta-blocker combination are shown in Table 8-5. Because adverse effects can occur from this combination (heart block, severe bradycardia, CHF), patients must be carefully selected and observed. The hemodynamic effects of combined nitrate/calcium-channel blocker therapy are shown in Table 8-6. Hypotension should be avoided. Different calcium-channel blockers may also be combined (nifedipine with verapamil or diltiazem) with added benefit; however, compared with monotherapy, adverse effects may be prohibitive.

Arrhythmias
See also Chapter 17, Antiarrhythmic Drugs.

Sinus Tachycardia
In an intensive care setting, intravenous diltiazem has been used successfully to treat sinus tachycardia in critically ill patients with contraindications to beta blockers or in whom beta blockers were contraindicated.

Atrial Fibrillation
Except in rare situations, verapamil and diltiazem are ineffective in converting acute and chronic atrial fibrillation

---

**Table 8-5. Hemodynamic Effects of Calcium-Entry Blockers, Beta Blockers, and Combination Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Calcium Blockers</th>
<th>Beta Blockers</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓↑↑reflex</td>
<td>↓</td>
<td>↓↑↑</td>
</tr>
<tr>
<td>Contractility</td>
<td>↓↑reflex</td>
<td>↓</td>
<td>↓↑↑</td>
</tr>
<tr>
<td>Wall tension</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Left ventricular volume</td>
<td>↓↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Coronary resistance</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↑↑</td>
</tr>
</tbody>
</table>

↑ = increase; ↓ = decrease; ↔ = no change.


**Table 8-6. Hemodynamic Rationale for Combining Nitrates and Calcium-Channel Blockers in Angina Pectoris**

<table>
<thead>
<tr>
<th></th>
<th>Nitrates</th>
<th>Calcium-Channel Blockers</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↑reflex</td>
<td>↓↑↑</td>
<td>↑↑↑reflex</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↓</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Heart size</td>
<td>↓/0</td>
<td>↓↑↑</td>
<td>0</td>
</tr>
<tr>
<td>Contractility</td>
<td>↑reflex</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Venomotor tone</td>
<td>↓</td>
<td>0</td>
<td>↓↓</td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td>↓</td>
<td>↓</td>
<td>↓↓?</td>
</tr>
<tr>
<td>Coronary resistance</td>
<td>↓</td>
<td>↓</td>
<td>↓↓?</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>↑</td>
<td>↑</td>
<td>↑↑?</td>
</tr>
<tr>
<td>Collateral blood flow</td>
<td>↑</td>
<td>↑</td>
<td>↑↑?</td>
</tr>
</tbody>
</table>

↑ = increase; ↓ = decrease; ↓↓? = questionable additive effects; ↔ = no change.

to normal sinus rhythm, and verapamil does not prevent long-term tachycardia-induced atrial electrical remodeling\(^\text{82,83}\) (Table 8-7). However, both diltiazem and verapamil (oral and intravenous) are effective for decreasing and controlling ventricular rate during atrial fibrillation by prolonging AV-nodal conduction and refractoriness and thereby increasing AV block both at rest and during exercise.\(^\text{84}\) Clinical trials with verapamil in patients with atrial fibrillation have shown that its ability to decrease ventricular rate appears to be unrelated to the chronicity of the arrhythmia, its etiology, or the patient’s age.\(^\text{85}\) Verapamil appears to be more effective than digoxin in slowing the rapid ventricular rate in response to physical activity.\(^\text{86}\) Either diltiazem or verapamil can be used orally in combination with digoxin in treating rapid heart rates in patients with acute and chronic atrial fibrillation and flutter.\(^\text{86}\)

It has been demonstrated that verapamil treatment can maintain normal sinus rhythm in patients undergoing electrocardioversion for atrial fibrillation.\(^\text{85}\) Pretreatment with diltiazem has been shown to prevent atrial arrhythmias after thoracic surgery.\(^\text{86}\)

Paroxysmal Supraventricular Tachycardia (SVT)

Virtually all cases of SVT due to intranodal reentry and those related to circus movement type of tachycardia in pre-excitation respond promptly and predictably to intravenous verapamil or diltiazem, whereas only about two-thirds of ectopic atrial tachycardias convert to sinus rhythm after adequate doses of the drug (Table 8-7).\(^\text{36,89,90}\) Intravenous verapamil and diltiazem are highly efficacious in treating re-entry paroxysmal SVT regardless of etiology or age.\(^\text{90}\) The recommended dosage range of verapamil for terminating paroxysmal SVT in adults is 0.075 to 1.5 mg/kg infused over 1 to 3 minutes and repeated at 30 minutes.\(^\text{90}\) In patients with myocardial dysfunction, the dose should be reduced. Children have safely been treated with a regimen of 0.075 to 0.15 mg.\(^\text{90}\) The recommended dose of diltiazem is 0.25 mg/kg infused over 2 minutes, repeated at 0.35 mg/kg after 15 minutes.

There have been few clinical studies comparing intravenous verapamil and diltiazem with other standard regimens in the treatment of paroxysmal SVT.\(^\text{91}\) However, in a number of clinical situations, verapamil and diltiazem may offer an advantage over either digitalis preparations or beta-adrenergic blockers. For instance, verapamil would be preferable in cases where there is an urgent need to terminate paroxysmal SVT, since it can produce therapeutic responses within 3 minutes of infusion, whereas the effects of digoxin are not evident for approximately 30 minutes.\(^\text{36}\) Also, if drug therapy fails to achieve normal sinus rhythm, the short duration of action of verapamil and diltiazem permit earlier cardioversion without some of the dangers that accompany electrical cardioversion during digoxin therapy. Verapamil and diltiazem also offer distinct advantages over beta-adrenergic blocking drugs in patients whose arrhythmias are associated with chronic obstructive lung disease and or peripheral vascular disease.\(^\text{36}\)

Oral verapamil has been approved for prophylaxis against paroxysmal SVT in doses of 160 to 480 mg per day, and the treatment experiences have yielded favorable

<table>
<thead>
<tr>
<th>Effective</th>
<th>Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia</td>
<td>Nonparoxysmal automatic atrial tachycardia</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Atrial fibrillation and flutter in WPW syndrome (ventricular rate may not decrease)</td>
</tr>
<tr>
<td>AV-nodal re-entrant PSVT</td>
<td>Ventricular tachyarrhythmias*</td>
</tr>
<tr>
<td>Accessory pathway re-entrant PSVT</td>
<td></td>
</tr>
<tr>
<td>PSVT SA-nodal re-entrant PSVT</td>
<td></td>
</tr>
<tr>
<td>Atrial re-entrant PSVT</td>
<td></td>
</tr>
<tr>
<td>Atrial flutter (ventricular rate decreases but arrhythmia will only occasionally convert)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (ventricular rate decreases but arrhythmia will only occasionally convert)</td>
<td></td>
</tr>
</tbody>
</table>

AV = atrioventricular; PSVT = paroxysmal supraventricular tachycardia; SA = sinoatrial; WPW = Wolff-Parkinson-White syndrome.

* There is only limited experience in this area.

results. Diltiazem is not yet approved in oral form as an antiarrhythmic agent.

### Atrial Flutter

The immediate effect of intravenous verapamil and diltiazem in atrial flutter in most patients is an increase in AV block that slows the ventricular response, rarely followed by a return to sinus rhythm (Table 8-7). In some, the response occurs through the development of atrial fibrillation with a controlled ventricular response. A single intravenous dose of verapamil or diltiazem has been found to be of diagnostic value in differentiating rapid atrial flutter from paroxysmal SVT when these 2 arrhythmias are indistinguishable on electrocardiography (ECG). If the rhythm is atrial flutter, the AV block increases immediately, revealing the true nature of the arrhythmia. Oral verapamil has also been used to convert paroxysmal atrial flutter and reduce the rapid ventricular rates associated with this arrhythmia.

### Pre-excitation

Verapamil and diltiazem have been found to induce reversion of most cases of accessory pathway supraventricular tachycardia. Using intracardiac recordings of electrical activity during programmed electrical stimulation of the heart, data have become available regarding the actions of verapamil on the electrophysiologic properties of the accessory pathway in overt cases of the Wolff-Parkinson-White (WPW) syndrome. The drug has a minimal effect on the antegrade and retrograde conduction times and on the refractory period. Verapamil and diltiazem, therefore, terminate accessory pathway paroxysmal supraventricular tachycardia in the same manner as they do AV-nodal re-entrant paroxysmal SVT: by slowing AV-nodal conduction and increasing refractoriness. The minimal effect of verapamil and diltiazem on the electrophysiologic properties of the bypass tract is consistent with the observation that the drug is ineffective in atrial fibrillation, complicating WPW syndrome, in which fibrillatory impulses, as with digoxin, conduct predominantly through the anomalous pathway. Under these circumstances, radiofrequency catheter ablation of the accessory pathways appears to be the therapy of choice.

### Ventricular Arrhythmias

Intravenous verapamil and diltiazem have no apparent benefit in ventricular arrhythmias except in acute MI. Oral verapamil has no demonstrated role in the management of ventricular tachyarrhythmias. Verapamil may be useful in reducing the ECG QT interval in patients with drug-induced QT prolongation syndrome.

### Precautions in Treating Arrhythmias

A diseased SA node is much more sensitive to slow-channel blockers and may be depressed to the point of atrial standstill. Sinus arrest can also occur without overt evidence of sick sinus syndrome. Calcium-channel blockade also may suppress potential AV-nodal escape rhythms that need to arise if atrial standstill occurs. In patients with the Brady-achy form of sick sinus syndrome, either digoxin or beta-adrenoceptor blocking drugs should probably not be combined with either verapamil or diltiazem in the prophylaxis of tachyarrhythmias unless a demand ventricular pacemaker is first inserted.

### Systemic Hypertension

Calcium-channel blockers are effective in the treatment of systemic hypertension and hypertensive emergencies. Calcium-channel blocking drugs can be considered potential first-line therapy for initiating treatment in many patients with chronic hypertension. A vast experience in the United States has been collected using verapamil, diltiazem, nifedipine, nisoldipine, felodipine, nicardipine, and isradipine in patients with hypertension. Verapamil, nifedipine, nisoldipine, felodipine, and diltiazem are available in the United States in both conventional and sustained-release oral formulations, allowing once- and twice-daily dosing. Verapamil and diltiazem are available in delayed-onset sustained-release delivery systems to provide a peak blood level at the time of blood pressure elevation during awakening.

Multiple studies have been carried out evaluating the effects of calcium-channel blockers in elderly patients with isolated systolic hypertension. The Systolic Hypertension in Europe Study (SYST-EUR) was limited to patients 60 years of age and older with a resting systolic pressure of 160 to 219 mm Hg and a diastolic pressure < 95 mm Hg. Patients were randomized to receive nitrendipine or a placebo. If additional blood pressure control was necessary, patients received an angiotensin-converting enzyme (ACE) inhibitor and then a diuretic. Compared to the placebo, nitrendipine therapy was associated with significant reductions in the rate of stroke, major cardiovascular events, and cognitive disorders. Based on this study, the guidelines presented in the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) include the use of dihydropyridine calcium antagonists in addition to thiazide diuretics as first-line treatment for isolated systolic hypertension (ISH) in the elderly.

The Systolic Hypertension in China (SYST-CHINA) study also looked at nitrendipine as a first-line treatment modality compared to the placebo in elderly patients with ISH. Compared to the placebo, nitrendipine was associated with a reduction in stroke events, major cardiovascular events, and mortality. The Stage I Systolic Hypertension in the Elderly (SHEP) was a pilot trial that enrolled elderly patients (>
Calcium Channel Blockers

55 years of age) with mild (stage 1) systolic hypertension (140-155 mm Hg), a population not studied in SHEP, SYST-EUR, or SYST-CHINA. Felodipine was compared to the placebo in an attempt to reduce systolic blood pressure by 10%. Felodipine was shown to be more effective than the placebo in reducing blood pressure. In addition, the drug was shown to reduce ventricular wall thickness and improve ventricular function. Amlodipine has also been shown to be as useful as chlorthalidone in reducing blood pressure in patients with stage 1 hypertension.

A number of studies have been completed comparing various calcium-channel blockers to other antihypertensive drugs in older subjects with combined systolic and diastolic hypertension. The Swedish Trial in Old Patients with Hypertension (STOP-2) enrolled 6600 patients ranging in age from 70 to 84 years with a supine blood pressure of 180/105 mm Hg or higher. The original STOP trial compared the effects of diuretics and beta blockers in elderly hypertensives in terms of cardiovascular morbidity and mortality. STOP-2 compared these 2 treatments with a calcium-channel blocker (felodipine or isradipine) or an ACE inhibitor (enalapril or lisinopril). There was no difference between the 3 treatment groups with respect to the combined endpoints of fatal stroke, fatal MI, and other cardiovascular diseases. There was a lower incidence of nonfatal MI and CHF in the ACE inhibitor group compared to the other treatment modalities.

In the International Nifedipine Study Intervention as a Goal in Hypertension Treatment (INSIGHT), 6321 elderly patients aged 55 to 80 years were randomized to double-blind treatment with either long-acting nifedipine GITS or the combination drug co-amilozide (hydrochlorothiazide and amiloride). The study endpoints were overall cardiovascular morbidity and mortality, and both treatments appeared equally effective in preventing vascular events. In the Nordic Diltiazem Study (NORDIL), 10,881 patients aged 50 to 74 years with systemic hypertension were randomized to receive first-line therapy with either diltiazem, diuretics, or a beta blocker. Diltiazem was as effective as the other treatments in reducing the incidence of combined study endpoints of stroke, MI, and other cardiovascular death. Another smaller study was conducted among Japanese patients 60 years or older (National Intervention Cooperative Study in Elderly Hypertensives [NICS-EH]). Inclusion criteria were systolic blood pressure 160 to 220 mm Hg and diastolic blood pressure < 115 mm Hg after a 4-week placebo period and no history of cardiovascular complications. The number of cardiovascular events was low owing to the small sample size and to the inclusion criteria. There was no difference in combined cardiovascular endpoints.

The Hypertension Optimal Treatment (HOT) trial studied 18,000 patients aged 50 to 80 years. The study examined whether maximal reduction of diastolic blood pressure with antihypertensive drugs and aspirin could cause a further reduction in cardiovascular events (MI or stroke) or be associated with harm (J-curve hypothesis). Felodipine, a long-acting dihydropyridine, was used as the first-line treatment for all patients, and aspirin (75 mg) or a placebo was also given. An ACE inhibitor, a beta blocker, and a thiazide diuretic could be given to achieve the desired diastolic blood pressure goal. The study results showed that maximal protection with antihypertensive therapy was seen when a diastolic blood pressure of 82.6 mm Hg was achieved; in diabetic patients, an additional reduction in diastolic blood pressure (below 80 mm Hg) was needed to achieve maximal benefit. A J-curve response was not observed despite major reductions in blood pressure. The HOT study demonstrated a greater success in achieving blood pressure targets among the oldest subjects, with a low incidence of medication adverse effects.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), sponsored by the National Heart, Lung, and Blood Institute, was one of the largest prospective, randomized studies ever undertaken. The study enrolled 42,418 patients over the age of 55 years. The goal of the study was to compare 4 antihypertensive interventions—long-acting calcium antagonist (amlodipine), ACE inhibitor (lisinopril), diuretic (chlorothalidone), and alpha blocker (doxazosin), in terms of their ability to impact coronary artery disease-related events. Fifty percent of the patients also received pravastatin to test the benefits of lowered cholesterol in older patients. The study showed that amlodipine performed admirably in comparison with chlorthalidone relative to all endpoints other than the new onset CHF. Based on the ALLHAT findings, calcium channel blockers can be considered an acceptable treatment alternative in diuretic-intolerant patients. However, ALLHAT did not explore the issue of adding calcium channel blockers to ongoing diuretic therapy. There is experimental support for such a combination in reducing blood pressure, more so than with either component alone.

The Controlled-Onset Verapamil Investigation of Cardiovascular Events (CONVINCE) trial was designed to compare a delayed/slow-release verapamil delivery system to atenolol or hydrochlorothiazide in 15,000 hypertensive patients aged 55 years of age or above. The study was stopped by the sponsor for cost reasons, and the accumulated data from the trial showed no advantage of using the verapamil delivery system on morbidity and mortality cardiovascular events.

The calcium-channel blockers reduce both systolic and diastolic pressures with minimal adverse effects, including orthostasis. They can cause left ventricular hypertrophy to regress in patients with hypertension. These drugs may also exhibit antiadrenergic and natriuretic activities and can normalize the abnormal coronary vasomotion often observed in hypertensive patients.
can be combined with other antihypertensive drugs if necessary (beta blockers, ACE inhibitors, angiotensin receptor blockers [ARBs], and diuretics).97

There is also a growing experience with combination antihypertensive products13,123 that use a calcium channel blocker as part of the formulation. Innovative combination products that are approved for clinical use include: enalapril/extended-release diltiazem, benazepril/amiodipine,125 trandolapril/extended-release verapamil,123 extended-release felodipine/enalapril, amlopidine/valsartan,124 amloidipine/olmesartan,125 and amlodipine/valsartan/diuretic. A combination of extended-release felodipine/extended-release metoprolol has been evaluated in the United States,126 but is not yet available for clinical use.

Combination benazepril/amlopidine was shown to be more effective than a benazepril/hydrochlorothiazide combination in reducing the risk of MI and stroke in the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial.127,128 Other trials that compared thiazide/beta blocker combination therapy to calcium blocker/ACE inhibitor combination therapy have shown no significant difference in the primary outcomes.129,130

Calcium-channel blockers are equally effective in both black and white patients and in the young as well as the old.97,131 Women may have greater blood pressure–lowering effects than men with comparable doses of drug.132 They do not lower the pressures of normotensive patients.97 These drugs may be most useful in patients with low-renin, salt-dependent forms of hypertension.133 Despite the widespread use of calcium-channel blockers as a class for treating hypertension, there are still questions regarding their relative cardioprotective efficacy compared to other antihypertensive agents.138

Hypertension with Concomitant Diabetes

Compared with the placebo, nitrendipine has been shown to reduce the risk for subsequent cardiovascular events and mortality. In the SYST-EUR study,106 10.5% of patients had diabetes mellitus. Among those, systolic blood pressure was slightly higher than among patients without diabetes mellitus. Compared with the placebo, the relative risk reduction for fatal and nonfatal strokes was 73%; the relative risk reduction for cardiovascular mortality was 76%, which clearly exceeded the benefit seen in non-diabetic patients.115 Although not statistically significant, there was a 57% reduction in relative risk for MI. In line with these findings are the results of the SYST-China, trial with a large risk reduction among the subgroup of patients with diabetes mellitus.109

Although calcium-channel blockers in diabetic subjects are associated with a clear risk reduction compared with the placebo, the results of studies where calcium-channel blockers were compared with other blood pressure–lowering drugs, in particular ACE inhibitors and ARBs, appear to be less favorable. In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial,136 nisoldipine was compared with enalapril among patients with non-insulin-dependent diabetes mellitus with or without hypertension. Among the primary aims of the study was to test the effect of the calcium-channel blocker nisoldipine on risk of cardiovascular events. The trial was terminated early because in the subgroup of patients with hypertension receiving nisoldipine, there was a significant excess of MI. Compared with enalapril, the secondary endpoint fatal and nonfatal MI was strongly increased 25 versus 5.

Similarly, in the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET),137 compared with fosinopril, patients randomized to calcium-channel blockers had a twofold excess in combined cardiovascular endpoints (27 versus 14). However, in a subanalysis of the STOP-2 trial113 that included a large number of patients with diabetes mellitus, the potential disadvantage of calcium-channel blockers compared with other treatments was less impressive.

Compared with the placebo, calcium antagonists apparently reduce the risk for clinical endpoints among patients with diabetes mellitus and hypertension; but in head-to-head comparison, there is evidence that ACE inhibitors are superior to calcium blockers in reducing cardiovascular endpoints and for reducing the rate of progression of renal disease.138 However, the superiority of other treatments over calcium blockers may be small or even absent.

Hypertension with Concomitant Heart Disease

Despite the widespread use of calcium-channel blockers for the treatment of systemic hypertension, there are still questions regarding their relative cardioprotective efficacy compared to other antihypertensive agents.139

In 1995, there were 2 published reports suggesting an increased risk of MI and mortality in hypertensive patients receiving the short-acting calcium-channel blockers (verapamil, diltiazem, nifedipine) as treatment compared with patients receiving other antihypertensive therapies, which included diuretics and beta blockers.140,141 These reports were case-control studies that have built into their experimental design significant methodologic flaws. Subsequently, a great debate appeared in the medical literature regarding the safety of calcium-channel blockers as a class for treating hypertension.142-144 Based on the available evidence, the US Food and Drug Administration (FDA) has advised physicians not to use the short-acting dihydropyridine calcium-channel blockers for treating hypertension, but it placed no restrictions on the first-line supplementary use of sustained-release calcium-channel blocker formulations or longer-acting formulations available for this indication where there appears to be no apparent harm with their use.138

In the treatment of hypertension, dihydropyridine calcium-blockers appear to be as efficacious as diuretics in reducing cardiovascular and cerebrovascular morbidity
and mortality. In hypertensive patients with angina, beta blockers should be the initial treatment of choice, with calcium blockers used as an add-on treatment or as an alternative monotherapy in individuals intolerant of beta blockers. In patients with hypertension and heart failure, ACE inhibitors, beta blockers, and diuretics are the treatment of choice, with calcium blockers as a possible add-on treatment. In patients with diabetes mellitus, there is strong evidence for the use of ACE inhibitors or angiotensin II blockers over calcium blockers. The ACE inhibitors seem also to provide a greater venoprotective effect than calcium blockers in hypertensive patients.\textsuperscript{145}

In addition, calcium channel blockers are not as effective as drugs that inhibit the renin-angiotensin system on reducing proteinuria and the rate of progression of renal disease in diabetic patients.\textsuperscript{146,147}

In patients without evidence of coronary artery disease, heart failure, renal disease, or diabetes mellitus, calcium-channel blockers can be considered a front-line therapy with efficacy similar to that of other antihypertensive agents.

Hypertensive Emergencies and Perioperative Hypertension

Some of the calcium-channel blockers have also been shown to be beneficial and safe in patients with severe hypertension and hypertensive crises.\textsuperscript{97,148,149} Single oral, sublingual, and intravenous doses of these drugs have rapidly and smoothly reduced blood pressure in adults and children without causing significant untoward effects.\textsuperscript{148,149} The absolute reduction in blood pressure with treatment appears to be inversely correlated with the height of the pretreatment blood pressure level, and few episodes of hypotension have been reported.\textsuperscript{144} Intravenous nicardipine\textsuperscript{150,151} and clevidipine\textsuperscript{152} are available for parenteral treatment of hypertensive emergencies and perioperative hypertension, and both therapies require the hemodynamic monitoring of patients. A nicardipine infusion is initiated at a dose of 5 mg/h, which can be titrated to a dose of 15 mg/h. Its onset of action is within 1-5 minutes but it has a long terminal half-life of 6 hours. A clevidipine infusion is initiated at a dose of 1-2 mg/h, which can be titrated to 16 mg/h (the usual dose is 4-6 mg/h). Its onset of action is within 2-4 minutes; however, because it is rapidly metabolized by blood esterases, its terminal half life is 5-15 minutes, providing a possible safety advantage over nicardipine. Since clevidipine is in a lipid emulsion, lipid intake may need to be restricted in patients with disorders of lipid metabolism.

Silent Myocardial Ischemia

In addition to their favorable effects in relieving painful episodes of myocardial ischemia, the calcium blockers are also effective in relieving transient myocardial ischemic episodes (detected by ECG) that are unrelated to symptoms (silent myocardial ischemia).\textsuperscript{153} Diltiazem,\textsuperscript{154} nifedipine (low-dose), amiodipine,\textsuperscript{168} and verapamil alone and in combination with beta blockers and nitrates have all been shown to be effective in reducing the number of ischemic episodes and their duration.\textsuperscript{154,155} The prognostic importance of relieving silent myocardial ischemia with calcium blockers and other treatments was evaluated in a study sponsored by the National Heart Lung and Blood Institute, the Asymptomatic Coronary Ischemia Pilot (ACIP).\textsuperscript{156,157}

Myocardial Infarction

Several experimental studies have indicated that nifedipine, verapamil, and diltiazem can reduce the size of myocardial necrosis induced in experimental ischemia.\textsuperscript{158} Ischemia can lead to diminished ATP production, which can eventually affect the sodium and calcium ion pumps, with the ultimate consequence of calcium ion accumulation in the cytoplasm and calcium overload in the mitochondria. Calcium-channel blockers can diminish myocardial oxygen consumption and inhibit the influx of calcium ions to the myofibrils and thus favorably influence the outcome of experimental coronary occlusion.\textsuperscript{158} These experimental observations have suggested the use of calcium-channel blockers for reducing or containing the extent of MI during acute coronary artery occlusions in human beings and as an adjunct to cardioplegia during open heart surgery. However, there have been no adequate studies in human beings to support these approaches.

Compared with the established protective actions of some beta-blocking drugs used intravenously or orally in prolonging life and reducing the risk of nonfatal reinfarction in survivors of an acute MI, the results with calcium-channel blockers (diltiazem, lidoflazine, nifedipine, verapamil) have not been as favorable.\textsuperscript{159} The results of a meta-analysis looking at the effects of immediate-release nifedipine in patients surviving MI even suggested the potential for harm,\textsuperscript{160} which also prompted a debate in the literature\textsuperscript{145} regarding the safety of calcium-channel blockers as a treatment class for patients surviving MI.

The plausibility of these mortality results with calcium blockers are supported by a failure to show a beneficial effect on infarct size, development of MIs, or reinfarctions in most trials of patients with MIs or unstable angina.\textsuperscript{159} A trial using diltiazem in patients with non-Q-wave infarction reported a reduction in recurrent MI in the diltiazem-treated patients but no reduction in mortality.\textsuperscript{161} In a larger trial with diltiazem in infarction survivors, no favorable effects on mortality were seen.\textsuperscript{162} A subgroup of patients with LV dysfunction did worse with diltiazem therapy than with the placebo; however, diltiazem therapy appeared to be effective in patients with relatively normal LV function.\textsuperscript{162} Similarly, a study did show...
benefit of verapamil compared with the placebo in infarction survivors, with less benefit observed in patients with LV dysfunction. 163

A double-blind study was completed comparing oral diltiazem and aspirin with aspirin alone (Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis [INTERCEPT]) in patients with MI who had received thrombolytic therapy. The study, which enrolled 874 subjects and treatment with diltiazem, did not reduce the cumulative occurrence of cardiac death, nonfatal reinfarction, or refractory ischemia during a 6-month follow up, but it did reduce composite endpoints of nonfatal cardiac events, particularly the need for myocardial revascularization. 164 In another study, intravenous diltiazem given as an adjunct to thrombolysis in acute MI was shown to have protective effects, with no effect on coronary artery patency and LV function and perfusion. 165

Prophylactic use of calcium-channel blockers to improve patient survival following MI cannot be recommended as a first-line therapy unless there are specific indications for using these drugs. 166 However, in patients with contraindications to beta-adrenergic blockade, one can consider using verapamil or diltiazem in survivors of MI who have good LV function. 159, 167

Hypertrophic Cardiomyopathy

Propranolol remains the therapeutic agent of choice 168 for symptomatic patients with hypertrophic cardiomyopathy. The beneficial effects produced by propranolol derive from its blocking of sympathetic stimulation of the heart. 169

Clinical studies have shown that the administration of verapamil can also improve exercise capacity and symptoms in many patients with hypertrophic cardiomyopathy. 170, 171 The exact mechanism by which verapamil produces these beneficial effects is not known. Acute and chronic verapamil administration reduces LV outflow obstruction, but examination of indices of LV systolic function during chronic therapy shows that this effect does not result from a reduction in LV hypercontractility. 172 Since patients with hypertrophic cardiomyopathy also exhibit abnormal diastolic function, it is likely that improvement in diastolic filling may be responsible in part for the benefit conferred by verapamil. 170 Enhanced early diastolic filling and improvement in the diastolic pressure-volume relation might be expected to result in an increase in LV end-diastolic volume, which would decrease the Venturi forces that act to move the anterior mitral valve leaflet across the outflow tract toward the septum. 170 This decrease would cause a diminution of obstruction, reducing LV pressure and myocardial wall stress and thus raising the threshold at which symptoms occur. 170

In a large study of patients with hypertrophic cardiomyopathy refractory to beta blockers, 170 verapamil proved to be effective on a long-term basis, with almost 50% of patients showing either a significant improvement in exercise tolerance, an improvement in symptoms, or a reduction in myocardial ischemia. 171 Approximately 50% of patients who were considered to be candidates for surgery because of moderately severe symptoms unresponsive to propranolol showed significant improvement on verapamil, and surgery was no longer considered necessary. 170

Other studies have reported that chronic administration of verapamil cannot only improve symptoms in patients with hypertrophic cardiomyopathy but also reduce the LV muscle mass and the ventricular septal thickness measured by echocardiographic and ECG analyses. 171 Verapamil and nifedipine were shown to improve the impaired LV filling characteristics. 172, 173 This beneficial effect on LV diastolic relaxation has not occurred after propranolol. 173

There may be serious and fatal complications of verapamil treatment in patients with hypertrophic cardiomyopathy. 170 These complications result from the accentuated hemodynamic or electrophysiologic effects of the drug. It is not clear whether the fatal complications occur as a result of verapamil-induced reduction in blood pressure with a resultant increase in LV obstruction or the negative inotropic effects of the drug. 170 Verapamil probably should not be used in patients with clinical CHF. The loss of sequential atrial ventricular depolarization caused by the electrophysiologic effects of the drug could also compromise cardiac function. The adverse electrophysiologic effects are often transient; however, they could prevent the use of larger drug doses that might provide better relief. 170

If the calcium-entry blocking effects of verapamil are responsible for its therapeutic actions in hypertrophic cardiomyopathy, other drugs in this class may also be useful. However, the results of a double-blind trial comparing verapamil with nifedipine indicated that verapamil is more effective than nifedipine in improving exercise tolerance and clinical symptoms. 174 Diltiazem was recently shown to improve active diastolic function in patients with hypertrophic cardiomyopathy; however, certain patients had a marked increase in outflow obstruction. 175

Congestive Cardiomyopathy

The potent systemic vasodilatory actions of nifedipine and other dihydropyridine calcium-entry blockers make them potentially useful as afterload-reducing agents in patients with LV failure. 29, 34, 176, 177 Unlike other vasodilatory drugs, however, nifedipine also exerts a direct negative inotropic effect on the myocardium that is consistent with its ability to block transmembrane calcium transport in cardiac muscle cells. 29, 30 The successful use of nifedipine as a vasodilator in patients with LV failure would be dependent on its effect to reduce ventricular afterload exceeding its direct negative inotropic actions, thereby...
leading to an improvement in hemodynamics and forward flow.\textsuperscript{59}

Studies evaluating the effect on hemodynamics of nifedipine used in combination with other vasodilators in patients with heart failure have uniformly demonstrated significant reductions in systemic vascular resistance, usually associated with increases in cardiac output.\textsuperscript{39,178} It has been found that resting ejection fractions also rise with nifedipine therapy.\textsuperscript{178} Reflex increases in heart rate have been reported,\textsuperscript{179} but most investigators have found heart rate to remain the same\textsuperscript{179} and, in isolated cases, to fall.\textsuperscript{180} LV filling pressures usually decrease\textsuperscript{179} or do not change significantly,\textsuperscript{180} but there are instances where pulmonary capillary wedge pressures rise with the use of nifedipine in heart failure.\textsuperscript{181} Patients with LV dysfunction and nearly normal levels of LV afterload—that is, disproportionately low wall stress—and those with intrinsic fixed mechanical interference to forward flow, such as aortic stenosis, appear most likely to have unfavorable hemodynamic responses to nifedipine therapy.\textsuperscript{34} Most of the published data have dealt only with the acute hemodynamic effects of the agent after single sublingual dosing, with little work done on the use of nifedipine as chronic oral therapy for LV failure.

Initially, there was a promising experience in clinical trials with the newer dihydropyridine calcium blockers amiodipine and felodipine in patients with congestive cardiomyopathy.\textsuperscript{182,184} A study has demonstrated the efficacy and safety of diltiazem in patients with idiopathic cardiomyopathy.\textsuperscript{185}

Although evidence is incomplete, there are indications that a cardiac tissue renin-angiotensin system may counteract the actions of calcium-channel blockers, especially in patients with heart failure.\textsuperscript{34} However, since calcium-channel blocking drugs are potent vasodilators, particularly on the arterial circulation, the combination of an ACE inhibitor and a calcium-channel blocker might appear to be useful in further augmenting vasodilation, thus improving myocardial perfusion and ejection fraction. Hence, the Third Vasodilator-Heart Failure Trial (V-HeFT III) was conducted to test the efficacy of the combination of felodipine, enalapril, digoxin, and a diuretic in patients with CHF.\textsuperscript{186} The endpoints evaluated were exercise tolerance, quality of life, LV function, levels of plasma norepinephrine and atrial natriuretic factor, and reduction in occurrence of arrhythmias and mortality.\textsuperscript{187} A similar pilot multicenter, placebo-controlled study was carried out using amlodipine in addition to ACE inhibitors, digoxin, and diuretics. This study, known as the Prospective Randomized Amlodipine Survival Evaluation (PRAISE), indicated no clear overall mortality or harm from the use of the drug in patients with severe CHF.\textsuperscript{188} Contrary to the prior experiences of the investigators, there appeared to be little beneficial effect in the large subgroup of patients who had coronary artery disease and a barely significant reduction in morbidity and mortality in the minority of patients who did not have coronary artery disease.\textsuperscript{189}

The investigation was followed up in a study (PRAISE II) comparing amlodipine to the placebo in a study of 1800 patients having cardiomyopathy without coronary artery disease who were receiving digoxin, diuretics, and ACE inhibitors with no additional benefit from the calcium blocker being observed.\textsuperscript{190}

In a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) where enalapril was compared with the placebo in patients with class I to III heart failure, it was observed that those patients who were receiving concomitant immediate-release calcium-channel blocker treatment had a higher mortality than subjects who were receiving concomitant beta-blocker therapy.\textsuperscript{191}

Use of long-acting dihydropyridine calcium blockers as adjunctive vasodilator therapy in patients with LV failure should be considered only if additional clinical reasons for their administration exist—that is, angina, systemic hypertension, and aortic regurgitation,\textsuperscript{192,193} particularly if these conditions play important contributory roles in the development or exacerbation of LV dysfunction. Some investigators now propose that calcium antagonists may provide some benefit to patients with predominant diastolic ventricular dysfunction,\textsuperscript{193,194} but more clinical data are needed to substantiate this claim.

**Aortic Regurgitation**

Dihydropyridine calcium blockers have been used successfully as arterial vasodilators in patients with chronic asymptomatic aortic and mitral regurgitation. These beneficial hemodynamic effects may postpone the need for valve replacement.\textsuperscript{195}

**Primary Pulmonary Hypertension**

Primary pulmonary hypertension is an entity characterized by excessive pulmonary vasoconstriction and increased pulmonary vascular resistance induced by unknown stimuli.\textsuperscript{196} It has been suggested that endothelial cell dysfunction and injury may be responsible for the disease process.\textsuperscript{197}

Based on the available data, it may be concluded that some calcium-channel antagonists provide beneficial responses in selected patients with pulmonary hypertension.\textsuperscript{196,198} In general, patients with less severe pulmonary hypertension appear to respond better than those with more advanced disease.\textsuperscript{199} Furthermore, early treatment may serve to attenuate progression of the disease (see also Chapter 25, Prostacyclins, Endothelin Inhibitors, and Phosphodiesterase-5 Inhibitors in Pulmonary Hypertension).

In patients with chronic hypoxia-induced pulmonary vasoconstriction, the use of calcium-channel blockers
Cerebral Arterial Spasm and Stroke

A major complication of subarachnoid hemorrhage is cerebral arterial spasm, which may occur several days after the initial event. Such a spasm may be a focal or diffuse narrowing of one or more of the larger cerebral vessels, which may cause additional ischemic neurologic deficits (see also Chapter 33, Drug Therapy of Cerebrovascular Disease). Although the exact etiology of this spasm is unknown, a combination of various blood constituents and neurotransmitters has been postulated to produce a milieu that enhances the reactivity of the cerebral vasculature. The final pathway for the vasoconstriction, however, involves an increase in the free intracellular calcium concentration. Accordingly, it is reasonable to postulate that the calcium-channel antagonists may have a beneficial effect in reducing cerebral spasm.

Although verapamil and nifedipine have been shown to prevent cerebral arterial spasm in experimental studies, nimodipine and nicardipine, both analogues of nifedipine, have demonstrated a preferential cerebrovascular action in this disorder. The lipid-solubility of nimodipine enables it to cross the blood-brain barrier; this may account for its more potent cerebrovascular effects. In a multicenter placebo-controlled study involving 125 patients, it was demonstrated that nimodipine significantly reduced the occurrence of severe neurologic deficits following angiographically demonstrated cerebral arterial spasm.

All patients had a documented subarachnoid hemorrhage and a normal neurologic status within 96 hours of entry into the study. Although 8 of the 60 placebo-treated patients developed a severe neurologic deficit, only 1 of 55 nimodipine-treated patients experienced such an outcome. Nimodipine is approved for the improvement of neurologic outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured congenital aneurysms who are in good neurologic condition after ictus. The recommended dose is 60 mg by mouth every 4 hours for 21 consecutive days.

Subsequent investigations have suggested that increased cellular calcium concentration may be implicated in neuronal death after ischemia. Nimodipine administered to laboratory animals after global cerebral ischemia had a more favorable effect on neurologic outcome than did the placebo. The results of a prospective double-blind placebo-controlled trial of oral nimodipine administered to 186 patients within 24 hours of an acute ischemic stroke showed a reduction in both mortality and neurologic deficit with active treatment. The benefit was confined predominantly to men. However, subsequent studies where nimodipine therapy was begun up to 48 hours after the onset of symptoms revealed no benefit of therapy.

Migraine and Dementia

Classic migraine is characterized by prodromal symptoms with transient neurologic deficits (see also Chapter 33, Drug Therapy of Cerebrovascular Disease). Cerebral blood flow is reduced during these prodromes and then is increased during the subsequent vasodilatory phase, causing severe headache. Because the entry of calcium ions into the smooth muscle cells is the final common pathway that controls vasomotor tone, calcium antagonists may prevent or ameliorate the initial focal cerebral vasoconstriction.

Results from controlled studies have demonstrated that 80%-90% of patients with vascular headaches benefit from nimodipine, confirming the selectivity of this agent for the cerebral blood vessels. Verapamil and nifedipine have also been reported to be effective in the prophylaxis of migraine but are less selective for the cephalic blood vessels and thus cause more systemic adverse effects. Relief from the migraine prodrome usually began 10 to 14 days after initiation of the drugs but could be delayed 2 to 4 weeks. Cerebral vascular resistance was decreased by all 3 established calcium antagonists, but only nimodipine reduced the cerebral vasoconstriction induced by inhalation of 100% oxygen. None of the calcium-entry blocking drugs are effective against muscle contraction or tension headaches.

Multiple clinical trials have been carried out to examine the effects of calcium-entry blockers on the progression of dementing illness, including both vascular and Alzheimer types, with the results showing equivocal benefit from treatment. However, the SYST-EUR trial showed a reduction in the incidence of cognitive decline in elderly patients receiving nitrrendipine for isolated systolic hypertension compared to the placebo.

Other Vascular Uses

Amaurosis Fugax

Hypoperfusion of the retinal circulation may lead to a brief loss of vision in one eye, a syndrome known as amaurosis fugax. This brief loss of sight has been attributed to embolism from the heart or great vessels or to carotid occlusive disease. In a small group of patients with amaurosis but no signs of emboli or carotid hypoperfusion, administration of aspirin or warfarin did not relieve symptoms. However, oral doses of either verapamil or nifedipine abolished attacks. In several patients,
the attacks returned when the calcium-blocking agent was discontinued.

High-Altitude Pulmonary Edema
Hypoxic pulmonary hypertension appears to play a role in the pathogenesis of high-altitude pulmonary edema. Nifedipine has been used for the emergency treatment of this condition, its benefit coming from its ability to reduce pulmonary artery pressure.216

Raynaud’s Phenomenon
Raynaud’s phenomenon (see also Chapter 34, Drug Treatment of Peripheral Vascular Disorders) is characterized by well-demarcated ischemia of the digits with pallor or cyanosis ending abruptly at one level on the digits.217 Nifedipine has been shown to decrease the frequency, duration, and intensity of vasospastic attacks in approximately two-thirds of patients with primary or secondary Raynaud’s phenomenon.218,219 Patients with primary Raynaud’s phenomenon usually demonstrate the most improvement; digital ulcers have been reported to heal in patients with scleroderma. Doses of 10 to 20 mg of nifedipine thrice daily have been used. Amlodipine, felodipine and isradipine are as effective as nifedipine. Diltiazem, 60 to 360 mg daily, was also useful in patients with primary or secondary Raynaud’s phenomenon in multiple placebo-controlled trials.217

Atherosclerosis
Atherosclerosis develops through numerous and interrelated processes involving the accumulation of cholesterol, calcium, and matrix materials in the major arteries and at lesion sites. Many of the intracellular and extracellular processes involved in atherosclerotic plaque formation require calcium, and it has been suggested that large deposits of cholesterol may trigger physiologic changes in membranes that favor uptake of calcium into the vascular smooth muscle.220

The results of controlled studies employing angiography have suggested that some calcium-channel blockers may retard the progression of atherosclerosis in humans.221–223 In the International Nifedipine Trial on Atherosclerosis Coronary Therapy (INTACT) study,221 it was shown that nifedipine reduced the formation of new lesions when compared with the placebo. However, nifedipine had no effect on the progression or regression of already existing coronary lesions, and an increased mortality compared to the placebo was observed.

There is a suggestion from available experimental and clinical data that calcium blockers have an atherosclerotic plaque-stabilizing action.224 However, in a study with amlodipine, it was shown that the drug had no demonstrable effects on the progression of coronary atherosclerosis or the risk of major cardiovascular events.225 Amlodipine is combined with atorvastatin in a single pill formulation for the treatment of both hypertension and hyperlipidemia.226

The administration of nicardipine for 24 months also had no effect on the progression or retardation of advanced stenoses in patients with coronary atherosclerosis as confirmed by arteriography.210 However, the drug did appear to retard the progression of small lesions. Diltiazem was shown to retard the development of coronary artery disease in heart transplant recipients,227 an action independent of the drug’s blood pressure-lowering effect.

In the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS),228 which was a 3-year, double-blind, randomized trial designed to compare the effectiveness of isradipine and hydrochlorothiazide in retarding the progression of atherosclerotic lesions in the carotid arteries, no apparent benefit was seen with either treatment. A similar study to MIDAS was carried out with lacidipine, a newer dihydropyridine calcium antagonist, in the 4-year European Lacidipine Study on Atherosclerosis (ELSA).229

Calcium blockers have also been used to treat patients with intermittent claudication and mesenteric insufficiency.230

Other Cardiovascular Uses
Diltiazem has been used as part of an ice-cold cardioplegia solution in patients undergoing coronary surgical procedures.231 The addition of diltiazem appeared to preserve high-energy phosphate levels with an improvement in hemodynamics in the postoperative period.232 Concomitant use of nifedipine appears to reduce the incidence of MI and transient ischemia in patients undergoing bypass surgery.232

Intracoronary diltiazem has been used to reduce the severity and delay the onset of ischemic pain in patients undergoing percutaneous transluminal angioplasty.233 Calcium blockers have also been used as a long-term treatment to prevent restenosis following balloon angioplasty with questionable benefit.234 They have also been used to prolong graft patency in patients with radial artery coronary bypass grafts with no apparent benefit seen.

It has been shown that coronary artery vasospasm may be an important pathophysiologic mechanism in explaining some types of experimental cardiomyopathy. Experimentally, verapamil has been shown to reduce vasospasm in response to myocarditis and by this mechanism to prevent the development of cardiomyopathy.235 Calcium blockers (diltiazem and verapamil) have also been found to preserve the functioning of human renal transplants.236 The drugs dilate the preglomerular afferent arterioles and appear to possess
inherent immunosuppressive properties and the ability to ameliorate the nephrotoxic effects of cyclosporine.237

Adverse Effects

In addition to their widely varying effects on cardiovascular function, these agents also have differing spectra of adverse effects (Table 8-8).1,97 Immediate-release nifedipine is associated with a very high incidence of minor adverse effects (approximately 40%), but serious adverse effects are uncommon.218 The most frequent adverse effects reported with nifedipine and other dihydropyridines include headache, pedal edema, flushing, paresthesias, gingival hyperplasia, and dizziness; the most serious adverse effects of this drug include exacerbation of angina and occasional hypotension.238 These adverse effects are reduced in number with the long-acting formulation of nifedipine240 and may also be fewer in number with some of the long-acting dihydropyridine calcium antagonists. The adverse effect of pedal edema is often reduced when dihydropyridines are combined with ACE inhibitors.

Diltiazem and verapamil can exacerbate sinus node dysfunction and impair AV nodal conduction, particularly in patients with underlying conduction system disease.1,4 The most frequent adverse effect of verapamil is constipation.497 The drug may also worsen CHF, particularly when used in combination with beta blockers or disopyramide.497 There have been recent reports of verapamil-induced parkinsonism.241 Most of the adverse effects noted with diltiazem have been cardiovascular, with occasional headache and gastrointestinal complaints.497 The adverse effects of calcium blockers may increase considerably when these agents are used in combination.54

An increased risk of gastrointestinal hemorrhage in older patients has been reported with calcium-channel blockers, as well as intraoperative bleeding during coronary artery bypass surgery.242 An increased risk of developing cancer in older subjects has also been reported.243 These findings have not been confirmed by subsequent studies.244,245

Drug Withdrawal

Serious problems that appear to be related to heightened adrenergic activity54 have been reported with abrupt withdrawal of long-term beta-blocker therapy in patients with angina. Clinical experiences with the withdrawal of calcium-entry blockers suggest that although patients with angina get worse after treatment when a calcium-entry blocker is stopped abruptly, there is no evidence of an overshoot in anginal symptoms.55,54

Drug Overdose

Calcium-entry blocker overdosage has been described with increasing frequency. The cardiovascular problems associated with this condition are hypotension, LV conduction, bradycardia, nodal blocks, and asystole. Treatment approaches are described in Table 8-9.246-248

Drug–Drug Interactions

There are few data on the interactions of diltiazem with other drugs.1,54 Rifampin severely reduces the bioavailability of oral verapamil by enhancing the first-pass liver metabolism of the drug. Both nifedipine and verapamil increase serum digoxin levels, an observation not made with diltiazem (see Chapter 31, Cardiovascular Drug–Drug Interactions). Verapamil has been reported to increase serum digoxin levels by approximately 70%55,249 apparently by decreasing renal clearance,249 nonrenal clearance, and the volume of distribution.250 Studies of the time course of this effect show that it begins with the first dose and reaches steady state within 1 to 4 weeks. Nifedipine also has been reported to increase serum digoxin concentrations in patients but to a lesser extent (about 45%).251 Verapamil249 and diltiazem252 have additive effects on AV conduction in combination with digitalis. They can be used to cause further decreases in heart rate compared with digitalis alone when patients are in atrial fibrillation.

Combinations of propranolol with nifedipine or verapamil have been extensively studied for the therapy of angina. Several studies have shown improved efficacy for the combination of atenolol and nifedipine compared with any of the drugs used alone.253 Hemodynamic studies have shown mild negative inotropic effects of verapamil in patients on a beta blocker.257 There are also slight decreases in heart rate, cardiac output, and LV ejection fraction.258

Combinations of propranolol and propranolol or metoprolol and of verapamil and propranolol are well tolerated by patients with normal LV function, but there may be a greater potential for hemodynamic compromise in patients with impaired LV function with combined verapamil-propranolol treatment.259 Combinations of diltiazem, nifedipine, or verapamil with nitrates are well tolerated and clinically useful.3 When diltiazem is combined with nifedipine, blood levels of nifedipine increase significantly, which may contribute to an increased frequency of adverse reactions with this combination.54 The combination of verapamil and nifedipine is less effective in lowering pressure than diltiazem plus nifedipine, perhaps related to the diltiazem-nifedipine pharmacokinetic interaction.254
### Table 8-8. Adverse Effects of Orally-Active Calcium-Channel Blockers

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Headache</th>
<th>Dizziness</th>
<th>GI</th>
<th>Flushing</th>
<th>Paresthesia</th>
<th>Decreased SA and/or AV Conduction</th>
<th>CHF</th>
<th>Hypotension</th>
<th>Pedal Edema</th>
<th>Worsening of Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>3+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Diltiazem SR</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>3+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Verapamil</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>3+</td>
<td>0</td>
<td>0</td>
<td>3+</td>
<td>2+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Verapamil SR</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>3+</td>
<td>0</td>
<td>0</td>
<td>3+</td>
<td>2+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>15</td>
<td>2+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>2+</td>
</tr>
<tr>
<td>Isradipine</td>
<td>15</td>
<td>2+</td>
<td>2+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>2+</td>
<td>0</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>20</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>3+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>2+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Nifedipine SR</td>
<td>40</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>2+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>GITS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>3+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>2+</td>
<td>+</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>15</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>15</td>
<td>2+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>2+</td>
<td>2+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Felodipine</td>
<td>20</td>
<td>2+</td>
<td>2+</td>
<td>+</td>
<td>2+</td>
<td>+</td>
<td>0</td>
<td>2+</td>
<td>+</td>
<td>2+</td>
<td>0</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; SA = sinoatrial node; AV = atrioventricular node; CHF = congestive heart failure; 0 = no report; + = rare; 2+ = occasional; 3+ = frequent; SR = sustained-release; GITS = gastrointestinal therapeutic system.


### Table 8-9. Cardiovascular Toxicity with Calcium-Channel Blockers and Recommendations for Treatment

<table>
<thead>
<tr>
<th>Effects*</th>
<th>Suggested Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profound hypotension</td>
<td>10% calcium gluconate or calcium chloride; epinephrine, norepinephrine or dopamine</td>
</tr>
<tr>
<td>Severe LV dysfunction</td>
<td>10% calcium gluconate or calcium chloride; insulin; isoproterenol or dobutamine; glucagon; milrinone, norepinephrine or dopamine</td>
</tr>
<tr>
<td>Profound bradycardia</td>
<td>Atropine sulfate (not always effective)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>10% calcium gluconate or calcium chloride</td>
</tr>
<tr>
<td>SA- and AV-nodal block</td>
<td>Isoproterenol or dobutamine</td>
</tr>
<tr>
<td>Asystole</td>
<td>External cardiac massage and cardiac pacing (if above measures fail)</td>
</tr>
</tbody>
</table>

AV = atrioventricular; LV = left ventricular; SA = sinoatrial.

*These effects are seen more frequently in patients who have underlying myocardial dysfunction and/or cardiac conduction abnormalities and who are receiving concomitant beta-adrenergic blocker treatment.


**Conclusion**

Each of the calcium antagonists exerts its effects through inhibition of slow-channel–mediated calcium ion transport. However, many of the drugs appear to accomplish this by different mechanisms and with differing effects on various target organs. These differences allow the clinician to select the particular drug most suitable for the specific needs of the patient. In addition, the adverse-effect profiles of these drugs (with little overlap between them) assure that most patients will tolerate at least one of these agents.

*Note: References for this chapter can be found here: www.cvpct3.com*
Over the past 3 decades, the renin-angiotensin-aldosterone system (RAAS) has been increasingly viewed as an important effector system in hypertension, cardiovascular (CV), and cardiorenal disease; thus, it has emerged as an important target for pharmacologic intervention. Of those drugs known to interrupt the RAAS axis, by far, the greatest treatment experience exists for angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).1-4 ACE inhibitors have earned an important place in medical therapy since captopril, the initial compound released in this class, became available in 1981. This compound proved to be an extremely effective blood-pressure (BP)-lowering agent as established in a wide range of renin-dependent models of hypertension.2 The ACE inhibitor field thereafter quickly mushroomed, and there are currently 10 ACE inhibitors available in the United States;3,5 and others (imidapril and delapril) are being investigated. Losartan, the first ARB, was released in 1995, and there currently are 7 ARBs on the United States market with others in development. In addition to their vasodepressor properties, ACE inhibitors and thereafter ARBs were quickly recognized for their ability to slow the progression of renal, cardiac, and or vascular disease. Thus, it was a logical step in their development to seek additional indications in the areas of heart failure (HF), post-myocardial infarction (post-MI), and diabetic nephropathy (Tables 9-1 and 9-2). More recently, a therapeutic indication for the treatment of the high-risk vascular disease in patients without discernible left ventricular (LV) dysfunction has emerged for the ACE-inhibitors ramipril and perindopril.6,7 A full description of the tissue-protective properties of ACE inhibitors and ARBs exceeds the scope of this chapter. The reader is referred to a number of comprehensive reviews on this topic.2,4-16

Mechanism of Action

An understanding of how ACE inhibitors and ARBs work requires an appreciation of how each class interacts with the RAAS and how they differ from other compounds, such as β-blockers, that also diminish RAAS activity. For example, ACE inhibitors alter RAAS activity by decreasing plasma angiotensin-II production; β-blockers decrease plasma renin activity (PRA) and in so doing, reduce an upstream substrate for angiotensin-II; and ARBs block the type I angiotensin receptor (AT₁-R) to curb angiotensin-II effect.17,18

The locus of activity of ACE inhibitors within the RAAS axis is at ACE. ACE is a pluripotent enzyme in that it catalyzes both the conversion of angiotensin-I to angiotensin-II and breaks down a range of vasoactive peptides including the vasodilator bradykinin.2,3,19 Although ACE inhibitors effectively rein in the generation of angiotensin-II from angiotensin-I, they do not stop the generation of angiotensin-II by non-ACE-dependent pathways.20 These alternate pathways utilize chymase and other tissue-based proteases to generate angiotensin-II,21 a process, which represents the dominant mode of angiotensin-II generation in both myocardial and vascular tissue.21,22 The long-term administration of ACE inhibitors is often marked by a gradual rise in angiotensin-II levels, termed angiotensin escape, presumably due to an upregulation in the activity of these alternate pathways.23-25 The economy of angiotensin-II in the ACE inhibitor (and ARB)-treated patient is also influenced by certain feedback loop considerations. Within the RAAS, a negative feedback loop exists wherein downstream components of this cascade, such as angiotensin-II, serve as suppressors of upstream activity. When an ACE inhibitor is administered, by virtue of its diminishing angiotensin-II there is a disinhibition of renin secretion from
### Table 9-1. FDA-Approved Indications for ACE Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>HTN</th>
<th>HF</th>
<th>Diabetic Nephropathy</th>
<th>High-Risk Patients Without Left-Ventricular Dysfunction</th>
<th>Pediatric Hypertension (6–16 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Captopril</td>
<td>·</td>
<td>· (post-MI)</td>
<td>·</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Enalapril</td>
<td>.</td>
<td>·†</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>·</td>
<td>· (post-MI)</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Moexipril</td>
<td>.</td>
<td></td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Perindopril</td>
<td>.</td>
<td></td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Quinapril</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Ramipril</td>
<td>·</td>
<td>· (post-MI)</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>·</td>
<td>· (post-MI)</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
</tbody>
</table>

Captopril and lisinopril are indicated for heart failure treatment both post-myocardial infarction and as adjunctive therapy in general heart failure therapy.

† Enalapril is indicated for asymptomatic left-ventricular dysfunction and to reduce the risk of stroke with hypertension and left ventricular hypertrophy, but there is no evidence that this benefit is seen in black patients.


### Table 9-2. FDA-Approved Indications for Angiotensin Receptor Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>HTN</th>
<th>HF</th>
<th>Diabetic Nephropathy</th>
<th>Post-myocardial Infarction</th>
<th>High-Risk Patients Without Left-Ventricular Dysfunction</th>
<th>Pediatric Hypertension (6–16 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Losartan</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Valsartan</td>
<td>·</td>
<td>· (post MI)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
</tbody>
</table>

* Indicated for reducing the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is no evidence of this benefit in black patients.

† Patients 55 years or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors.

the juxtaglomerular apparatus (JGA) with a time-wise increase in the concentration of plasma renin (activity and concentration) and angiotensin I. This increase in the levels of PRA and angiotensin-I emerges as a potential source of substrate for alternative pathway action and therein the process of angiotensin escape. The rise in angiotensin-I, which accompanies ACE inhibition, also seems to originate from an enhanced release of active renin rather than an accumulation of angiotensin-I per se and is effectively blunted by β-adrenergic antagonism.

Because ACE inhibitors reduce angiotensin-II levels transiently (days → weeks), other mechanisms for their BP-lowering effect need to be considered, particularly if the pattern of BP response to ACE inhibition is laid out. When first administered, ACE inhibitors reduce BP in parallel with the level of RAAS activation. With more long-term therapy, any relationship between the fall in BP and the pretreatment levels of RAAS components diminishes. This latter observation makes renin profiling of limited practical value in predicting the degree to which an ACE inhibitor will reduce BP in a particular patient; instead, the BP response achieved shortly after beginning an ACE inhibitor appears to provide a better indication of any long-term response. This pattern of response and limited predictive value of pretherapy PRA values is similar with the ARBs. The utility of PRA profiling as a means to determine responder status to either an ACE inhibitor or an ARB is still, however, a debated issue.

The persistence of the antihypertensive effect of ACE inhibitors despite angiotensin escape argues for an active role of alternative vasodepressor systems, such as bradykinin, in reducing BP; however, most such studies with bradykinin inhibitors have only evaluated their contribution to BP in short-term studies. How ACE inhibitors interact with the kinin system, though, is a matter of some considerable interest. ACE processes several vasoactive peptides other than angiotensin-II, with one being bradykinin. Therefore, in theory, administration of an ACE inhibitor should elevate tissue and circulating bradykinin levels, although the reproducibility of such measurements has proven methodologically complex. Bradykinin levels also increase with ARB administration, although by a different mechanism. Angiotensin receptor blockers, although primarily blocking the AT₁ receptor, lead to stimulation of the AT₂ receptor in that their administration results in a reactive rise in angiotensin-II levels by their breaking the short feedback loop for release of renin. AT₂-receptor stimulation appears to be associated with increased bradykinin, nitric oxide, and cyclic guanosine monophosphate (GMP) levels in renal interstitial fluid. The therapeutic significance of these changes is uncertain.

The rise in bradykinin, which accompanies ACE inhibitor administration, also stimulates the production of endothelium-derived relaxing factor and the release of prostacyclin (PGL), although the exact contribution of prostaglandins to the antihypertensive effect of ACE inhibitors is still unknown. ARBs have been studied in a limited fashion relative to their BP-lowering effect relating to any effect on components of the prostaglandin axis. Although circulating levels of prostaglandin E₂ (PGE₂) and PGI₂ metabolites are not significantly changed following ACE-inhibitor administration, it has been recognized for some time that nonsteroidal anti-inflammatory drugs (NSAIDs) blunt the BP-lowering effect of ACE inhibitors (see “Class and Agent-Specific Drug Interactions” later in this chapter). Low-dose aspirin (≤100 mg/d) has no significant effect on ACE inhibitor or ARB-induced BP reduction. Higher doses, generally > 236 mg/d, can occasionally blunt the antihypertensive response to ACE inhibitors in susceptible patients.

A portion of ACE inhibitor and ARB effect is also believed to be due to their reducing activity in the sympathetic nervous system (SNS). This is attributable to a change in both central and peripheral SNS activity as well as to an attenuation of sympathetically mediated vasoconstriction, although these have not been consistent findings. ACE inhibitors are poorly differentiable as to their individual effect on the SNS, which may relate to differences among the various class members in tissue compartmentalization and/or penetration through the blood-brain barrier. In the instance of ARBs, there is little to distinguish one compound from the other as to their central nervous system (CNS) effects. Where differences are noted between the various compounds in this class, confounding variables such as route of administration, dose amount, duration of dosing, and a compound’s ability to cross the blood-brain barrier have limited the generalizability of the findings. There is, however, some evidence to suggest a differential effect of the ARB eprosartan on reducing SNS activity; however, this still requires additional study. ACE inhibitors and ARBs also do not alter either circulatory reflexes or baroreceptor function; thus, they do not reflexively increase heart rate when BP is lowered. This latter property explains why both of these drug classes are hardly ever accompanied by postural hypotension.

ACE inhibitors and ARBs also improve endothelial function, facilitate vascular remodeling, and favorably alter the viscoelastic properties of blood vessels. These added properties of both ACE inhibitors and ARBs may provide an explanation for the observation that the BP reduction over the long-term with these drug classes typically exceeds that initial response. Finally, the heptapeptide angiotensin 1–7, which can be formed directly from angiotensin-I by at least 3 endopeptidases, is a bioactive component of the RAAS that may offset the actions of angiotensin-II. ACE hydrolizes angiotensin 1–7 to
inactive peptide fragments, a process, which is blocked by ACE inhibition. The counter-regulatory role of angiotensin 1–7 to the pressor and proliferative actions of angiotensin-II relates, in part, to its interaction with kinins.63

Pharmacology

ACE Inhibitors

The first orally active ACE inhibitor was the drug captopril, which was released in 1981. Captopril is a sulphydral-containing compound, with a rapid and not particularly prolonged duration of action requiring that it be dosed multiple times per day; subsequently, the more long-acting compound enalapril maleate became available. Enalapril is a prodrug requiring in vivo esterolysis, which occurs both in the liver and the intestinal wall, to yield the active diacid inhibitor enalaprilat. All ACE inhibitors are given as prodrugs, with the exception of lisinopril and captopril, in order to improve their absorptive profile.64 It was originally believed that the formation of the active diacid metabolite of an ACE inhibitor prodrug, such as enalapril, could be slowed in a meaningful fashion in the presence of advanced HF, but this has proven not to be the case.65 The extent of absorption, the degree of hydrolysis, and the bioavailability of enalapril in HF patients appear to be similar to those values observed in normal subjects with the exception of the rates of absorption and hydrolysis being slightly slower in HF.66

ACE inhibitors are structurally heterogeneous. All ACE inhibitors reduce the activity of ACE but do so in a compound-specific manner based on their different ACE binding side chains. The chemical structure of this ligand serves as a criterion for separating ACE inhibitors into 3 classes. For example, the active chemical side group or ACE ligand for captopril is a sulphydral moiety, and for fosinopril, a phosphinyl group; each of the remaining ACE inhibitors contains a carboxyl side chain. The side chain group on an ACE inhibitor is 1 factor, which has been suggested as being responsible for the occasionally observed difference in pharmacologic response among these compounds.67 In that regard, the sulphydryl group on captopril is ostensibly suggested to serve as a recyclable free-radical scavenger and therein to differentially retard the process of atherogenesis and to afford protection from MI and the development of diabetes mellitus;68 however, this pharmacologic difference has not been substantiated by convincing clinical trial findings. In addition, captopril directly stimulates prostaglandin synthesis, whereas other ACE inhibitors accomplish this indirectly by increasing bradykinin activity.69 Alternatively, the sulphydryl side group found on captopril is thought to lead to a higher rate of skin rash, usually in the form of maculopapular rashes, and dysgeusia.70 The presence of a phosphinyl group on fosinopril has been offered as the reason for its low incidence of cough71,72 and its seeming ability to improve diastolic dysfunction.73,74 In the instance of the latter, the phosphinyl group may facilitate the myocardial penetration and/or retention of fosinopril and therein boost myocardial energetics.75

Although ACE inhibitors can be distinguished by differences in absorption, protein binding, half-life, and metabolic disposition, they behave quite similarly in how they lower BP (Table 9-3).64,76,77 Rarely should these pharmacologic subtleties (beyond the issue of frequency of dosing) govern selection of an agent.57 This being said, 2 pharmacologic considerations for the ACE inhibitors, route of systemic elimination and tissue-binding, have generated considerable debate and merit additional discussion.78,79,80,81

Pharmacokinetics

There is no evidence for accumulation of the prodrugs ramipril, enalapril, fosinopril, trandolapril, or benazepril in chronic kidney disease (CKD), which suggests that they undergo biliary clearance as the prodrug or that the metabolic conversion of these drugs to their active diacid is unaffected by renal failure.81-86 These findings have been offered by some as evidence for a dual route of elimination for these compounds. Although technically true, it is not pertinent to dosing of ACE inhibitors in renal failure because these prodrugs are only marginally active. True dual-route-of-elimination ACE inhibitors are those whose active diacid form is proportionally hepatically and renally cleared. Only the active diacids of the ACE inhibitors fosinopril and trandolapril are significantly hepatically cleared.84,85 For all other ACE inhibitors, systemic elimination is mainly renal occurring by filtration and tubular secretion.78 Tubular secretion as a mode of elimination for ACE inhibitors varies by compound and occurs via the organic anion secretory pathway.87,88 This property of dual renal and hepatic elimination minimizes accumulation of these compounds in CKD as dosing to steady-state occurs.85,89,90 To date, a direct adverse effect from ACE-inhibitor accumulation has not been identified, although cough has been suggested, but not proven, to be an ACE-inhibitor concentration-dependent side-effect. It is probable, however, that the longer drug concentrations remain elevated, once a response occurs, the more likely BP will remain reduced. Thus, the major adverse consequence of ACE inhibitor accumulation may be that of extended periods of hypotension and its organ-specific sequelae.91

Tissue Binding

The second debated pharmacologic feature of the ACE inhibitor class relates to the concept of tissue binding.79,80
Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

The physicochemical differences among ACE inhibitors, including binding affinity, potency, lipophilicity, and depot effect, allow for the arbitrary classification of ACE inhibitors according to affinity for tissue-ACE.\(^7^9,93-97\) The degree of functional \textit{in vivo} inhibition of tissue ACE with an ACE inhibitor corresponds to 2 compound properties: the inhibitor's binding affinity and the free-inhibitor concentration within the tissue under study. The free-inhibitor concentration, in turn, reflects a state of dynamic equilibrium, which arises from the shuttling of ACE inhibitor to the tissue and its subsequent washout and return into the blood compartment.

Free-inhibitor tissue concentrations are driven by traditional pharmacologic variables, including dose frequency and amount, absolute bioavailability, plasma half-life, tissue penetration, and ongoing retention at the tissue level. Bioavailability and half-life in blood are readily determined and are an important consideration in the choice of the starting dose of an ACE-inhibitor. When blood levels of an ACE inhibitor are high, typically in the first half of the dosing period, tissue retention of an ACE inhibitor is unlikely to significantly impact functional ACE inhibition. However, as ACE-inhibitor blood levels drop near the end of the dosing period, 2 factors appear to be central to prolonging functional ACE inhibition: (1) inhibitor-binding affinity and (2) tissue retention, which will have an important bearing on the free inhibitor concentration in tissue.

The rank order of potency for various ACE inhibitors has been determined by using competition analysis\(^93,94,98,99\) and by direct binding of tritium-labeled ACE inhibitors to tissue-ACE (Table 9-4).\(^100\) The typical rank order of potency is quinaprilat = benazeprilat > ramiprilat > perindoprilat > lisinopril > enalaprilat > fosinopril > captopril.\(^93-96\) Tissue retention of ACE inhibitors has also been studied in isolated organ bath studies, which examined the duration of ACE inhibition following the removal of ACE inhibitor from the external milieu. These studies have shown that functional inhibition of ACE lasts well beyond (2 to 5 times longer) the time predicted solely on the basis of inhibitor dissociation rates or binding affinity.\(^100\) The rank order of tissue retention is quinaprilat > lisinopril > enalaprilat > captopril and reflects both the binding affinity and lipophilicity of these inhibitors.\(^79\)

The question arises as to whether the degree of tissue-ACE inhibition imparted by an ACE inhibitor extends to differences in its BP-lowering effect. This issue differs from the question of whether an ACE inhibitor is superior within class if it exhibits tissue-protective effects independent of the degree to which it lowers BP, as was the case for ramipril in the Heart Outcomes Prevention Evaluation (HOPE) Study.\(^6\) As to the latter, improved endo-

### Table 9-3. Pharmacokinetic Parameters of ACE Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset/Duration (hours)</th>
<th>Peak Hypotensive Effect (hours)</th>
<th>Protein Binding (%)</th>
<th>Effect of Food on Absorption</th>
<th>Half-Life Elimination†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>1/24</td>
<td>2–4</td>
<td>&gt; 95</td>
<td>None</td>
<td>10–11 Renal biliary</td>
</tr>
<tr>
<td>Captopril</td>
<td>0.25/Dose related</td>
<td>1–1.5</td>
<td>25–30</td>
<td>Reduced</td>
<td>&lt; 2 Renal, as disulfides</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1/24</td>
<td>4–6</td>
<td>50</td>
<td>None</td>
<td>11 Renal</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>1/24</td>
<td>2–6</td>
<td>95</td>
<td>None</td>
<td>11 Renal = hepatic</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1/24</td>
<td>6</td>
<td>10</td>
<td>None</td>
<td>13 Renal</td>
</tr>
<tr>
<td>Moexipril</td>
<td>1/24</td>
<td>4–6</td>
<td>50</td>
<td>Reduced</td>
<td>2–9 Renal/some biliary</td>
</tr>
<tr>
<td>Perindopril</td>
<td>1/24</td>
<td>3–7</td>
<td>10–20</td>
<td>Reduced</td>
<td>3–10 Renal</td>
</tr>
<tr>
<td>Quinapril</td>
<td>1/24</td>
<td>2</td>
<td>97</td>
<td>Reduced</td>
<td>2 Renal &gt; hepatic</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1–2/24</td>
<td>3–6</td>
<td>73</td>
<td>Reduced</td>
<td>13–17 Renal</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>2–4/24</td>
<td>6–8</td>
<td>80–94</td>
<td>None</td>
<td>16–24 Renal &gt; hepatic</td>
</tr>
</tbody>
</table>

Protein binding may vary for the prodrug and the active diacid of an ACE inhibitor.

The concept of renal elimination of an ACE inhibitor takes into account both prodrug elimination and that of the active diacid where such is applicable.

thelial function and increased nitric oxide bioavailability represent mechanisms by which ACE inhibitors may potentially confer vascular protection. The effect of ACE inhibitors on endothelium-dependent relaxation is variable and is dependent on the agent used and the experimental design. Consistent improvement in endothelial function is reported with those ACE inhibitors exhibiting the highest tissue affinity, such as quinapril and ramipril. Despite the appealing nature of these vascular relationships, there have been few direct head-to-head trials between ACE inhibitors with differing tissue binding. In situations where such comparisons have occurred, the results fail to convincingly support the claim of overall superiority for lipophilic ACE inhibitors relating to BP.

Application of Pharmacologic Differences
Since there is very little that functionally separates 1 ACE inhibitor from another in the treatment of hypertension, price has become a leading issue. Allowing cost to be a major factor for the selection of an ACE inhibitor neglects the fact that only a small number of ACE inhibitors have been studied specifically for their ability to afford end-organ protection. Class effect is a phrase invoked to legitimate use of a less-costly ACE inhibitor when a higher-priced agent in the class was the one specifically studied in a disease state, such as HF or diabetic nephropathy. The concept of class effect may be most pertinent to the use of ACE inhibitors in the treatment of hypertension, and therein little appears to distinguish 1 ACE inhibitor from another beyond half-life and frequency of dosing. Alternatively, it is unclear as to what represents dose equivalence among ACE inhibitors when they are used in the treatment of proteinuric renal disease or HF. In the treatment of proteinuric renal disease, the dose-response relationship for an ACE inhibitor and proteinuria reduction is incompletely explored, a situation made more complex in its interpretation by the observation that the antiproteinuric effect of an ACE inhibitor is greater the higher the baseline urine protein excretion. Because there are very few hard endpoint studies in nephropathic patients with ACE inhibitors, it would seem prudent to not specifically use cost as a criterion for selection of an ACE inhibitor in a nephropathic patient.

Alternatively, in the case of HF, there are no readily measured treatment goals, unlike BP normalization and/or reduction in urine protein excretion in the nephropathic patient. In the HF patient, the dose titration of an ACE inhibitor is to a presumed maximal tissue-effect dose.

<table>
<thead>
<tr>
<th>Table 9-4. Pharmacologic Properties of Various Angiotensin-Converting Enzyme Inhibitors in Plasma and Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitor Potencies</strong> (mmol/L x 10⁻⁹, ID₅₀⁻⁹⁻¹)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>High</strong></td>
</tr>
<tr>
<td>Quinaprilat</td>
</tr>
<tr>
<td>Benazeprilat</td>
</tr>
<tr>
<td>Ramiprilat</td>
</tr>
<tr>
<td>Perindoprilat</td>
</tr>
<tr>
<td>Lisinopril</td>
</tr>
<tr>
<td>Enalaprilat</td>
</tr>
<tr>
<td>Fosinoprilat</td>
</tr>
<tr>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>Captopril</td>
</tr>
</tbody>
</table>

NA = not available.
Radioligand binding studies using the active drug moiety.95
ID₅₀ is the inhibitor concentration needed to displace 50% of [¹²⁵I]531A bound to human plasma.96
Comparison of 50% inhibition of enzymatic activity (IC₅₀⁻¹) with 50% displacement of [¹²⁵I]-351A (DD₅₀⁻¹) from human plasma ACE.96
Values cited for quinaprilat and ramiprilat are for dissociation from tissue ACE; ie, terminal half-life.97
Lipid solubility based on log P logarithm of the octanol/water partition coefficient of the active drug moiety, except for captopril;
+ signs represent increased lipid solubility.96

Adapted with permission from Elsevier from Dzau VJ, Bernstein K, Celermajer D, et al. The relevance of tissue angiotensin-converting enzyme: Manifestations in mechanistic and end-point data. Am J Cardiol. 2001;88(Suppl 9):1L.
since improvement in the morbidity and mortality of HF with ACE inhibitors is dose-dependent, although the differences are relatively modest with upward titration of an ACE inhibitor.108-113 Because not all ACE inhibitors have been thoroughly studied in HF specific interchangeable doses of various ACE inhibitors are not known; therefore, all ACE inhibitors are not approved for HF survival by merely being a class member (Table 9-1).

Angiotensin-Receptor Blockers

ARBs comprise another RAAS inhibitor class commonly employed in the treatment of hypertension. These agents work selectively at the AT1-receptor subtype, the receptor that mediates all of the known physiologic effects of angiotensin-II that are believed relevant to cardiovascular and cardiorenal homeostasis. Similar to ACE inhibitors, each ARB has a distinctive pharmacologic profile.114 The pharmacologic differentiation of the various ARBs is a topic of only modest relevance in that the ability to reduce BP differs little among the drugs making up this class.115,116 Since the release of the first ARB losartan (Cozaar) in 1995, 6 other ARBs have been developed and are now marketed in the United States. These compounds include candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), olmesartan (Benicar), telmisartan (Mircardis), and valsartan (Diovan). These compounds are now commonly given together with hydrochlorothiazide (HCTZ) as fixed-dose combination antihypertensive products. Currently available information does not suggest that any meaningful pharmacologic differences exist for an ARB if administered alone or when given together with HCTZ.117

Pharmacokinetics

Bioavailability

The bioavailability of the individual ARBs is rather variable (Table 9-5).118-132 Three of the ARBs are administered in a prodrug form (losartan, candesartan cilexetil, and olmesartan medoxomil), although, strictly speaking, losartan is an active compound, notwithstanding the fact that it is one ultimately converted to a more potent E-3174 metabolite. The bioavailability of eprosartan is very low (= 13%), a process that appears not to be due to high first-pass elimination.121 Eprosartan absorption is saturable over the dose range of 100 to 800 mg, most likely due to the physicochemical properties of the drug.122 Irbesartan has a bioavailability profile with an absorption range between 60%–80% and does not have a food effect.124,125 Losartan has a moderate bioavailability (= 33%), with 14% of an administered dose being transformed to its active E-3174 metabolite.126,127 Telmisartan appears to have a saturable first-pass effect for its absorption; thus, the higher the dose, the greater the absolute bioavailability.128,129 Unfortunately, the most pertinent absorption characteristic of individual ARBs, which is day-to-day variability in bioavailability, is seldom reported.

Dose Proportionality

The concept of dose proportionality is important to the concept of dose escalation for an antihypertensive agent in order to attain BP control. One pattern of dose proportionality is displayed by irbesartan. In this regard, the results of 2 double-blind, placebo-controlled studies involving 88 healthy subjects show irbesartan to display linear, dose-related pharmacokinetics for its area-under-the-curve (AUC) with escalating doses over a dose range from 10 to 600 mg. The maximum plasma concentration (Cmax) over this same dose range was related to the dose in a linear but less-than-dose-proportional manner. Increases in plasma AUC and Cmax in subjects receiving 900 mg of irbesartan were less than dose proportional.133,134 Explanations for this phenomenon are that intestinal absorption of irbesartan is dose limited, perhaps due to saturation of a carrier system at high drug concentrations, or that its dissolution characteristics are dose-dependent.135 The terminal half-life of irbesartan is independent of dose suggesting that its intestinal absorption saturates at higher doses but that its metabolism and excretion are not so dose-effectuated. Each of these proposed mechanisms may be invoked to explain the absence of dose proportionality with the ARB eprosartan at doses exceeding 400 mg.135 Of note, the absence of dose proportionality for several of the ARBs is of limited relevance since the doses in question are rarely used in the treatment of hypertension.

Volume of Distribution

The ARBs typically have a volume of distribution (Vd), which approximates extracellular fluid (ECF) volume, in that these compounds are extensively protein bound. For example, the Vd for losartan and its E-3174 metabolite are 34 L and 12 L, respectively, while the Vd for candesartan, olmesartan, valsartan, and eprosartan are 10 (0.13 L/kg body weight), 30 L, 17 L, and 13 L, respectively. Alternatively, telmisartan and irbesartan have the highest Vd of any of the ARBs, with values of 500 and 53 to 93/L, respectively. That telmisartan has such a high Vd is likely a function of its loose binding with its predominant protein carrier, albumin.136 To date, the clinical significance of a high Vd for an ARB remains unclear. The Vd of various ARBs in disease states, such as renal failure, is unreported. Parenthetically, it has been suggested, though, that the greater the Vd for an ARB, the more likely it is that extravascular AT1-receptors can be accessed and, therefore, at least in theory, the greater the BP-lowering response.
Protein Binding

The protein binding of all ARBs typically exceeds 95% other than for irbesartan (free fraction 4-5%). In general, ARBs do not bind to red blood cells in a pharmacokinetically significant fashion. Furthermore, the extent of protein binding for the ARBs remains fairly constant over a wide concentration range. Typically, protein binding dictates the $V_d$ for a compound and, in fact, irbesartan demonstrates a $V_d$ somewhat higher than that of the other ARBs, with the exception of telmisartan.

Table 9-5. Bioavailability of the Angiotensin Receptor Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Food Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan cilexetil</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>6–29 AUC ↓ = 25%</td>
<td></td>
</tr>
<tr>
<td>Irbesartan</td>
<td>60–80</td>
<td>No</td>
</tr>
<tr>
<td>Losartan</td>
<td>33 AUC ↓ = 10%</td>
<td></td>
</tr>
<tr>
<td>Olmesartan</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>42–58 AUC ↓ = 6–24%</td>
<td></td>
</tr>
<tr>
<td>Valsartan</td>
<td>25 AUC ↓ = 50%</td>
<td></td>
</tr>
</tbody>
</table>

Table 9-6. Mode of Elimination for ARBs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>Losartan</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>E-3174</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>Valsartan</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>

Protein Binding

The protein binding for a specific ARB remains to be determined.

Metabolism and Active Metabolite Generation

There are 2 ways to view metabolic conversion of an ARB. First, it may be a step required in order to produce an active metabolite; such is the case with losartan, candesartan cilexetil, and olmesartan medoxomil. Alternatively, metabolic conversion may factor into the change of a compound to a physiologically inactive metabolite, as in the case of irbesartan. Losartan, an active substrate molecule, is converted via the P450 isozyme system (2C9 and 3A4) to its more active metabolite, E-3174, whereas candesartan cilexetil, a prodrug, is hydrolyzed to the active compound candesartan in the course of absorption.

It has also been suggested that inhibitors of the P450 2C9 and 3A4 isozymes, such as fluconazole and ketoconazole, might interfere with the conversion of losartan to its E-3174 metabolite. In the absence of certain variants of CYP2C9 decreases the conversion of losartan to its active E-3174 metabolite. To date, less than 1% of the population of patients exposed to losartan has this abnormal variant of CYP2C9, making it unlikely that a polymorphism for losartan metabolism will ever be found in sufficient numbers of patients to be of clinical significance. A final consideration with losartan is its level of interaction with grapefruit juice. Although not formally tested as to its influencing the BP-lowering effect of losartan, grapefruit juice given together with losartan will both reduce its conversion to E3174 and activate P-glycoprotein, which, together significantly increases the AUC (losartan)/AUC (E-3174) ratio. Telmisartan is exclusively metabolized by conjugation to glucuronic acid. This absence of cytochrome P450-dependent metabolism distinguishes telmisartan from other ARBs.
Route of Elimination

It is well recognized that the systemic clearance of a compound depends on the integrity of both renal and hepatic function. As a result, if renal and/or hepatic dysfunction exists in a patient, repeated dosing of an antihypertensive compound will lead to drug accumulation and the occasional need to dose adjust in order to lessen concentration-related effects. All ARBs drugs undergo predominant hepatic elimination with the exception of olmesartan, candesartan, and the E-3174 metabolite of losartan, which are 40%, 60%, and 50% hepatically cleared, respectively (Table 9-6). Valsartan and eprosartan each undergo about 70% hepatic clearance.

Ibuprofen undergoes the greatest degree of hepatic elimination among the ARBs, with each having > 95% hepatic clearance. Valsartan and eprosartan each undergo about 70% hepatic clearance.

The mode of elimination for an ARB is an important variable in the renally compromised patient dictating how renal function can change with these compounds. In those who develop acute kidney injury with a hepatically cleared ARB, the duration of any renal failure episode is shortened by the expected hepatic disposition of the compound, a process that does not occur when the compound in question is mainly renally cleared.

To date, very few studies have assessed the BP-lowering effect of ARBs in the renally compromised patient. In the studies reported to date, the BP-lowering effect of these compounds is evident in the renal failure patient, and in certain instances, may be quite significant. Dose adjustment, or more so, cautious use, in CKD is advocated with some of the ARBs, such as valsartan and olmesartan, that are partially renally cleared. This is more so because of presumed heightened sensitivity to these compounds rather than any greater likelihood of adverse effects other than possibly hyperkalemia; however, this may be less so than is the case with ACE inhibitors in the CKD patient. A final consideration with the ARBs is that as a class they are not dialyzable.

Receptor Binding and Half-Life

The half-life ($t_{1/2}$) of a compound is a pharmacokinetic term that often correlates poorly with the duration of effect of various antihypertensive compounds including ACE inhibitors and ARBs. This has typically been the case with antihypertensive compounds, including both ACE inhibitors and ARBs. The discrepancy between the pharmacokinetic and pharmacodynamic $t_{1/2}$ of a compound derives from the fact that the predominant site of drug action for many compounds is often outside the vascular compartment. Because of the inability to sample at these extravascular sites of action, the more meaningful tissue-based $t_{1/2}$ cannot be determined for many compounds. This is particularly the case for ARBs, in that AT₁-receptors have been identified in multiple locations outside the vascular compartment and blocking AT₁-receptors at these extravascular locations may influence the manner in which they reduce BP.

With the above in mind, the pharmacokinetic $t_{1/2}$ of an ARB will but roughly approximate its duration of its BP-lowering effect. Several of the ARBs, including candesartan, olmesartan, telmisartan, and irbesartan, are once-daily compounds in pharmacokinetic terms. The true impact of a longer pharmacokinetic $t_{1/2}$ for these compounds rests in the fact that drug remains available for a longer period of time and therein can binds to new AT₁-receptors as they are formed during a dosing interval; thus, half-life has an important role in how well an ARB reduces BP, particularly at the end of the dose interval. However, drug half-life is not the only factor controlling BP lowering with an ARB in that responses are highly individualized and very much dependent on the prevailing sodium intake state.

Application of Pharmacologic Differences/Receptor Affinity

Receptor affinity is just one of several factors that determine the action of an ARB. An ARB demonstrates insurmountable or noncompetitive blockade if incrementally higher concentrations of angiotensin-II fail to overcome receptor blockade. The terms surmountable, competitive, insurmountable, and noncompetitive are often used interchangeably but often inconsistently. Surmountable antagonism implies that receptor blockade can eventually be overcome if high enough concentrations of angiotensin-II are made available. Angiotensin receptor blockers that exhibit surmountable antagonism (such as losartan) shift concentration-response curves parallel and rightward without diminishing the maximal response to an agonist. In the instance of competitive antagonism, as occurs with eprosartan, mass action kinetics prevail, and agonists and antagonists each compete for receptor binding. Noncompetitive, irreversible antagonism reflects a loss of receptor numbers through chemical modification.

Insurmountable antagonism mimics noncompetitive antagonism. Insurmountable antagonists bind to their receptor in a semi-irreversible fashion, which differs from the permanent binding that occurs with noncompetitive antagonists. An insurmountable antagonist releases from its receptor slowly; thus, its drug-receptor dissociation constant can be very prolonged. Insurmountable antagonists, such as valsartan, irbesartan, telmisartan, and the E-3174 metabolite of losartan, produce a parallel shift of the agonist concentration-response curves with a depression in the maximal agonist response that is not overcome by increasing agonist concentrations.

Insurmountable antagonists, such as candesartan, can also elicit nonparallel shifts of the agonist concentration-
response curves, again depressing the maximal agonist response, a process that still cannot be overcome by increasing agonist concentrations.\textsuperscript{173-175} To date, the specific mode of receptor occupancy and/or differential pharmacokinetic features of an ARB have not been specifically linked with differential BP responses to these drugs; thus, the basis for the superior efficacy of drugs, such as candesartan and irbesartan, as compared with losartan in terms of reduction in BP, is unclear.\textsuperscript{176} Instead, compound-specific differences in angiotensin-II receptor blockade, a surrogate for the BP-lowering response of these drugs, can be explained by dosing differences, as was recently shown, wherein the effects of 160-mg or 320-mg doses of valsartan hardly differed from those obtained with top-end doses of irbesartan and candesartan.\textsuperscript{177}

**Hemodynamic Effects**

A number of well-described hemodynamic effects occur with the administration of an ACE inhibitor (Table 9-7).\textsuperscript{3} Although ACE inhibitors and ARBs have not been comprehensively examined in a head-to-head fashion, they seem to produce similar hemodynamic profiles with an occasional difference, which may be study-design dependent.\textsuperscript{178} The underlying disease being treated often determines the magnitude change in many of these hemodynamic parameters. This is particularly so in the treatment of HF, wherein hemodynamic responses may exaggerate and the BP falls significantly. In addition, many of these hemodynamic changes are more noticeable in the presence of an activated RAAS, as may occur with diuretic therapy and/or a low-salt diet. Both of these factors are established risk factors for the occurrence of first-dose hypotension with an ACE inhibitor and/or an ARB.\textsuperscript{179}

In the treatment of hypertension, the observed reduction in BP with an ACE inhibitor or an ARB is not accompanied by either a decrease in cardiac output or an increase in heart rate.\textsuperscript{18,55,180} Occasionally, cardiac output increases with ACE inhibitor therapy, particularly if output is reduced before therapy has begun.\textsuperscript{181} The fall in peripheral vascular resistance with an ACE inhibitor or

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Effect</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Increased or no change</td>
<td>These parameters contribute to a general decrease in systemic BP</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Preload and afterload</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>Usually increased</td>
<td>Contributes to the renoprotective effect of these agents</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>Variable, usually unchanged but may \textsuperscript{-} in renal failure</td>
<td></td>
</tr>
<tr>
<td>Efferent arteriolar resistance</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral Nervous System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biosynthesis of noradrenaline</td>
<td>Decreased</td>
<td>Enhances blood pressure-lowering effect and resets baroreceptor function</td>
</tr>
<tr>
<td>Reuptake of adrenaline</td>
<td>Inhibited</td>
<td></td>
</tr>
<tr>
<td>Circulating catecholamines</td>
<td>Decreased</td>
<td></td>
</tr>
</tbody>
</table>

Table 9-7. Predominant Hemodynamic Effects of ACE Inhibitors and ARBs

an ARB is occasionally marked by a decrease in filling pressures.55 Angiotensin-II can influence both coronary blood flow and vascular tone, particularly if the RAAS is activated. In turn, treatment with an ACE inhibitor or an ARB can reverse angiotensin-II-mediated reductions in coronary blood flow.182 Several small trials, which have typically been of short duration, have assessed the effects of ACE inhibitors on the severity of angina and/or on objective measures of myocardial ischemia but have yielded conflicting results.183,184

In addition, ACE inhibitors lower BP without diminishing cerebral blood flow.185,186 This phenomenon is believed to represent a favorable effect of ACE inhibition on cerebral autoregulatory ability and is potentially relevant to the treatment of hypertension in the elderly. Furthermore, ACE inhibitors and ARBs decrease capacitance vessel tone, which may explain why these compounds can lessen the peripheral edema associated with calcium-channel blocker therapy.187 ACE inhibitors do not limit the peak heart-rate response to exercise, although they do effectively reduce the peak BP response.188 The addition of a diuretic to an ACE inhibitor does not alter its hemodynamic profile except in the instance of exercise, in which case, the exercise-related increase in cardiac output may be blunted.189

ACE inhibitors and ARBs routinely increase effective renal plasma flow (ERPF) while maintaining or lowering glomerular filtration rate (GFR). The rise in ERPF produced by these 2 drug classes is characterized by a preferential vasodilatation of the post-glomerular or efferent arteriolar vascular bed.9,178,190 The functional consequence of these renal hemodynamic changes is a drop in the filtration fraction (GFR/ERPF), a well-accepted marker for a reduction in angiotensin-II effect on the kidney. When glomerular filtration is heavily reliant on preserved efferent arteriolar tone (as in advanced HF, dehydration, and/or renal artery stenosis) and an ACE inhibitor or an ARB is administered, the GFR may suddenly and precipitously fall.91,191

**Blood Pressure-Lowering Effect**

Angiotensin-converting enzyme inhibitors and, more recently, ARBs are increasingly viewed as suitable first-step therapies in the treatment of hypertension, having in large measure supplanted calcium blockers and β-blockers.192-195 The enthusiasm for the use of ACE inhibitors goes beyond efficacy in that they have a pattern of efficacy comparable to (and no better than) most other drug classes, with response rates from 40%-70% in Stage 1 or Stage 2 hypertension.196 A similar range of response rates is evident with ARBs. In head-to-head trials comparing ACE inhibitors and ARBs, there appears to be scant difference between the 2 drug classes as to BP reduction when top-end doses are matched.197,198 Clinical trial results, obviously, do not reflect conditions in actual practice where the favorable side-effect profile of ACE inhibitors and ARBs and their highly touted end-organ protection features seem to overly influence the thinking of many practitioners. In addition, both ACE inhibitors and ARBs are extensively used because they are well tolerated and drugs that patients will continue to take over a long period, which is particularly so with the ARB class.198-199

The enthusiasm for these 2 drug classes must be put in proper perspective because in uncomplicated non-diabetic hypertensive patients, a number of drug classes given at low doses can prove effective and well tolerated. Heretofore, the cost of ACE inhibitors and ARBs was viewed as a reason to limit their use, but, in that regard, several ACE inhibitors are now available generically and the ARB losartan will become available generically in 2010 with other compounds in this class to follow suit thereafter. Alternatively, increasing evidence supports the preferential use of ACE inhibitors and ARBs in the diabetic and/or at-risk cardiac/renal patient with either established atherosclerotic disease or proteinuric chronic kidney disease.5-10,200-202 Recent clinical trials offer a more positive view of these drugs than was available from prior comparator trials with ACE inhibitors and β-blockers.203 For many of these at-risk cardiac/renal patients the recommendations for ACE inhibitor use are not based on the BP-lowering ability of these drugs, but rather on proposed tissue-based anti-inflammatory and antiproliferative effects, which are probably class- and not agentspecific.6,203 However, these pleiotropic properties for ACE inhibitors and ARBs are increasingly viewed as being less relevant than the BP reduction that occurs with either of these drug classes.204 There are no consistent predictors of the BP response to an ACE inhibitor or an ARB. When hypertension is accompanied by significant activation of the RAAS, such as in renal artery stenosis, the response to an ACE inhibitor or an ARB can be immediate and profound.205,206 In most other cases, there is a limited relationship between the pre- and/or post-treatment PRA value, which is used as a marker of RAAS activity, and the vasodepressor response to either an ACE inhibitor or an ARB. Certain patient types demonstrate lower response rates to ACE inhibitor and ARB monotherapy including low-renin, salt-sensitive individuals such as the diabetic, black, or elderly hypertensive.3-207 The low-renin state, characteristic of the elderly hypertensive, differs from other low-renin forms of hypertension in that it develops not as a response to volume expansion, but rather because of senescence-related changes in the activity of this axis.208 The elderly generally respond well to ACE inhibitors at conventional doses, although senescence-
related renal failure, which slows the elimination of these drugs, complicates interpretation of dose-specific treatment successes.\textsuperscript{80,196} The elderly hypertensive, with systolic-predominant hypertension, also responds well to ARBs.\textsuperscript{209} Black hypertensives, who as a group tend to have reduced activity in the RAAS, are perceived as being poorly responsive to ACE inhibitor monotherapy when compared to whites;\textsuperscript{210} however, in many instances, if careful dose titration occurs, BP will eventually be reduced with either monotherapy\textsuperscript{211} or an appropriately constructed multidrug regimen based on ACE-inhibitor therapy.\textsuperscript{212} This response pattern suggests that eliminating even small amounts of activity in the RAAS is important to BP control in this ethnic group.

All 10 ACE inhibitors are currently FDA-approved for the treatment of hypertension. In the early part of the 2000s the Joint National Committee (JNC) on the Detection, Evaluation, and Treatment of High Blood Pressure and the World Health Organization/International Society of Hypertension recognized ACE inhibitors as an option for first-line therapy in patients with essential hypertension, especially in those with diabetes mellitus who also have renal disease/proteinuria and in patients with HF.\textsuperscript{1,2,13} This position has not changed over the last several years as multiple other guideline-promulgating committees have weighed in on this issue. Considerable dosing flexibility exists with the available ACE inhibitors. Enalaprilat is the only ACE inhibitor available in an intravenous form (Table 9-8).\textsuperscript{3} The dosing frequency for ACE inhibitors is somewhat arbitrary and should take into consideration the fact that these drugs can lose their effect at the end of the dosing interval, necessitating a second dose. Likewise, in the treatment of HF, ACE inhibitors indicated for once-daily dosing might require split dosing when BP drops

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Usual Total Dose and/or Range: Hypertension (Frequency per day)</th>
<th>Usual Total Dose and/or Range: Heart Failure (Frequency per day)</th>
<th>Comment</th>
<th>Fixed-Dose Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>Lotensin</td>
<td>20–40 (1)</td>
<td>Not FDA approved</td>
<td></td>
<td>Lotensin HCT, Lotrel</td>
</tr>
<tr>
<td>Captopril</td>
<td>Capoten</td>
<td>12.5–100 (2–3)</td>
<td>18.75–150 (3)</td>
<td>Generic and IV Vaseretic</td>
<td>Capozide\textsuperscript{†}</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vasotec</td>
<td>5–40 (1–2)</td>
<td>5–40 (2)</td>
<td>Renal and hepatic elimination</td>
<td>Monopril-HCT</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril</td>
<td>10–40 (1)</td>
<td>10–40 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Prinivil Zestril</td>
<td>2.5–40 (1)</td>
<td>5–20 (1)</td>
<td>Generically available Prinzide Zestoretic</td>
<td></td>
</tr>
<tr>
<td>Moexipril</td>
<td>Univasc</td>
<td>7.5–30 (1)</td>
<td>Not FDA approved</td>
<td>Uniretic</td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>Aceon</td>
<td>2–16 (1)</td>
<td>Not FDA approved</td>
<td>Indicated in high-risk vascular patients</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>Accupril</td>
<td>5–80 (1)</td>
<td>10–40 (1–2)</td>
<td>Accuretic</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>Altace</td>
<td>2.5–20 (1)</td>
<td>10 (2)</td>
<td>Indicated in high-risk vascular patients</td>
<td>Tarka</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Mavik</td>
<td>1–8 (1)</td>
<td>1–4 (1)</td>
<td>Renal and hepatic elimination</td>
<td></td>
</tr>
</tbody>
</table>

Fixed-dose combinations in this class typically contain a thiazide-like diuretic or a calcium-channel blocker. \textsuperscript{†}Capozide is indicated for first-step treatment of hypertension.

excessively with an administered dose.

Results from a number of head-to-head trials support the comparable antihypertensive efficacy and tolerability of the various ACE inhibitors. However, there are differences among the ACE inhibitors as to the time to onset of effect and/or the time to maximum BP reduction, which may relate to the absorption characteristics of the various compounds. These differences, however, do not translate into different response rates if comparable doses of the individual ACE inhibitors are being given. Typical variables that confuse the interpretation of the findings in BP studies with ACE inhibitors have included differences in study design/methodology as well as dose frequency and/or amount. ACE inhibitors labeled as “once-daily” vary in their ability to reduce BP for a full 24 hours, as defined by a trough:peak ratio > 50%. Unfortunately, the trough:peak ratio, as an index of duration of BP control, is often prone to misrepresent the true BP reduction seen with a compound. As stated previously, dosing instructions for many of these compounds include the qualifier that a second-daily dose be administered if the antihypertensive effect has dissipated by the end of the dosing interval.

The question is often raised as to what to do if an ACE inhibitor fails to normalize BP. One approach is simply to raise the dose; however, the dose-response curve for ACE inhibitors, like most antihypertensive agents, is fairly steep at the beginning doses and thereafter becomes shallow-to-flat. Responders to ACE inhibitors typically do so at doses well below those necessary for prolonged 24-hour suppression of ACE. In addition, the maximal vasodepressor response to an ACE inhibitor does not occur until several weeks after therapy is begun and may involve factors, such as vascular remodeling, that are above and beyond inhibition of ACE; thus, only with complete failure to respond to an ACE inhibitor should an alternative drug class be substituted. If a partial response has occurred and a patient is near goal BP, then therapy with an ACE inhibitor can be continued in anticipation of an additional drop in BP over the next several weeks. Alternatively, an additional compound such as a diuretic, calcium channel blocker (CCB), or peripheral α-blocker can be combined with an ACE inhibitor to effect better BP control (see Chapter 21, New Aspects of Combination Therapy: Focus on Hypertension).

Virtually all of the previous comments directed to the pharmacotherapeutic response to ACE inhibitors apply to the ARBs (Table 9-9). This includes considerations of predictors of response, onset and duration of response, the contour of their dose-response curves, and their capacity to have a late onset additional BP response. A number of head-to-head studies have been conducted between different ARBs. The results of these comparisons suggest that candesartan cilexetil, irbesartan, and olmesartan may be more effective than the prototype ARB, losartan. Moreover, studies mimicking the common event of a missed or delayed dose of antihypertensive medication show that the antihypertensive effect of candesartan cilexetil extends well beyond the 24-hour dosing interval, while the effect of losartan declines rapidly over this period. ARBs are aggressively marketed and, as such, comparison studies provide the basis for a superiority claim at least from a sales perspective. Appreciating that point, there are two important considerations in comparing one ARB to another: (1) whether maximal drug doses are used as well as whether the treated populations are comparable in age, gender, and ethnicity; (2) that 24-hour ambulatory blood pressure monitoring has been employed as the measure of BP lowering.

Few studies have directly compared more than 2 ARBs. Two instances where this has occurred include a meta-analysis of randomized controlled trials by Conlin et al and a crossover study by Fogari et al. Both of these studies compared the efficacy of losartan, valsartan, irbesartan, and candesartan at low doses (50, 80, 150, and 8 mg, respectively) and after titration to double these doses. This meta-analysis revealed no differences among these drugs in their ability to reduce BP, either at the starting dose or after forced or elective titration. In the crossover study, valsartan and irbesartan reduced BP more effectively than losartan when the drugs were used at their respective starting doses, although the difference was not maintained following elective dose titration. In attempting to evaluate real or perceived differences among the ARBs, a meta-analysis can be useful in determining dose-response relationships for individual drugs, but randomized, prospective, double-blind, head-to-head comparative studies remain the most accurate way to compare efficacy between drugs and would seem to favor several of the more recent additions to the ARB class over losartan. Recently, the FDA allowed an additional labeling claim for candesartan and irbesartan as being superior to losartan in its antihypertensive efficacy.

ACE Inhibitors and ARBs in Combination with Other Agents

To date, there appears to be little difference in the BP-lowering effect between ACE inhibitors and ARBs given in combination with other drug classes including diuretics and CCBs. The BP-lowering effect of an ACE inhibitor or an ARB is enhanced with the simultaneous administration of a diuretic, particularly in the black hypertensive. This pattern of response has spurred the development of a number of fixed-dose combination products comprised of an ACE inhibitor and low-to-moderate doses of thiazide-type diuretics. The ratio-
The rationale for combining these 2 drug classes derives from the observation that the sodium depletion produced by a diuretic increases activity in the RAAS. As such, BP shifts to an angiotensin-II dependent mode, which is the optimal circumstance for an ACE inhibitor or an ARB to reduce BP. Even very low-dose diuretic therapy, such as 12.5 mg of HCTZ, can evoke this synergistic response, suggesting that even subtle alterations in sodium balance are sufficient to bolster the effect of an ACE inhibitor.227 (see Chapter 11, Diuretic Therapy in Cardiovascular Disease and Chapter 21, New Aspects of Combination Therapy: Focus on Hypertension).

ACE inhibitors have been given together with β-blockers. The rationale behind combining these 2 classes is that the β-blocker will presumably abort the reactive rise in PRA induced by an ACE inhibitor.228,230 It was presumed that by preventing this hyper-reninemic response, the response to an ACE inhibitor might become more robust. Although this hypothesis at first seemed attractive, in practice only a modest additional vasodepressor response occurs when these 2 drug classes are combined.231 When BP substantially falls after addition of a β-blocker to an ACE inhibitor, it is generally because pulse rate has been reduced in a patient whose BP is pulse-rate dependent. The addition of a peripheral α-antagonist, such as doxazosin, to an ACE inhibitor can be followed by a significant additional lowering of BP even as the mechanism behind this additive response remains to be more fully elucidated.232 Finally, the BP-lowering effect of either an ACE inhibitor or an ARB is considerably enhanced by the coadministration of a CCB.187,228,233-235a This additive response occurs whether the CCB being given is a dihydropyridine (eg, felodipine or amlodipine)187,234 or a nondihydropyridine, such as verapamil.235 The potency of this combination has provided the practical basis for the development of a number of fixed-dose combination products comprised of an ACE inhibitor (and more recently ARBs) and a CCB.236 The CCB and ARB combination has also been developed in combination with HCTZ as a triple-drug combination and has proven effective for severe hypertension.236 Adding an ACE inhibitor or an ARB to a CCB is also useful in that either drug class attenuates the peripheral edema that accompanies CCB therapy.187,237 The combination of benazepril and amlodipine was found to be superior to the combination of benazepril and HCTZ in reducing cardiovascular morbidity and mortality and the progression of nephropathy.237a

The efficacy of both ACE inhibitors and ARBs as individual monotherapies is well documented. Each of these drug classes has also been shown to provide survival benefits for patients with HF, proteinuric chronic kidney disease, and/or a high cardiac-risk profile. The individual gains seen with each of these drug classes has led to speculation that their combination might offer additive, if not synergistic effects on outcomes as well as for BP reduc-

### Table 9-9. Angiotensin Receptor Blockers: Dosage Strengths and Treatment Guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Usual Dose/Range (Frequency per day)</th>
<th>Comment</th>
<th>Fixed-Dose Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>Atacand</td>
<td>2–32 (1)</td>
<td>Indicated in heart failure</td>
<td>Atacand-HCTZ</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Teveten</td>
<td>400–800 (1)</td>
<td></td>
<td>Teveten-HCTZ</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Avapro</td>
<td>75–300 (1)</td>
<td>Indicated in diabetic nephropathy</td>
<td>Avalide</td>
</tr>
<tr>
<td>Losartan</td>
<td>Cozaar</td>
<td>25–100 (1)</td>
<td>Indicated in diabetic nephropathy; uricosuric</td>
<td>Hyzaar</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Benicar</td>
<td>10–40 (1)</td>
<td></td>
<td>Benicar-HCTZ, Benicar-HCTZ-Amlodipine</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Micardis</td>
<td>20–80 (1)</td>
<td></td>
<td>Micardis-HCTZ</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan</td>
<td>80–320 (1)</td>
<td>Indicated in heart failure</td>
<td>Diovan-HCTZ, Diovan-HCTZ-Amlodipine, Diovan-Aliskiren, Diovan-Amlodipine</td>
</tr>
</tbody>
</table>

tion. The foundation of this hypothesis, although biologically possible, has thus far not been shown to support the everyday use of these 2 drug classes in combination for either BP reduction or for outcomes benefits in the high-risk vascular disease patient. It remains to be determined as to the best positioning for an ACE inhibitor and ARB combination in proteinuric chronic kidney disease and/or HF.238-242 Recently, a combination of the ARB valsartan and the direct renin inhibitor aliskiren has been introduced for clinical use in hypertension; however, more clinical experience needs to be obtained in patients with HF and proteinuria.

Finally, a number of studies have demonstrated the utility of ACE inhibitors in the management of hypertensive patients otherwise unresponsive to multidrug combinations.243,244 Typically, such combinations have included a diuretic as well as either minoxidil, a CCB, and/or a peripheral α-blocker. The key to this approach, as with 2-drug combination therapy with ACE inhibitors, is that agents with different and complementary mechanisms of actions are being employed. In addition, if an acute reduction in BP is desired, it can be achieved with either oral or sublingual captopril in that its onset of action is as soon as 15 minutes after its administration.245 An additional ACE inhibitor use is in the management of hypertensive emergencies where parenteral therapy with enalaprilat is available.246 Compounds that interrupt RAAS activity, such as ACE inhibitors, should be administered cautiously in patients suspected of a marked activation of the RAAS (eg, prior treatment with diuretics). In such subjects, sudden and extreme drops in BP have occasionally been observed with the first dose of an ACE inhibitor.247

ACE Inhibitors and ARBs in Hypertension Associated with Other Disorders

ACE inhibitors and ARBs effectively regress left ventricular hypertrophy (LVH) in the face of prolonged lowering of BP, although there is some data to suggest that this can occur in a BP-independent fashion with RAAS inhibitors.248-253 The combination of an ACE inhibitor and an ARB does not regress LVH any more so than either drug class given alone. This is an important feature of RAAS inhibitors in that the presence of LVH portends a significant future risk of sudden death or MI.254 The question of whether LVH regression is followed by a positive outcome has been answered with completion of the Losartan Intervention for End-Point Reduction in Hypertension study (LIFE). The main LIFE study randomized 9,193 patients aged 55 to 80 years with essential hypertension to a > 4-year, double-blind treatment with losartan versus atenolol-based therapy. There was a clearly greater effect on LVH regression with losartan compared to atenolol, and the primary composite outcome of death, stroke, and CV morbidity showed a significant benefit in favor of losartan. This study also showed a substantially reduced rate of stroke in the losartan-treated group despite comparably reduced BP readings in both treatment groups.255

ACE inhibitors and ARBs can be safely used in patients with stable coronary artery disease.256 Although they do not specifically vasodilate coronary arteries, they do improve hemodynamic factors, which dictate myocardial oxygen consumption and thereby reduce the risk of ischemia (Table 9-7). For example, ACE inhibitors do not reflexively increase myocardial sympathetic tone in hypertensive patients with angina, as can occur with several vasodilating antihypertensives.257

ACE and ARBs are also useful in the treatment of either isolated systolic hypertension or systolic-predominant forms of hypertension, which, in part, relates to their ability to improve small- and medium-vessel compliance.258,259 In addition, ACE inhibitors are useful in the treatment of patients of cerebrovascular disease because they preserve cerebral autoregulatory ability even as they reduce BP, which is a useful feature in the treatment of the older patient with hypertension.250-252,260 ACE inhibitors also dilate both small and large arteries, can be used safely in patients with peripheral vascular disease, and may, on occasion, improve symptoms of claudication.261 As an example, the HOPE study measured ankle-brachial BP in 8,986 patients with 3,099 having peripheral arterial disease, defined by a history of peripheral arterial disease, claudication, or an ankle-brachial index of < 0.90. These patients had a similar reduction in the primary endpoint when compared with those without peripheral arterial disease, thus demonstrating that an ACE inhibitor (ramipril) was effective in lowering the risk of fatal and nonfatal ischemic events among patients with peripheral arterial disease.262

ACE inhibitors and ARBs are also touted as agents of choice in patients with diabetes mellitus and hypertension, whether or not they have diabetic nephropathy. Such enthusiasm needs to be tempered by the realization that these compounds, when given as single-drug therapy, are relatively ineffective in bringing BP to goal. This may relate to the fact that many diabetics have a low-renin, volume-expanded form of hypertension, which is generally less responsive to either an ACE inhibitor or an ARB. This efficacy hurdle can be overcome by addition of a diuretic to the treatment regimen or, alternatively, a different antihypertensive drug class may be considered for use; thus, the utility of RAAS inhibitors is considerably enhanced when they are part of a multidrug regimen as opposed to their use as monotherapy.263 Such was the case
in the African American Study of Kidney Disease and Hypertension (AASK) study conducted in blacks with hypertensive nephrosclerosis without diabetes mellitus. It demonstrated an advantage of the ACE inhibitor ramipril over the β-blocker metoprolol and the calcium antagonist amlodipine in preventing adverse renal outcomes when used as a component of a multidrug regimen.  

A final consideration with ACE inhibitors in the patient with hypertension and diabetes mellitus relates to their effect on hyperlipidemia and/or insulin resistance. There has been considerable debate about the ability of RAAS inhibitors to lessen the occurrence of new-onset diabetes mellitus in at-risk patients. Except in rare cases where patients with diabetes mellitus develop hypoglycemia when they start using ACE inhibitors, it remains doubtful whether ACE inhibitors or ARBs significantly improve glucose metabolism. In that regard, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial showed that among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of ramipril for 3 years did not significantly reduce the incidence of diabetes mellitus but did significantly increase regression to normoglycemia. More recently, among patients with impaired glucose tolerance and CV disease or risk factors, the use of valsartan for 5 years, along with lifestyle modification, led to a relative reduction of 14% in the incidence of diabetes mellitus but did not reduce the rate of CV events. As of now, while some improvement in glucose tolerance may be an added benefit for patients who take ACE inhibitors or ARBs for other indications, especially hypertension, these drugs cannot be recommended solely with the intention of preventing type 2 diabetes mellitus.

## End Organ Effects

### Stroke

Given the significant public health impact of stroke and the identification of both nonmodifiable (age, gender, race/ethnicity) and modifiable (BP, diabetes mellitus, lipid profile, and lifestyle) risk factors, early prevention strategies are increasingly relevant. When a patient and, in particular, a patient with diabetes mellitus and hypertension suffers a stroke, the focus of care becomes the prevention of recurrent events. This can be accomplished with antiplatelet and lipid-lowering therapies, as well as by bringing the patient to and maintaining them at goal BP. Despite the clear risk reduction with implementation of these preventive strategies, new approaches or novel ways to implement existing treatments are always being sought. One issue with stroke that is still unresolved is whether antihypertensive agents and, in particular, RAAS inhibitors offer stroke protection (primary or secondary) independent of their BP reduction. A number of clinical trials have examined the efficacy of ACE inhibitors or ARBs for primary and secondary prevention of stroke (see Chapter 33, Drug Therapy of Cerebrovascular Disease). In the large majority of these studies, stroke was a secondary endpoint. Among the studies that assessed primary stroke prevention and used an ACE inhibitor, the HOPE trial assessed the ability of ramipril to reduce the occurrence of a composite CV outcome in high-risk patients with no LV dysfunction or HF. Despite its modest effect on BP, treatment with ramipril resulted in a 22% reduction in CV events and a 32% reduction in stroke. Stroke was a secondary outcome in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and therein patients who were treated with the ACE inhibitor lisinopril had an overall 15% higher rate of fatal and nonfatal stroke than patients given the diuretic chlorthalidone despite similar baseline and magnitude changes in BP; however, this finding may have been a consequence of outcomes in black patients who had poorer control of systolic BP with the lisinopril-based regimen. Several recent trials have shown reduction in stroke with combination regimens based on diuretics or CCBs that also included ACE inhibitor therapy as needed to lower BP. The Hypertension in the Very Elderly Trial (HYVET) evaluated the diuretic indapamide (1.5 mg/d) plus the ACE inhibitor perindopril (2 or 4 mg/d) as needed to achieve target BP (<150/80 mm Hg) in 3845 patients as a primary endpoint of fatal or nonfatal stroke. At 2 years, 73.4% of patients were receiving perindopril in combination with the diuretic (mean sitting BP decreases 15.0/6.1 mm Hg, active treatment versus the placebo) and active treatment reduced the rate of fatal or nonfatal stroke and the rate of death from stroke by 30% and 39%, respectively. In the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA), which evaluated 19,257 patients [median follow-up of 5.5 yrs], treated with either amlodipine (5 to 10 mg/d) plus perindopril (4 to 8 mg/d) as needed, or with atenolol (5 to 100 mg/d) plus bendroflumethiazide (1.25 to 2.5 mg/d) as needed to reach target BP, a mean of 50% of patients in the amlodipine-based arm was also taking an ACE inhibitor by study’s end. Combination therapy with amlodipine and perindopril reduced the secondary endpoint of fatal and nonfatal stroke by 23% compared with the atenolol-based regimen. Finally, the Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial showed greater benefit for the prevention of stroke with
the ACE inhibitor benazepril added to the CCB amlodipine compared to benazepril and HCTZ with there being equivalent levels of BP reduction between each group. This trial was terminated early because of the greater benefit for the ACE inhibitor/CCB combination.275

The Perindopril Protection Against Recurrent Stroke (PROGRESS) study was a secondary prevention trial that reported that antihypertensive therapy with a combination of the ACE inhibitor, perindopril, and the thiazide diuretic indapamide reduced the recurrence of stroke even in patients with normal BP.276 In this study, 6105 hypertensive and nonhypertensive patients who had stroke and no major disability within the past 5 years were randomized to a 4-mg dose of perindopril with or without a 2.5-mg dose of indapamide. After 4 years of follow-up (40% received perindopril alone and 60% received combination therapy), there was a considerable disparity in the BP findings between these 2 treatment groups. In the subgroup of patients receiving perindopril and indapamide, BP was reduced by 12/5 mm Hg and the risk of stroke was reduced by 43%. Perindopril monotherapy reduced BP by 5/3 mm Hg, and yielded no significant reduction in the risk of stroke.276 Based on the degree of BP reduction in the perindopril group, a 20% reduction in stroke risk would have been anticipated; thus, the findings in PROGRESS are difficult to interpret. A similar observation was made in the Captopril Prevention Project (CAPPP) trial where, despite its design problems, fatal or nonfatal stroke was 1.25 times more common in patients randomized to captopril, than in those assigned to conventional therapy with diuretics and/or β-blockers.277 Nevertheless, the beneficial effect of combination therapy with perindopril and indapamide is consistent with prior studies that showed a positive effect of diuretics on recurrent stroke rate.

A number of primary prevention trials have been conducted with ARBs as to their effect on stroke. The first trial to assess the effect of an ARB on stroke was the LIFE study where the results, in terms of stroke, showed it to be reduced by 25% in the losartan group compared with the atenolol group despite comparable BP reduction (30.2/16.6 versus 29.1/16.8 mm Hg in the losartan and atenolol groups, respectively). It has been offered that these findings in the LIFE study were evidence of a benefit beyond BP reduction on stroke rate.278 The Study on Cognition and Prognosis in the Elderly (SCOPE) tested whether treatment with candesartan could reduce CV events, cognitive decline, and dementia in elderly patients aged 70 to 89 with mild to moderate hypertension.277 Treatment with candesartan resulted in a 27.8% reduction in non-fatal stroke and a 23.6% reduction in all strokes (mean sitting BP decreases 21.7/10.8 mm Hg: 18.5/9.2 mm Hg, active treatment versus the placebo). The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) tested whether an ARB-based regimen with valsartan would reduce cardiac morbidity and mortality more than one using the CCB amlodipine for an equivalent reduction in BP in a population of high-risk patients (N = 15,245) with treated or untreated hypertension. The combination of fatal and nonfatal strokes was a secondary endpoint in this study. In this study, the incidence of stroke was 15% higher in the valsartan group albeit in a statistically insignificant fashion (HR, 1.15; 95% CI, 0.98–1.35; P = .08). Interpretation of the results of this study proved difficult in that there was a significantly greater reduction in BP (4.0/2.1 mm Hg at 1 month; 2.1/1.6 mm Hg after 6 months) in the amlodipine-treated group during the early time points of the study.278

The Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) evaluated the ARB telmisartan, compared with the placebo, in addition to standard of care in subjects with CV disease or high-risk diabetes mellitus and who were intolerant of ACE inhibitor therapy. The primary endpoint in TRANSCEND was the composite of CV death, MI, stroke, or hospitalization for HF. For the secondary outcome of stroke, the rate of occurrence was 3.8% with telmisartan versus 4.6% for the placebo (HR, 0.83; 95% CI, 0.64–1.06; P = .136). The higher use of lipid-lowering therapy, β-blockers, and antiplatelet drugs in TRANSCEND (reflecting the current standard of care) may have resulted in lower event rates and may have influenced the effect of additional therapies.279

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) evaluated telmisartan (80 mg/d), ramipril (10 mg/d), and their combination in 25,620 high-risk patients with CAD, peripheral vascular disease, or cerebrovascular disease or diabetes mellitus with evidence of end-organ damage. The incidence of stroke was 4.3% in the telmisartan group compared with 4.7% in the ramipril group (relative risk, 0.91; 95% CI, 0.79–1.05) with no greater stroke benefit with combination therapy.280

Several secondary prevention trials have been undertaken with ARBs. The Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study assessed the influence of modest BP reduction with candesartan (4 mg titrated to a maximum dose of 16 mg [and additional medications as needed to reduce BP to < 140/90 mm Hg]) on safety and adverse events during early treatment of 500 survivors with recent ischemic stroke. This study was of some importance in that existing recommendations favor not treating acute hypertension in the setting of cerebral ischemia lest infarct extension occurs in the peri-infarct penumbra. The primary endpoint in this study was a composite of fatality, disability, and cerebral complications. If hypertension persisted, both groups were given candesartan and additional medi-
cations as necessary to reduce BP to \(< 140/90\) mm Hg. Despite similar BPs in both treatment groups at baseline and during all subsequent phases of the study, treatment with candesartan during the first 7 days after stroke resulted in a significant reduction of 52% in mortality and vascular events compared with the placebo \((P = .026)\). The fact that no CV or cerebrovascular event occurred in this study as a result of hypotension is of significant clinical importance.280

The recent Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study compared the ARB eprosartan \((600\) mg/day) and the calcium blocker nitrendipine \((10\) mg/day) [doses could be titrated and other medications added as needed to achieve a BP of \(< 140/90\) mm Hg] for reducing cerebrovascular and CV morbidity and mortality in 1,405 patients with hypertension and a previous cerebral event.281 Following treatment, BP decreased 13.2/3.2 and 16/7 mm Hg with eprosartan and nitrendipine, respectively; however, eprosartan decreased CV and cerebrovascular events by 21% \((P = .014)\) and the incidence of cerebrovascular events by 25% \((P = .026)\). As was the case with the LIFE study results, these results were held to represent a beyond the BP cerebroprotective effect for ARB therapy in a high-risk population having sustained a previous stroke.281

Finally, the effectiveness of telmisartan versus the placebo (in addition to antiplatelet therapy) was evaluated in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study \((N = 20,332)\) as to a primary outcome of recurrent stroke.282 During mean follow-up of 2.5 years, mean BP was 3.8/2.0 mm Hg lower in the telmisartan group versus the placebo group. Therapy with telmisartan for a mean follow-up of 2.5 years did not significantly lower the rate of recurrent stroke \((HR, 0.95; 95\% CI, 0.86–1.04; P = .23)\); major cardiovascular events \((HR, 0.94; 95\% CI, 0.87–1.01; P = .11)\); or diabetes mellitus \((HR, 0.82; 95\% CI, 0.65–1.04; P = .10)\). Post hoc exploratory analyses suggest that the study duration may not have been sufficient. After 6 months, a significantly lower rate of recurrent stroke was observed with telmisartan compared with the placebo \((HR, 0.88; 95\% CI, 0.78–0.99; P = .04)\). As observed in HOPE\(^9\) and PROGRESS,283 there was little or no apparent benefit in the first 6 months, whereas in PROFESS there was a gradual and continuing lowering in the rates of stroke and major cardiovascular events thereafter.282

The body of evidence relative to RAAS inhibitors and reduction in either primary or secondary stroke rate is large and hopelessly intermingled with the independent effect of BP reduction on cerebrovascular events. A careful review of these data would seem to suggest that BP reduction in and of itself may be the most important factor in reducing stroke rate. Since multidrug antihypertensive regimens are increasingly the norm in the treatment of hypertension, an RAAS inhibitor is likely to still be used in many patients independent of the clinician specifically selecting a cerebroprotective antihypertensive agent. As such, there is no evidence of specific benefit when comparing ARBs with ACE inhibitors and with CCBs.283,284

Renal

JNC 7 recommends the use of ACE inhibitors or ARBs in patients with hypertension and CKD to both control hypertension and to slow the rate of progression of CRF.1 There is now a wealth of information supporting the use of ARBs for their nephroprotective effect, with less hard outcomes data available for ACE inhibitors; however, ACE inhibitors and ARBs continue to be used interchangeably for this purpose.200,201,285 Irrespective of the drug class being used to lower BP, the most important element in the management of the patient with hypertension and CKD remains tight BP control. The joint recommendations of the American Society of Nephrology and the National Kidney Foundation provide useful guidelines for management of hypertensive patients with CKD. They recommend a goal BP for all CKD patients of \(< 130/80\) mmHg and the need for more than 1 antihypertensive drug to achieve this goal. Patients with CKD and proteinuria and/or diabetes mellitus should receive RAAS inhibitor therapy; however, because of the volume dependency of the hypertension in this group of patients, ACE inhibitor and ARB therapy alone do not always provide the desired level of BP control. For example, in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study and Irbesartan Diabetic Nephropathy Trial (IDNT), the average number of medications required to achieve BP control, which was 140/90 and 135/85, respectively, in these studies, was 3 plus the study medication.280,281 Thus, it is not uncommon in the treatment of these patients that diuretics and/or other drugs, such as CCBs, are needed to reach goal BP.280

Proteinuria has emerged as a strong marker for CKD development and progression in diabetes mellitus as well as being an independent risk factor for cardiovascular disease.286 Microalbuminuria typically augurs the development of progressive diabetic nephropathy, and it is now routinely measured in all diabetics on an annual or semi-annual basis. Not only is screening for microalbuminuria recommended in diabetes mellitus, but it is also suggested for other patient types at increased risk for renal or CV disease. The National Kidney Foundation recently reviewed the evidence relating proteinuria and renal and CV risk leading to their recommendation that therapies used to treat hypertension should also target reductions in proteinuria.287 ACE inhibitors and ARBs have a num-
ACE inhibitors have proven useful in the setting of established type 1 insulin-dependent diabetes mellitus (IDDM) nephropathy, non-insulin-dependent diabetes mellitus (NIDDM) nephropathy, normotensive type 1 IDDM patients with microalbuminuria, and a variety of nondiabetic renal diseases. Not all studies have demonstrated beneficial effects of ACE inhibitors. The Ramipril Efficacy in Nephropathy (REIN) study failed to detect a renoprotective effect in type 2 diabetic nephropathy patients treated with ramipril. Interestingly, those patients treated with ramipril lost renal function at a significantly faster rate than patients treated with a conventional non-ACE inhibitor-based regimen. ACE inhibitor regimens shown to slow the rate of CKD progression include captopril 25 mg tid, enalapril 5 to 10 mg/d, and ramipril 2.5 to 5 mg/d. It is presumed that renal failure increases the pharmacologic effect of these ACE inhibitor doses by reducing renal clearance of these compounds.

ARBs have also been found in recently published clinical trials to be useful in the setting of type 2 diabetes mellitus, both in established diabetic nephropathy with proteinuria, and in patients with microalbuminuria and diabetes mellitus. Results of these trials are similar to what has been seen in type 1 diabetic nephropathy treated with captopril and a range of microalbuminuria trials treated with any of several different ACE inhibitors (Table 9-10). In the IDNT and RENAAL studies, which assessed hard renal outcomes, irbesartan 150 to 300 mg/d and losartan 50 to 100 mg/d were used (Table 9-11). The antiproteinuric response to an ARB has been studied more exhaustively than has been the case with ACE inhibitors, and, in so doing, it would appear that there is a greater antiproteinuric effect with upward-dose titration, when given in combination with an ACE inhibitor and/or when administered preferentially at night.

Therapies directed at reducing the production or effects of angiotensin-II have a variety of potentially beneficial effects on the kidney. ACE inhibitors transiently reduce GFR secondary to their reducing glomerular capillary pressures. Such decrements in GFR (ordinarily in the order of a 10%-15% drop) are readily reversible and actually predictive of the degree of long-term renal protection with an RAAS inhibitor. Current practice would suggest that there is not a specific level of renal function that precludes starting an ACE inhibitor or an ARB; alternatively, if significant hyperkalemia precedes the start of RAAS inhibitor therapy or the same is anticipated, then this is a reason to either not start such therapy and/or proceed with low doses and slow upward titration.

As already mentioned, reduction in proteinuria has been utilized as an indicator of the beneficial effects of RAAS inhibitor therapy. Reducing proteinuria may, in and of itself, also favorably affect the progression rate of CKD. The renoprotective effect of RAAS inhibitor therapy is most evident in patients with heavy proteinuria (> 3 g/d) who, if left untreated, generally experience a rapid decline in renal function. ACE inhibitors and ARBs also modify a range of tissue-based growth factors, such as transforming growth factor (TGF)-β, which are activated by prior/ongoing renal disease and are further stimulated in the presence of angiotensin-II. Inhibition of these tissue-based processes may further slow the progression of CKD. There may be differences in the tissue-based effects of ACE inhibitors and ARBs because the effect of ACE inhibitors on renal hemodynamics might be lessened by the non-ACE-dependent generation of angiotensin II.

Several factors are potential modifiers of the renal response to an ACE inhibitor. First, a low sodium (Na⁺) intake enhances the antiproteinuric effect, and, conversely, a high Na⁺ intake blunts the antiproteinuric effect of ACE inhibition. Addition of a diuretic to a treatment regimen can restore the antiproteinuric response to an ACE inhibitor in the setting of a high Na⁺ intake. Second, short-term studies suggest that dietary protein restriction augments the ACE-inhibitor effect on protein excretion in patients with nephrotic syndrome. This would seem to imply that combining ACE inhibitors and protein restriction might prove more effective than an ACE inhibitor alone in slowing the progression of CKD, although this has not been a consistent finding. A third factor influencing ACE inhibitor effect is that of the inherited variation in ACE activity. Two common forms of the ACE gene I (insertion) and D (deletion) give rise to 3 potential genotypes: II, ID, and DD. The DD phenotype is associated with higher circulating ACE levels and a greater pressor response to the infusion of angiotensin-I as compared to the II phenotype, with the ID phenotype displaying intermediate characteristics. These phenotypic characteristics seemingly influence the response to ACE inhibitors and ARBs, but in an as-of-yet-not-fully-defined fashion. The finding that DD patients are at increased risk for MI and ischemic cardiomyopathy first established the clinical significance of the inherited variation in ACE activity. In this regard, recent work suggests that GFR declines more rapidly in DD than II patients and that such patients do not demonstrate significant reductions in proteinuria or slowing in the rate of progression of renal failure when administered an ACE inhibitor or an ARB.

Cardiac

Data from both placebo-controlled and open trials suggest that ACE inhibitors substantially reduce the risk of
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Design</th>
<th>Drug</th>
<th>UAE</th>
<th>GFR</th>
<th>SCr</th>
<th>Clcr</th>
<th>Arterial BP</th>
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<tr>
<td>Mathiesen et al&lt;sup&gt;288&lt;/sup&gt;</td>
<td>44 type 1 DM, Microalbuminuria</td>
<td>Open-label, Randomized, prospective</td>
<td>Captopril 25–100 mg/d</td>
<td>↓†</td>
<td>0†</td>
<td>NE</td>
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<td>Ahmad et al&lt;sup&gt;286&lt;/sup&gt;</td>
<td>103 type 2 DM, persistent microalbuminuria</td>
<td>Prospective, randomized, single-blind, placebo-controlled</td>
<td>Enalapril 10 mg/d</td>
<td>↓†</td>
<td>0</td>
<td>NE</td>
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</tr>
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<td>Nielsen&lt;sup&gt;305&lt;/sup&gt;</td>
<td>43 type 2 DM, persistent macroalbuminuria</td>
<td>Prospective, randomized, double and then single-blind</td>
<td>Lisinopril 10–20 mg/d vs atenolol 50–100 mg/d</td>
<td>Greater ↓ with lisinopril</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>Similar reductions in both treatment limbs</td>
</tr>
<tr>
<td>Bakris&lt;sup&gt;306&lt;/sup&gt;</td>
<td>52 type 2 DM with persistent proteinuria</td>
<td>Randomized, prospective</td>
<td>Lisinopril vs atenolol vs verapamil or diltiazem Captopril vs atenolol</td>
<td>↓ that was comparable in lisinopril and CCB groups</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>Similar reductions in all three treatment limbs</td>
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<td>UKPDS&lt;sup&gt;307&lt;/sup&gt;</td>
<td>758 type 2 DM some with microalbuminuria</td>
<td>Randomized, prospective</td>
<td>Captopril vs atenolol</td>
<td>↓ that was comparable in captopril and atenolol groups</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>Similar reductions in both treatment limbs</td>
</tr>
<tr>
<td>REIN&lt;sup&gt;293&lt;/sup&gt;</td>
<td>352 nephropathic patients</td>
<td>Randomized, prospective</td>
<td>Ramipril vs conventional therapy</td>
<td>Greater ↓ with ramipril only in nondiabetics</td>
<td>Similar reductions in both treatment limbs</td>
<td></td>
<td></td>
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<td>HOPE&lt;sup&gt;309&lt;/sup&gt;</td>
<td>980 patients with mild renal insufficiency with or without proteinuria</td>
<td>Randomized, prospective, double-blind</td>
<td>Ramipril 10 mg vs placebo</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>Greater CV event rate in placebo group despite minimal reduction in BP</td>
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<tr>
<td>Fogari et al&lt;sup&gt;304&lt;/sup&gt;</td>
<td>51 type 2 DM, persistent proteinuria &gt;300 and &lt;2000 mg/d</td>
<td>Randomized, prospective</td>
<td>Ramipril 5 mg vs nitrendipine 20 mg</td>
<td>↓</td>
<td>0</td>
<td>NC</td>
<td>NC</td>
<td>Similar reductions in both treatment limbs</td>
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<tr>
<td>Reference</td>
<td>Patients</td>
<td>Design</td>
<td>Drug</td>
<td>UAE</td>
<td>GFR</td>
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<td>Clcr</td>
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<td>Estacio et al</td>
<td>470 type 2 DM with or without proteinuria</td>
<td>Prospective, randomized, double-blind</td>
<td>Enalapril vs Nisoldipine</td>
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<td>**</td>
<td>**</td>
<td>**</td>
<td>Similar reductions in both treatment limbs</td>
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<td>Lebovitz et al</td>
<td>121 type 2 DM, persistent macroalbuminuria</td>
<td>Prospective, randomized, single-blind, positive control</td>
<td>Enalapril 10 mg/d</td>
<td>↓†</td>
<td>Enalapril slowed GFR decline</td>
<td>Equivalent reduction in treatment groups</td>
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<td>Lewis et al</td>
<td>409 type 1 DM, DN</td>
<td>Prospective, randomized, placeo-controlled</td>
<td>Captopril 25 mg tid</td>
<td>↓†</td>
<td>NE</td>
<td>1†</td>
<td>NE</td>
<td>1†</td>
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<td>EUCLID</td>
<td>530 type 1 DM, normoalbuminuria/microalbuminuria</td>
<td>Double-blind, randomized, placeo-controlled</td>
<td>Lisinopril 10–20 mg/d</td>
<td>↓†</td>
<td>NE</td>
<td>1†</td>
<td>NE</td>
<td>1†</td>
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<td>Ravid et al</td>
<td>94 type 2 DM, microalbuminuria</td>
<td>Randomized, placeo-controlled</td>
<td>Enalapril 10 mg/d</td>
<td>↓†</td>
<td>NE</td>
<td>0</td>
<td>NE</td>
<td>0</td>
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<tr>
<td>Ravid et al</td>
<td>156 type 2 DM</td>
<td>Randomized, double-blind, placeo-controlled</td>
<td>Enalapril 10 mg/d</td>
<td>↓†</td>
<td>NE</td>
<td>NE</td>
<td>1†</td>
<td>0</td>
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<tr>
<td>Viberti et al</td>
<td>92 type 1 DM, microalbuminuria</td>
<td>Randomized, double-blind, placeo-controlled</td>
<td>Captopril 50 mg bid</td>
<td>↓†</td>
<td>↓†</td>
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<td>0</td>
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<td>Sano et al</td>
<td>52 type 2 DM, persistent microalbuminuria</td>
<td>Randomized</td>
<td>Enalapril 5 mg/d</td>
<td>↓†</td>
<td>NE</td>
<td>NE</td>
<td>0</td>
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</table>

BP = blood pressure; CCB = calcium-channel blocker; Clcr = creatinine clearance; DM = diabetes mellitus; DN = diabetic nephropathy; GFR = glomerular filtration rate; NC = no change; NE = not evaluated; SCr = serum creatinine; UAE = urinary albumin excretion.

Compared with baseline.

† Statistically significant difference
‡ No statistically significant difference

death and hospitalization for HF while improving its symptomatology making ACE inhibitors first-line therapy for the treatment of systolic forms of HF.\textsuperscript{11,331–332} By modifying production of angiotensin-II, these agents interrupt the neurohumoral deterioration characteristic of advancing HF.\textsuperscript{110,111,333} While statistically significant reductions in mortality have been observed with enalapril, similar trends have been observed with other ACE inhibitors, including captopril, ramipril, quinapril, trandolapril, and lisinopril.\textsuperscript{11,334} Furthermore, these agents have demonstrated efficacy and tolerability in the treatment of HF based on the endpoints of improved exercise tolerance and improvement in core symptoms.

Although ACE inhibitors are almost universally recommended as a cost-effective strategy for the treatment of HF, physician-prescribing practice is quite variable. In dedicated HF clinics, usage is as high as 80% with an eye towards upward titration as tolerated.\textsuperscript{336} In general practice, usage is less, and dose titration occurs with much less regularity.\textsuperscript{336} As such, since dosages used in “real-world practice” are so much lower than those proven efficacious in randomized, controlled trials, there remains a considerable unmet need for guideline implementation in primary care circumstances.

Factors predicting the use and optimal dose administration of ACE inhibitors include variables relating to the

| Table 9-11. Studies with Angiotensin Receptor Blockers in Diabetic Nephropathy |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Study Design**                | **IDNT\textsuperscript{201}** | **IRMA 2\textsuperscript{205}** | **RENAAL\textsuperscript{200}** | **MARVAL\textsuperscript{312}** |
| N                               | 1715            | 590             | 1513            | 332             |
| **Patient Type**                | HT/Type 2 Diabetes/Nephropathy | HT/Type 2 Diabetes/Microalbuminuria | Type 2 Diabetes/Nephropathy | Type 2 Diabetes/Microalbuminuria; SBP <180 and/or DBP <105 mm Hg |
| **Duration**                    | Mean 2.6 years  | 2 years         | Mean 3.4 years  | 24 weeks        |
| **End-points**                  | Primary composite: doubling of serum creatinine/ESRD/death | Time to onset of nephropathy with UAER >200 \(\mu g/min\)/30\% greater than baseline | Primary composite: doubling of serum creatinine/ESRD/death | \(\approx\) UAER |
| **Results**                     | Risk of primary endpoint 20\% lower with IRB vs PLA; 23\% lower vs AML—lower doubling of serum creatinine ESRD with IRB; no difference in deaths | IRB was renoprotective; 5.2\% reached end-point in 300-mg groups; 9.7\% reached end-point in 150-mg group vs 14.9\% in PLA (\(P = .08\)) | Risk of primary endpoint lowered by 15\% (\(P = .02\)) with LOS—lower doubling of serum creatinine ESRD with LOS; no difference in deaths | VAL significantly lowered UAER (44\%) vs AML (17\%) (\(P < .001\)) |

IDNT = Irbesartan Diabetic Nephropathy Trial; IRMA-2 = Irbesartan Microalbuminuria Study; RENAAL = Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; MARVAL = Microalbuminuria Reduction With VALsartan Study

AML = amlodipine; DBP = diastolic blood pressure; ESRD = end-stage renal disease; HT = hypertension; IRB = irbesartan; LOS = losartan; PLA = placebo; UAER = urinary albumin excretion rate; SBP = systolic blood pressure; VAL = valsartan.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

setting (previous hospitalization, specialty clinic follow-up); the physician (cardiology specialty versus family practitioner or general internist); the patient (increased severity of symptoms, male, younger); and the drug (lower frequency of administration).317 The ability to reach recommended ACE inhibitor doses in the patient with HF can often prove difficult. The HF patient with reduced ejection fraction is prone to systemic hypotension and/or a decline in GFR with these compounds.331 Thus, reaching goal ACE inhibitor doses necessitates a keen understanding of the critical relationship between volume status, BP, and the final desired ACE-inhibitor dose. Probably the single most important variable, which allows effective dose titration, is an appreciation of the relationship between volume status and BP in the HF patient.338

Enalapril, captopril, lisinopril, and trandolapril significantly reduce morbidity and mortality rates in patients' post-MI across a wide range of ventricular function. There are presently insufficient data to determine whether clinically significant differences exist among the ACE inhibitors in the post-MI setting, given the paucity of head-to-head trials among these agents and the fact that many of the studies varied in length and duration.334,339 Currently, only captopril, lisinopril, ramipril, and trandolapril are approved specifically in post-MI LV dysfunction, although enalapril is approved in asymptomatic LV dysfunction. However, as in the case of patients with HF, numerous ACE inhibitors have demonstrated benefits in patients after MI, suggesting a class effect. Thus, ACE inhibitors are indicated in all patients with acute MI who can tolerate them. In a hemodynamically stable patient after an MI, an oral ACE inhibitor should be initiated, generally within 24 hours of the event, particularly if the MI is anterior in location and marked by depressed LV function.340,341 The hemodynamic effects and overall benefit of ACE inhibition are seen early, with 40% of the 30-day increase in survival observed in days 0 to 1, 45% in days 2 to 7, and approximately 15% after day 7.342 The benefits of ACE inhibitor therapy in the post-MI period appear not to be the result of a substantial decline in arrhythmia-related mortality.343

ARBs have been studied in the post-MI patient,344,345 in patients with systolic dysfunction,346-350 and in patients with preserved systolic dysfunction of HF,351-354 as well as in those patients with hypertension and a high CV risk.355-358 Two trials have been conducted with ARBs in the post-MI patient: the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) and the Valsartan in Acute Myocardial Infarction (VALIANT) study. In OPTIMAAL, losartan did not show non-inferiority versus captopril, which likely related to underdosing of losartan in that it was given at a maximum dose of 50 mg/day in comparison to a 50-mg three times daily dose of captopril; not unexpectedly, losartan was better tolerated than captopril.344 Conversely, in VALIANT, valsartan titrated to 160 mg twice daily afforded the same benefits in terms of survival and CV events, as captopril titrated to 50 mg three times daily. As was the case in ONTARGET; the combination of an ACE inhibitor (captopril) and an ARB (valsartan) in VALIANT did not provide any additional outcomes benefits and resulted in an increased frequency of adverse events.241,345 Valsartan was granted a labeled indication in clinically stable patients with LV dysfunction following an MI based on the results of the VALIANT study.345 In addition, ACE inhibitors appear to be of benefit in patients with coronary artery disease and preserved LV function without HF.356-358

Several trials have been conducted with ARBs in the patient with heart failure and a reduced ejection fraction including the Evaluation of Losartan in the Elderly (ELITE-I and ELITE-II), the Valsartan-Heart Failure Trial (Val-HeFT), and the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added and (CHARM)-Alternative.346-350 Taken together, these data suggest that in patients with stable HF, a reduced ejection fraction, and concomitant ACE inhibitor therapy, losartan was not superior to captopril in reducing all-cause mortality or CV events. These negative findings with losartan may have related to the relatively low dose of this compound used in these studies.347 Combination therapy with an ACE inhibitor and either valsartan 320 mg/day or candesartan titrated to 32 mg/day reduced the composite endpoint of all-cause mortality and HF hospitalization.348,349 The positive findings with dual RAAS inhibitor blockade in HF would suggest sufficient residual activity in this system when treatment occurs with an ACE inhibitor alone to warrant addition of an ARB; however, there still remains clinical indecision as to the timing of ARB addition to an ACE inhibitor in the context of competing therapies, such as β-blockers and aldosterone receptor antagonists. In that there are data for only ARBs (valsartan and candesartan) at a specific dose and dose frequency, within class substitution is ill-advised in the HF patient with a reduced ejection fraction. Lowering BP has been shown to improve diastolic function irrespective of the type of antihypertensive used. Two trials have been conducted with ARBs in patients with HF and preserved systolic function; neither has shown benefit relative to reducing a primary outcome of morbidity and mortality, although in the case of candesartan a modest benefit was observed in terms of fewer hospitalizations for HF.351,352 Although RAAS inhibitor therapy may be valuable in the management of co-morbidities in the HF patient with preserved ejection fraction, it is not associated with a sufficient-enough reduction in HF hospitalization or mortality to warrant a preferred therapy status.353,354,359
There have been only a small number of event-based studies with ARBs having evaluated their effect in patients with hypertension and high CV risk including ONTARGET, LIFE, VALUE, and the Jikei Heart Study.\textsuperscript{241,251,278,354} Taken together, these studies provide the following insights into ARB therapy in the patient with hypertension and high CV risk: (1) losartan-based therapy reduced CV morbidity and mortality more than atenolol-based therapy did, mainly by reducing stroke rate;\textsuperscript{255} (2) valsartan demonstrated comparable efficacy on CV morbidity and mortality compared to amlodipine in the VALUE study when evaluated over the long term. However, valsartan was less effective than amlodipine in the short-term relative to CV morbidity and mortality, which likely related to its being less effective in reducing BP\textsuperscript{278} in the Jikei Heart Study, valsartan, in addition to optimized treatment, reduced CV morbidity as the result of a positive effect on occurrence of stroke, angina, and HF.\textsuperscript{354} Finally, telmisartan in the ONTARGET study is the only ARB having been shown to have equivalence to an ACE inhibitor (ramipril) in patients with hypertension and a high CV risk; however, when given together with ramipril, it seems no better than ACE inhibitor therapy alone and has a higher adverse-effect rate.\textsuperscript{241,355,359a}

**Other Clinical Uses**

ACE inhibitors have been used in the diagnosis of renal artery stenosis (captopril-stimulated renography) and primary hyperaldosteronism. Patients suspected of having renovascular occlusive disease by clinical criteria are administered an oral dose of a rapid-acting ACE inhibitor, such as captopril, or intravenous enalaprilat 1 to 2 hours prior to injection of a nuclear imaging tracer. Subtle differences in intraglomerular pressure between the 2 kidneys are amplified by the sudden decline in local and circulatory angiotensin-II levels that result from administration of the ACE inhibitor. It has been reported that the diagnostic sensitivity of captopril-stimulated nuclear renography is 90%-100%.\textsuperscript{360}

With regard to hyperaldosteronism, it has been observed that aldosterone levels do not fall in patients with adrenal adenomas when given an ACE inhibitor or an ARB; alternatively, in the instance of adrenal hyperplasia, aldosterone levels usually decline by up to 50% with RAAS inhibitor therapy.\textsuperscript{361,362} ACE inhibitors have also been used to treat altitude polycythemia, and RAAS inhibitors in general have been used in the treatment of post-transplant erythrocytosis.\textsuperscript{363,365} RAAS inhibitors have for the most part provided little to no benefit in preventing post-angioplasty restenosis,\textsuperscript{366,367} however, administration of high-dose oral valsartan (160-320 mg/day) after implantation of a bare-metal stent in type B2/C coronary artery lesions reduces angiographic in-stent restenosis, target lesion revascularization, target vessel revascularization, late lumen loss, and major adverse cardiac event rates more effectively than low-dose valsartan (80 mg/day).

There is strong evidence that the RAAS is involved in the generation of atrial fibrillation.\textsuperscript{368-371} Data and ventricular tachyarrhythmias suggest that the ACE inhibitors and ARBs can prevent the atrial electrical and structural remodeling that is associated with atrial fibrillation.\textsuperscript{368-372} Preliminary data have demonstrated a benefit with this intervention.\textsuperscript{373-376a} However, more recent studies reveal no benefit in reducing the incidence of recurrent atrial fibrillation.\textsuperscript{377,378} There are ongoing studies in progress trying to resolve this issue.

Diabetic retinopathy remains a leading cause of visual loss. In type 1 diabetics, candesartan was shown to reduce the incidence of retinopathy with no apparent effect on retinopathy progression.\textsuperscript{379} In type 2 diabetics, candesartan might induce improvement of retinopathy.\textsuperscript{380}

In patients with impaired glucose tolerance and known cardiovascular disease or risk factors, the use of valsartan for 5 years was associated with a 14% reduction in the incidence of diabetes mellitus without affecting the rate of cardiovascular events.\textsuperscript{380a}

ACE inhibitors have been shown to reduce the risk of abdominal aortic aneurysms\textsuperscript{381,382} and to be of benefit in improving walking ability in patient with peripheral arterial disease.\textsuperscript{4}

**Cancer and ACE Inhibitors**

It went largely unnoticed in the prospective Studies of Left Ventricular Dysfunction (SOLVD) study that patients with LV dysfunction treated with enalapril showed a slightly higher incidence of malignancy than did those patients receiving the placebo (OR 1.59; confidence interval 0.90 to 2.82). In this study, there were 38 gastrointestinal malignancies in the enalapril group as compared with 22 in the placebo group (OR 1.7).\textsuperscript{383} Since the SOLVD study, several case reports/series have linked ACE inhibitors to the development of malignancies. For example, pemphigus vulgaris, which can be seen in association with internal malignancies, is a known adverse effect of ACE inhibitors. One case report linked enalapril to pemphigus vegetans with a simultaneously occurring internal malignancy.\textsuperscript{384} In an additional case report, Kaposi’s sarcoma appeared in a 70-year-old woman 8 months after starting captopril. Upon stopping the captopril, there was a marked reduction in both the cutaneous and gastric lesions of this disease, suggesting a cause-and-effect relationship between captopril and the malignancy.\textsuperscript{385}

A subsequent study disputed these findings in that it was shown that captopril inhibited angiogenesis in Kaposi’s sarcoma.\textsuperscript{386} These limited data are in contrast to a
greater body of evidence supporting the lack of a cancer risk with ACE inhibitors. In the recent large-scale HOPE trial, 9,297 high-risk patients who were treated either with ramipril or the placebo for a mean of 5 years had similar numbers of deaths from noncardiovascular causes in both groups. In addition, several other retrospective studies investigating the possible association between various antihypertensives and cancer risk failed to detect such a relationship with the use of ACE inhibitors. Finally, the Scottish retrospective cohort study by Lever et al, who compared 1,599 patients taking ACE inhibitors and 3,648 on other antihypertensive drugs, demonstrated a risk reduction for female sex-specific and lung cancers. Thus, the overall evidence available to date in those completed, there has not been a suggestion of excessive malignancies with this drug class.

### Adverse Effects of ACE Inhibitors and ARBs

Soon after their release, a syndrome of “functional renal insufficiency” was observed to occur as a class effect with ACE inhibitors, a process little different than what is occasionally seen with the ARBs. This phenomenon was initially recognized in patients with either a solitary kidney and renal artery stenosis, or in the setting of bilateral renal artery stenosis. Since these original reports, this phenomenon has been repeatedly observed. Predisposing conditions to this process include dehydration, HF, and/or or microvascular renal disease, as well as macrovascular renal disease. The mechanism common to all of these conditions is an initial fall in afferent arteriolar pressure/flow. When this occurs, glomerular filtration transiently drops. In response to this reduction in glomerular flow, there is a local release of angiotensin-II, which then preferentially constricts the efferent or postglomerular arteriole. With efferent arteriolar constriction, upstream hydrostatic pressures within the glomerular capillary bed are restored despite the initial and frequently continuing decline in afferent arteriolar flow. The abrupt removal of angiotensin-II, as occurs with either an ACE inhibitor or an ARB, dilates the efferent arteriole, which drops glomerular hydrostatic pressures and, as a consequence of this, GFR declines rapidly.

This phenomenon of “functional renal insufficiency” is best treated by discontinuation of the offending agent, either an ACE inhibitor or an ARB; careful volume repletion if intravascular volume contraction exists; and, if suspicion is high enough, investigation for the presence of renal artery stenosis. An additional adverse effect with ACE inhibitors is that of hyperkalemia. Relevant degrees of hyperkalemia with ACE inhibitor typically occur in predisposed patients, such as diabetic or HF patients with renal failure receiving potassium-sparing diuretics and/or potassium supplements. Typically, however, hyperkalemia is not that common with ACE inhibitors or ARBs unless they are being given in the setting of CKD and/or potassium supplements are in use. Alternatively, ACE inhibitors and ARBs are known to attenuate the drop in serum potassium values that occurs with diuretic therapy.

A dry, irritating, nonproductive cough is a common complication with ACE inhibitors, with its incidence as high as 44%. Cough is a class phenomenon with ACE inhibitors and has ostensibly been attributed to increased bradykinin levels or other vasoactive peptides such as Substance P, which may play a second-messenger role in activating the cough reflex. Although numerous therapies have been tried, few have eliminated ACE inhibitor-induced cough with any lasting success. An ACE inhibitor-related cough gradually disappears within 2 weeks after the offending agent is stopped. Alternatively, ARBs have been infrequently associated with cough, whether the cough incidence is determined in preselected patients having previously experienced ACE inhibitor-related cough or in parallel treatment studies directly comparing an ACE inhibitor to an ARB. Nonspecific ACE inhibitor-related adverse effects are uncommon with the exception of taste disturbances, leukopenia, skin rash, and dysgeusia, which are mainly seen in captopril-treated patients. The sulfhydryl-group found on captopril has been implicated in these abnormalities. Alternatively, ARBs have demonstrated a favorable safety and tolerability profile, which appears to be equivalent to, if not better than, that observed with the placebo. To date, no clear class-specific adverse effect has been seen with ARBs. In fact, certain adverse effects, such as headache, may occur less frequently with ARBs than with the placebo, which is probably a consequence of better BP reduction with an ARB than with the placebo.

Angioneurotic edema is a potentially life-threatening complication of ACE inhibitors that is more common in blacks than in other ethnic groups. The incidence rate for angioneurotic edema with an ACE inhibitor ranges from 0.1%-0.5% and it can be quite unpredictable in its occurrence. Among all-cause factors for angioedema, ACE inhibitors are etiologic as much as 20% of the time. Typically, ACE inhibitor-related angioedema is not a first-dose phenomenon. It is easily recognized because of its characteristic involvement of the mouth, tongue, and upper airway. Angioedema of the intestine can also occur with ACE inhibitor therapy. This typically presents with acute abdominal symptoms with or without facial and/or oropharyngeal swelling and is more common in females. Angioedema also occurs with ARBs but much less frequently. Limited evidence suggests that for patients who develop angioedema with an ACE inhibitor,
the risk of subsequent development of angioedema with an ARB is between 2%-17%; for confirmed angioedema, the risk is 0%-9.2%. The mechanism of angioedema with ARBs is unknown, although in ARB-treated patients who develop angioedema, up to one-third had previously developed angioedema on an ACE inhibitor.409 ARB use can be considered for use in a patient having previously experienced angioedema with an ACE inhibitor, but only if compelling indications exist, such as progressive HF and/or proteinuric renal disease, and only then with appropriate patient instruction.410,411

A final issue with ACE inhibitors and ARBs is their capacity to cause birth defects. These drugs, when used during the second and third trimester of pregnancy, can cause oligoamnios, neonatal anuria, hypocalvaria, pulmonary hypoplasia, and/or fetal or neonatal death in that the maturing fetus is heavily reliant on angiotensin-II for its proper development.412-414 Recent data would also suggest that infants with first trimester exposure to ACE inhibitors have an increased risk of major congenital malformations (risk ratio, 2.71; 95% CI, 1.72 to 4.27) as compared to infants with no exposure to antihypertensive medications. Infants exposed to ACE inhibitors were, in particular, at an increased risk for malformations of the CV system (risk ratio, 3.72; 95% CI, 1.89 to 7.30) and the central nervous system (risk ratio, 4.39; 95% CI, 1.37 to 14.02).415 Unintended pregnancy remains common in young women; thus, in women of gestational age, a clinician must be alert to this possibility when the treatment of hypertension is contemplated and an agent is to be selected. This is particularly so with ACE inhibitors and/or ARBs, which still appear to be commonly used antihypertensive medications in women of child-bearing potential.416,417 If ACE inhibitors or ARBs are required or are being incidentally used when a women is nursing, there appears to be minimal entry of these compounds into breast milk. Although not all ACE inhibitors or ARBs have been submitted to formal study, in most cases, breast milk selectively restricts the passage of these drugs.418

Class and Agent-Specific Drug Interactions

Several class-specific drug interactions occur with ACE inhibitors and ARBs. When either an ACE inhibitor or an ARB is given together with lithium, there is a greater likelihood of lithium toxicity occurring.419,420 Potassium supplements or potassium-sparing diuretics, when given with either an ACE inhibitor or an ARB and/or an aldosterone receptor antagonist, increase the probability of hyperkalemia developing.421 NSAIDs, such as indomethacin, reduce the antihypertensive effects of both ACE inhibitors and ARBs.422 NSAIDs also attenuate the natriuretic response seen with both ACE inhibitors and ARBs when a diuretic is co-administered or otherwise.423,424 In addition, both ACE inhibitors and NSAIDs can lead to functional renal insufficiency, particularly in those taking diuretics who become dehydrated. This combination of drugs should be administered with extreme care to highly vulnerable patients, such as the elderly.425 Finally, combining an ACE inhibitor with allopurinol is associated with a higher risk of hypersensitivity reactions with several reports of the Stevens-Johnson syndrome described with the combination of captopril and allopurinol.426 Quinapril reduces the absorption of tetracycline by ≈ 35%, which may be due to the high magnesium content of quinapril tablets. To date, no drug–drug interactions have been described relative to the absorption of ARBs.

Conclusion

ACE inhibitors and ARBs are commonly used in the treatment of hypertension and for end-organ protection in a number of disease states. These compounds reduce BP by mechanisms involving change in the quantity and/or effect of angiotensin-II and, in the case of ACE inhibitors, by increasing bradykinin levels. Moreover, there is increasing evidence that these compounds can also alter sympathetic outflow, although in a compound-specific manner. Early belief held that these drugs were minimally effective in low-renin forms of hypertension, such as in the case of blacks with hypertension. More recently, it has become clear that the black patient with hypertension can respond to these drugs, although with considerable interindividual variability in the pattern of response. A number of ACE inhibitors and ARBs are currently available, with distinctions between individual members of each drug class sometimes being quite subtle. Pharmacologic properties proposed as distinguishing features for both ACE inhibitors and ARBs include their tissue and receptor-binding potential and whether their mode of elimination is renal or renal/hepatic. ACE inhibitors and ARBs are of clearly proven benefit in slowing the progression of CKD, and both drug classes have a major influence on the morbidity and mortality that attends HF characterized by a reduced ejection fraction and/or that seen in the post-MI circumstance. ACE inhibitors are generally without significant adverse effects other than cough, which, unfortunately, can occur in a significant number of patients receiving these drugs. Alternatively, ARBs are virtually adverse-effect free, which is a substantial advantage supporting the expanded use of drugs in this class.

Note: References for this chapter can be found here: www.cvpc3.com
A s detailed in Chapter 9, the renin-angiotensin system (RAS) functions as a primary regulator in the physiologic control of blood pressure (BP) and fluid volume. Increased RAS activity is also a significant determinant for numerous pathological states since angiotensin II (Ang II) increases aldosterone and BP and contributes to the development of end-organ damage through direct effects on cardiac, vascular, and renal tissues (Figure 10-1). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been utilized effectively in treating systemic hypertension, heart failure (HF), and various states of renal injury (see Chapter 9, The Renin-Angiotensin Axis: Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers).1 In addition, studies have shown that ACE inhibitors are effective in reducing the risk of cardiovascular death, myocardial infarction (MI), and stroke, independent of BP lowering, in patients at high risk for cardiovascular events without concomitant left ventricular (LV) dysfunction or HF.2

Long-term treatment with ACE inhibitors does not completely suppress the circulating RAS, as plasma Ang II and aldosterone levels tend to return toward pretreatment levels. Various theories have evolved in an attempt to explain the higher-than-expected levels of Ang II and aldosterone despite continued ACE inhibitor treatment.3-5 The most popular of these theories relates to Ang II being produced via non-ACE pathways, such as a chymostatin-sensitive pathway, which also facilitates conversion of Ang I to Ang II.6-8 These alternative pathways have been identified in the human heart.7

A series of studies in healthy human patients has also measured the change in renal blood flow in response to several different ACE inhibitors, ARBs, and renin inhibitors all given at the high end of their dose range. These data have been summarized in a recent meta-analysis and in other studies showing that both ARBs and renin inhibitors produced a comparable step-up in renal blood flow that was greater than the response obtained with an ACE inhibitor.9,9a This series of observations has been presumed to reflect non-ACE-generated Ang II being present in the kidney, which is more completely blocked by either a renin inhibitor or an ARB. A potent peptide renin inhibitor was found to be more effective than ACE inhibition in blocking systemic Ang II formation,10 thus supporting this concept. The implications for therapeutics are important; if Ang II is responsible for tissue damage, direct renin inhibition might provide greater efficacy than ACE inhibition.5

This chapter reviews the development of a potentially more specific form of therapy for treatment of cardiovascular disease—direct renin inhibition—with a focus on aliskiren, the first in a new class of highly specific and orally active bioavailable renin antagonists.

**Renin and Its Actions**

The synthesis of renin begins with the formation of preprorenin, which is cleaved during translocation to prorenin, an inactive form of the enzyme, by removal of a 23-amino acid signal peptide (Figure 10-2).11,12 A 43-amino acid “pro” sequence is then removed from prorenin to produce renin that is packaged for storage and subsequent release. Prorenin and renin are stored in granules lying alongside the plasma membrane in the juxtaglomerular cells surrounding afferent arterioles. The release of both renin and prorenin from the storage granules is thought to occur through swelling of the granules in response to a reduction in glomerular afferent arteriolar pressure, sympathetic nerve stimulation, or a reduced rate of sodium delivery to the distal tubules.13
Renin is a single chain aspartyl protease. From 3-dimensional x-ray crystallography studies of aspartyl proteases, these proteins were revealed to be bilobal with a pronounced cleft between the 2 lobes, where the 2 aspartyl residues of the catalytic sites are located close together, one on each side of the cleft. Renin differs from other aspartyl proteases in its action at a neutral pH and in its specificity for only 1 known substrate, angiotensinogen. This high specificity for angiotensinogen makes renin an ideal target for pharmacologic intervention. In addition, several renin receptors have been identified. These receptors can also recognize prorenin. There is experimental evidence that binding of renin to the receptor can have profibrotic effects that are independent of Ang II, suggesting direct actions of renin and prorenin on organ pathophysiology.

Angiotensinogen is a 14-amino acid α2-globulin produced by the liver with a molecular weight of 55 to 65 kD, which varies depending on the extent of its glycosylation. Human angiotensinogen differs from rat or hog angiotensinogen by the presence of a Leu10-Val11 cleavage site instead of a Leu10-Leu11 bond and also by the residues that immediately follow on the C-terminal side of the scissile bond. The unique sequence of human angiotensinogen accounts for the high specificity of human renin for human angiotensinogen and explains the necessity of modeling renin inhibitors on the human angiotensinogen sequence and the need to conduct clinical testing in primates. Recent data have suggested a direct paracrine role for angiotensinogen in rodent renal vessels. In transgenic mice overexpressing angiotensinogen, a decrease in renal arteriole thickness was demonstrated, suggesting that angiotensinogen can affect vascular remodeling in the rodent. Although the mechanism(s) for these findings are not clear, in theory it would be expected that angiotensinogen levels would be elevated through antagonism of renin and potentially contribute to modulation of renal arteriolar wall thickness.

Enzymatic cleavage of angiotensinogen by renin is the rate-limiting step in the activation of the RAS (Figure 10-1). Renin, by virtue of the 2 aspartic acids within its active site, hydrolyzes angiotensinogen at a relatively fragile C-N bond proceeding through a tetrahedral transition state intermediary formed with the addition of a water molecule. One strategy in making transition state analog inhibitors of renin is to replace this fragile transition state tetrahedral C-N bond with a virtually uncleavable bond such as a C-C bond. Ang I, a 10-amino acid fragment, is cleaved from angiotensinogen after the interaction with renin. The released Ang I circulates in the blood stream until acted on by ACE, a carboxydi-peptidase that is predominately endothelium-bound and widely expressed. ACE acts on Ang I to produce Ang II, an octapeptide. ACE is not specific for Ang I in that it

Figure 10-1. The renin-angiotensin system indicating blockade of the pathway by renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, and angiotensin II-type 1 receptor blockers (ARBs). AT-R = angiotensin receptor.


Figure 10-2. Cascade of renin synthesis, activation, and release in the JG cell of the renal afferent arteriole, leading to enzymatic formation of ang II. JG–juxtaglomerular; cAMP = cyclic adenosine monophosphate; mRNA = messenger ribonucleic acid.

Renin.38 Pepstatin analogues have been synthesized, corenacting state for the scissile peptide bond cleaved by affinity of renin for pepstatin by acting as a mimic of the residues, the central one of which determines the binding renin activity (PRA).30-32 Although found to be effective antibodies were shown to lower both the BP and plasma occasionally generated from pure renin extracts. Administra- specific renin antibodies directed against the enzyme.28 Initially, the antibodies were generated against unpurified crude renal extracts, which had questionable specificity.29 Antibodies with a high degree of specificity were subsequently generated from pure renin extracts. Administration of antirenin antiserum, Fab fragments, and monoclonal antibodies were found to be effective for BP lowering, this immunologic approach was limited because the antibodies were orally inactive since they could not be absorbed intact from the gastrointestinal tract. In addition, with repeated intravenous administration, the antibodies could induce antigenic reactions. The second class of renin inhibitors were synthetic derivatives of a prosegment of the renin precursor. These agents could inhibit human renin activity but possessed low potency.33,34

The next development in the evolution of renin inhibitors was based on structure-activity relationships. The peptide sequence of angiotensinogen was modified to produce an inhibitor that would bind tightly to renin and would not be cleaved by renin or other proteases. The modification of angiotensinogen was based on the transition-state configuration that had the greatest stability and binding of the enzyme to the substrate. It was reasoned that inhibitors that mimic the transitional structure of the hydrolysis of the leu-val amide bond would interact more strongly with the enzyme than the substrate analogues, thus providing better inhibition.

Based on this principle, the third class of drugs was modeled on the activity of pepstatin, a natural pentapeptide isolated from actinomycetes that universally inhibits aspartyl protease.35-37 Pepstatin contains 2 statin residues, the central one of which determines the binding affinity of renin for pepstatin by acting as a mimic of the transition state for the scissile peptide bond cleaved by renin.39 Pepstatin analogues have been synthesized, corresponding to the general formula: A-X-Y-Stat-Sta-Ala-Sta-R, in which various changes in the nature of the A, X, and Y groups are made to improve the inhibitory potency against human renin.39 The analogues having a Phe in place of Val in the X position and His or an amino acid with an aliphatic side chain in the Y position showed the highest degree of inhibition of human PRA. 3-Methyl statin derivatives of pepstatin have been synthesized, and their renin inhibitory activity has been evaluated.40 Unfortunately, pepstatin analogues exhibited poor specificity and limited affinity for human renin, which has limited their experimental and potential clinical use.

The fourth class of renin inhibitors, the angiotensinogen (substrate) analogues, held great promise. The early substrate analogue inhibitors of renin were derivatives of the tetrapeptide sequence Leu10-Leu-Val-Tyr,13 found in equine angiotensinogen.41 Later, the use of an octapeptide substrate, which competes for renin activity to form an inactive product several amino acids shorter than A-I, was shown to effectively inhibit renin.42 The inhibitory effect of several other modified fragments of angiotensinogen was also evaluated. One alteration included the substitution of the d-enantiomer D-Leu for the Leu10-Leu11 of the scissile peptide bond, which was not cleaved by renin in the substrate.43 This change resulted in a significant increase in the inhibitory potency of this angiotensinogen fragment. Replacement of the Leu10-Leu11 scissile bond with a hydrophobic dipeptide (Phe-Phe) yielded the renin inhibitor peptide (RIP) Pro1-His-Pro-Phe-His-Phe-Val-Tyr-Lys.44 RIP was the first compound to demonstrate that stabilization of the scissile bond of renin substrate would produce a compound with in vivo pharmacologic effects.45 A series of angiotensinogen analogues were produced in which potent renin inhibitory activity was achieved by reducing the scissile peptide bond (CO-NH-) to form a reduced isostere (CH2-NH-), which renders the scissile bond uncleavable by renin.45 Several of these initial analogue inhibitors were found to exhibit μmol/L potency.41,43

The synthesis of more specific and more potent inhibitors of renin was accomplished by replacing the Leu10-Leu11 scissile bond of human angiotensinogen with a statin residue mimicking the central statin residue of pepstatin. In this case, the ability of the statin residue to act as an analogue of the transition state enables it to achieve a very high binding affinity and specificity for renin.48 Extensive studies have been made evaluating the interaction of the active sites and subsites of renin with angiotensinogen analogues incorporating statine46-48 as well

**Table 10-1. Classes of Renin Inhibitors**

| Renin antibodies (antisera, monoclonal antibodies, Fab fragments) |
| Synthetic derivatives of the prosegment of renin precursor |
| Pepstatin |
| Angiotensinogen analogues |
| Non-peptide transition-state mimetics |
as other transition-state analogues such as norstatine, difluorostatine, cyclohexylalanyl congeners of statine, cyclostatine, dihydroxyethylene, dehydro-hydroxyethylene, and phosphinic derivatives replaced at various substrate analogue subites. The presence of a phenylalanine residue or an aromatic group at P3 and a histidine or analogues of histidine at P2 positions of the substrate analogue confers high affinity to the inhibitor, whereas the P2’ and P3’ positions are not crucial in determining inhibitory activity.

The application of the concept of transition-state mimetics has revolutionized the organic chemistry of renin inhibition. In fact, potent and specific lower-molecular-weight substrate analogue inhibitors have been synthesized as tetrapeptides, tripeptides, dipeptides, pseudopeptides, and even nonpeptidic compounds. Specifically, the structure-based design of aliskiren, a nonpeptide, small molecule, transition-state mimetic human renin inhibitor, represents the first in a novel class of renin inhibitors discovered with the aid of molecular modeling. Using x-ray crystallography and computational modeling, various compounds were designed to optimize enzyme-inhibitor complexes. As such, to maximize the utilization of the hydrophobic surface of the large S3-S1 binding sites of renin, a series of compounds were designed as dipeptide-like hydroxyethylene transition state mimetics with a directly linked P3-P1 pharmacophore (therefore lacking the P1-P4 spanning backbone of previous peptide inhibitors). Further optimization ultimately resulted in the synthesis of aliskiren with the addition of a terminal carboxamide group providing additional hydrogen-bonding interactions and the insertion of methyl residues into the P2’ side chain providing hydrophobic van der Waals interactions with the S2’ site of renin (Figure 10-3). As the first in a new class of orally effective and highly potent non-peptide inhibitors of human renin, aliskiren has been proven to be an effective agent for the treatment of systemic hypertension and is currently under investigation as a treatment for other renovascular and cardiovascular diseases.

Aliskiren

Chemical Properties and Pharmacokinetics

Aliskiren (Tekturna), an octanamide, is the first of a new class of completely nonpeptide, low-molecular-weight, orally active transition-state renin inhibitors. Aliskiren is a potent and highly specific in vitro inhibitor of human and primate renin (IC$_{50}$ of 0.6 nmol/l). This high potency and specificity against human renin offsets the low absolute bioavailability of the drug, which is in the order of 2%-3% (mean absolute bioavailability of a 75-mg hard gelatin capsule is 2.6% with a negligible first-pass effect). There is a modest food effect with aliskiren (150-mg dose studied) with mean C$_{max}$ and AUC$_{0–\infty}$ values 19% and 38% lower, respectively, than those obtained in the fasting state.

Aliskiren has good water solubility and low lipophilicity and is resistant to biodegradation by peptidases found in the intestine, circulation, and/or the liver. The single- and multiple-dose oral pharmacokinetics of aliskiren have been explored over the dose range of 40 to 1800 mg in healthy male subjects. The plasma concentrations of aliskiren peak between 1 and 3 hours following its administration, and its mean steady-state t$_{1/2}$ is in the order of 23 to 36 hours. Aliskiren’s pharmacokinetics are not dose-proportional, deviating somewhat from dose linearity. In the 40 to 1800 mg dose range (C$_{max}$ and AUC$_{0–\infty}$) with doses above 80 mg. Consistent with a half-life of about 40 hours, aliskiren reaches a steady state after approximately 7 days. Aliskiren is subject to accumulation pharmacokinetics when dosed once daily to steady-state, with accumulation ratios ranging from 1.4 to 3.9; accumulation is more pronounced at higher doses.

After the administration of a single 20 mg intravenous dose of aliskiren over 20 minutes in healthy male subjects, plasma clearance was = 9 l/h, and the volume of distribution at steady-state was = 135 l. This latter figure points to there being extravascular distribution compartments for aliskiren. The mean protein-binding for aliskiren is 49.5% with concentration-independent binding in the range of 10 to 500 ng/ml. This degree of protein binding, in part, explains the large volume of distribution for aliskiren. The intersubject C$_{max}$ and AUC variability is, on average, 32%-70% over a 40 to 1800 mg dose range for orally-administered aliskiren. In vitro inhibition data for specific cytochrome P$_{450}$ enzyme activities and aliskiren in human liver microsomes point toward minimal-to-no interaction. Aliskiren is partially metabolized in the liver by CYP3A4. Approximately 25% of the drug is found unchanged in the urine. The pharmacokinetics of aliskiren is not affected by renal or hepatic dysfunction.

The pharmacology of aliskiren is most noteworthy for its limited bioavailability; however, this seems not to unduly influence the therapeutic response to this compound in the dose range of 150 to 300 mg/day. Limited bioavailability of a compound, in and of itself, will not necessarily impact drug action if the amount of drug absorbed still reaches and sustains a blood level for the desired pharmacologic effect. In the case of aliskiren, its IC$_{50}$ is sufficiently low that the bioavailability of this compound does not present a therapeutic hurdle. Moreover, aliskiren is retained in the kidney for a prolonged period of time. After a 3-week washout period, the renal concentration of aliskiren still exceeds its IC$_{50}$ of .6 nmol/L by 100-fold, with apparent localization in glomeruli and
renal arteries/arterioles and possibly in juxtaglomerular cells. This partitioning of aliskiren in the kidney has been offered as an explanation for the persistence of some antihypertensive activity of the drug for days-to-weeks after its withdrawal.\textsuperscript{76-78}

**Animal Studies**

Effects of Aliskiren on BP and PRA

The effects of once daily oral doses of aliskiren on PRA and BP were studied in sodium-depleted marmosets with treatments given for 8 consecutive days.\textsuperscript{69} BP was reduced by approximately 10 mmHg within 2 hours of treatment with 3 mg/kg of aliskiren and returned to baseline approximately 20 hours following dosing. A greater reduction in BP (13 ± 2 mmHg) was observed with 10 mg/kg of aliskiren after the first day of dosing, and BP also remained reduced 24 hours following treatment. Following 8 days of treatment with aliskiren at 3 mg/kg or 10 mg/kg, dose-dependent elevations in the protein levels of renin were observed, whereas PRA was completely inhibited after 2 hours and also after 24 hours on the first day following treatment with either dose level of aliskiren.\textsuperscript{69}

Comparative Studies in BP Reduction

In another series of studies in sodium-depleted marmosets, Wood et al examined the BP-lowering effects of single oral doses of aliskiren at various dose levels and compared this to the renin inhibitors remikiren and zankiren, the ACE-inhibitor benazepril, and the ARB valsartan.\textsuperscript{79} Single doses of aliskiren from 0.3 mg/kg to 10 mg/kg dose-dependently reduced mean arterial pressure (MAP). No significant reduction in MAP was observed at the lowest dose tested in comparison to vehicle, with a maximal reduction of MAP seen with 3 mg/kg of aliskiren compared to the vehicle. Although the magnitude of the MAP response did not increase with 10 mg/kg compared with 3 mg/kg, the MAP reduction was sustained for up to 10 hours longer with 10 mg/kg of aliskiren. Furthermore, plasma concentrations of aliskiren increased in a dose-dependent manner following oral dosing. PRA was completely inhibited after 1.5 and 3 hours with all the tested doses, and sustained inhibition of PRA was observed for up to 24 hours with the higher doses of 3 and 10 mg/kg. In these animals, comparative oral doses of 3 mg/kg of aliskiren, remikiren, or zankiren demonstrated markedly greater maximal reduction of MAP at 24 hours following treatment with aliskiren than with either remikiren

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**Figure 10-3. Effects of treatment on trough mean sitting DBP (A) and SBP (B) in patients with mild to moderate hypertension. Bars indicate placebo-corrected change in trough mean sitting DBP and SBP from baseline to study endpoint after treatment with aliskiren 150, 300, or 600 mg (filled bars) or irbesartan 150 mg (striped bars). Data are presented as least-squares mean ± SEM. *P < .05 vs irbesartan 150 mg.**

or zankiren. Additionally, the maximal reduction in MAP was significantly greater with aliskiren when compared with comparable oral doses of benazepril or valsartan in these animals. Aliskiren has also been shown to improve nitric oxide bioavailability; to limit atherosclerosis in experimental animals; and to play a role in post-infarction remodeling. Similarly, aliskiren has been shown to have protective effects in diabetic rats.

**Antihypertensive Response with Combination Therapies**

In a series of studies using spontaneously hypertensive rats, Wood et al examined the effects of various subcutaneous doses of aliskiren (10, 30, and 100 mg/kg/day) administered alone and in combination with either benazepril (1 and 3 mg/kg/day) or valsartan (1 and 3 mg/kg/day) over a course of 2 weeks. Weak but significant antihypertensive effects were observed only with the 30 and 100 mg/kg/day doses of aliskiren, which were sustained throughout the dosing period in this non-primate model. Both tested doses of either valsartan or benazepril were comparable in their maximal MAP-lowering with persistence of effect throughout the dosing period. Combining aliskiren at 30 mg/kg/day with either 1 mg/kg/day of valsartan or benazepril significantly lowered MAP more than either monotherapy used alone, with sustained reductions observed throughout the course of the 2-week dosing period. The antihypertensive effects were similarly potentiated with co-administration of 30 mg/kg/day of aliskiren and 3 mg/kg/day of either valsartan or benazepril. Since treatment with valsartan or benazepril increases PRA, co-treatment with aliskiren offsets the elevation of PRA, therefore synergizing the antihypertensive effects. It is noteworthy that since inhibition of PRA in this non-primate model is weaker than would be expected in the case of primate renin inhibition, a more robust enhancement of an anti-hypertensive response would be expected in human beings using combination therapy with these agents.

**Clinical Studies**

Dose-ranging studies of the antihypertensive effects and PRA inhibitory efficacy of aliskiren have been studied primarily in healthy volunteers and patients with mild to moderate hypertension. Clinical studies have also compared the actions of aliskiren to a placebo, standard doses of ACE inhibitor, ARB, and HCTZ therapy, and also in combination with ARB or HCTZ treatment.

**Antihypertensive Effects of Aliskiren Compared to Placebo and Active Comparators**

Short-term monotherapy with aliskiren 150 to 300 mg administered once daily was consistently superior to a placebo in lowering trough diastolic BP (DBP) and trough systolic BP (SBP) in patients with mild to moderate hypertension.

Gradman and colleagues examined the antihypertensive efficacy of various oral doses of aliskiren in a large, multicenter, randomized, double-blind, placebo-controlled, active-comparator 8-week trial in patients with mild to moderate hypertension (mean sitting DBP ≥ 95 and < 110 mm Hg). A study group of 652 patients were randomized to receive once-daily doses of aliskiren (150, 300, or 600 mg), irbesartan 150 mg, or a placebo after 2 weeks of single-blind placebo treatment. At study’s end, mean DBP was significantly reduced from baseline values with all 3 doses of aliskiren in comparison to a placebo (-9.3±0.8 mmHg, P < .004; -11.8±0.8 mmHg, P < .0001, and -11.5±0.8 mmHg, P < .0001, 150, 300, and 600 mg respectively, versus -6.3±0.8 mmHg for placebo). Mean SBP was similarly decreased from baseline values in all 3 aliskiren groups in comparison to the placebo following 8 weeks of treatment (-11.4±1.3 mmHg P < .0004; -15.8±1.2 mmHg, P < .0001; and -15.7±1.2 mmHg, P < .0001, versus -5.3±1.2 mmHg for placebo). The BP-lowering effects on DBP and SBP were dose-dependent up to 300 mg/day of aliskiren, with no additional reduction using the 600 mg daily dose. DBP and SBP were also significantly reduced with daily oral doses of 150 mg of irbesartan in comparison to the placebo (P < .05). The BP-lowering effects of 150 mg of irbesartan were comparable to that achieved with 150 mg of aliskiren, but considerably weaker than the effects seen with 300 or 600 mg of aliskiren (Figure 10.3). In a similar double-blind, active comparator, 4-week trial, Stanton and associates examined BP responses in 228 mild to moderately hypertensive patients randomized to receive daily oral doses of either 37.5, 75, 150, or 300 mg aliskiren or 100 mg losartan. A dose-dependent decrease in ambulatory SBP from pretreatment baseline measurement was observed with increasing doses of aliskiren. Ambulatory SBP did not change from baseline with 37.5 mg aliskiren (-0.4±11.7 mmHg). A significant decrease in SBP from baseline was observed with 75 mg of aliskiren (-5.3±11.3 mmHg) with further reductions with 150 and 300 mg doses of aliskiren (-8.0±11.0 and -11.0±11.0 mmHg, respectively, P < .0002). Daily oral dosing of 150 mg of losartan reduced ambulatory SBP from baseline (-10.0±13.8 mmHg) to a similar extent as with 75, 150, 300 mg of aliskiren after the 4-week treatment period. All tested doses of aliskiren decreased PRA in venous blood samples taken at the completion of study (mean percent change versus baseline PRA of -55%, -60%, -77%, and -83% for 37.5, 75, 150, and 300 mg of aliskiren, respectively, P = .0008). In contrast, PRA was increased at the end of the study (+110%) with daily dosing of 100 mg of losartan in comparison to pretreatment values. Interestingly, through additional analysis, it was
determined that 150 mg losartan and 300 mg aliskiren exerted greater reduction in ambulatory SBP in patients with higher baseline PRA.

In a published parallel-design clinical study, 1,123 patients were randomized to receive a placebo, once-daily aliskiren monotherapy (75, 150, or 300 mg), once-daily valsartan (80, 160, or 320 mg), and the combination of aliskiren with valsartan once daily (75/80, 150/160, or 300/320 mg), or once-daily valsartan/HCTZ (160/12.5 mg). Aliskiren 300 mg significantly reduced mean sitting DBP by 12 mmHg and SBP by 15 mmHg compared to decreases of 8 and 10 mmHg, respectively, with the placebo. The lower doses of aliskiren did not produce significant decreases in BP compared to the placebo. BP decreases with valsartan were similar. The combination of aliskiren with valsartan (300/320 mg) produced greater lowering of BP (12.9 mmHg DBP, 18 mmHg SBP) than with either drug used alone.

In a pilot study, aliskiren was found to be as effective as lisinopril with and without HCTZ in the treatment of severe hypertension.

Regarding the long-term effects of aliskiren in hypertensive patients, an open-label study was carried out in 1,625 patients with mild to moderate high BP who were followed for 12 months. Patients were randomized to receive once-daily treatment with aliskiren 150 or 300 mg. Those patients on the high dose whose BP was not controlled were allowed to receive HCTZ. In addition, after 11 months, 261 patients on aliskiren monotherapy were randomly assigned to continue on the drug or receive the placebo during a 4-week randomized, double-blind, placebo-controlled withdrawal phase. After 12 months of aliskiren monotherapy or the combination with HCTZ, both treatment groups achieved similar reductions in BP (17.4/3.3 mmHg and 18.7/12.1 mmHg, respectively). During the 1-month withdrawal period, patients taking the placebo experienced a gradual rise in their BP, while those patients on aliskiren maintained their BP reduction.

Combination Therapy

In a double-blind, placebo-controlled, randomized, cross-over study, Azizi and colleagues compared the changes in the hormonal constituents of the RAS and BP during the 48-hour period after administration of single oral doses of a placebo, 300 mg aliskiren, 160 mg valsartan, or their combination (each at half dose) in 12 mildly sodium-depleted normotensive individuals. Treatments were given in 4 periods followed by a 2-week washout period. PRA was completely inhibited at 1 hour and 48 hours after the intake of 300 mg of aliskiren. Conversely, PRA was significantly increased with 160 mg of valsartan at 4, 24, and 48 hours as compared with the placebo. However, with the combination of 150 mg of aliskiren and 80 mg of valsartan, PRA was reduced below control values at 1 hour, returned to baseline by 12 hours, and thereafter reached comparable levels to the placebo.

In comparison to the placebo, concentrations of plasma Ang I and Ang II were significantly decreased with 300 mg of aliskiren and remained reduced for greater than 24 hours following dosing. In contrast, 160 mg of valsartan increased Ang I and Ang II levels for up to 48 hours in comparison to the placebo. Ang I and Ang II levels after the combined administration of both agents were similar to those with the placebo. Plasma aldosterone concentration and urinary aldosterone excretion were equally decreased by all 3 treatments. Aliskiren alone or in combination with valsartan suppressed urinary aldosterone excretion for up to 8 hours longer than valsartan alone. All 3 treatments significantly reduced MAP to a similar extent within 4 hours of drug treatment. The antihypertensive effects were no longer evident after 24 hours with MAP reaching comparable levels to those of the placebo.

In a double-blind study, 1,797 patients with hypertension were randomly assigned to receive once-daily aliskiren 150 mg, valsartan 160 mg, a combination of aliskiren 150 mg and valsartan 160 mg, or the placebo for 4 weeks following a forced titration to double the dose to the maximum recommended dose for another 4 weeks. The combination of aliskiren and valsartan at maximum recommended doses provided significantly greater reductions in BP than monotherapy with either agent, with a tolerability profile similar to that with aliskiren and valsartan used alone. On the basis of this trial and other clinical data, a combination aliskiren-valsartan product was approved for clinical use.

In a multicenter, international study, aliskiren was compared to ramipril and the combination of both drugs in 837 patients with diabetes and uncontrolled hypertension. After a 2- to 4-week placebo period, patients were randomized to receive once daily aliskiren 150 mg, once daily ramipril 5 mg, or a combination of both drugs. After 4 weeks, the dose levels were doubled in all treatment groups. After 8 weeks, ramipril monotherapy reduced mean SBP and DBP by 12/10.7 mmHg, aliskiren by 14.7/11.3 mmHg, and combination therapy by 16.6/12.8 mmHg. The incidence of treatment-limiting cough was 4.7% with ramipril alone, 2.1% in the aliskiren group, and 1.8% in the combination treatment groups. The BP-lowering effects of aliskiren and the aliskiren-ramipril combination were found to be independent of blood sugar control.

In a 24-hour ambulatory BP substudy, it was found that aliskiren alone and in combination with ramipril provided better BP control than ramipril alone at the end of the dosing interval.

The BP-lowering effects of varying doses of aliskiren, HCTZ, and the 2 agents administered together were ex-
amined in a recently reported phase 3, double-blinded, randomized, placebo-controlled study.\textsuperscript{19} The study group of 2,776 mild to moderately hypertensive patients were randomized and treated for 8 weeks with daily oral doses of either aliskiren (75, 150, and 300 mg), HCTZ (6.25, 12.5, and 25 mg), or the 2 agents combined (75 mg aliskiren + 6.25 mg HCTZ, 150 mg aliskiren + 12.5 mg HCTZ, and 300 mg aliskiren + 25 mg HCTZ). After 8 weeks, all treatments caused a reduction in DBP in comparison to the placebo. Combination therapy appeared to exert a synergistic DBP-lowering effect as the lowest concentrations of aliskiren and HCTZ given together reduced DBP more than monotherapy with the highest dose of either agent used alone. Similarly, in comparison to the placebo, SBP was reduced with all tested doses of aliskiren or HCTZ with potentiation of the antihypertensive effects when the drugs were given in combination. Overall, combination therapies had significantly greater BP-lowering responses than both individual components. Furthermore, the combination of therapeutic doses of aliskiren with 12.5 mg HCTZ enhanced the patient responder rates (defined as > 10 mm Hg decrease, SBP < 140 or DBP < 90 mm Hg) at the end of the study. Renin inhibition with aliskiren neutralized the compensatory rise in PRA induced by HCTZ. On the basis of this trial and other clinical data, a combination HCTZ/aldiskiren combination has been approved for clinical use.

In a placebo-controlled, double-blind study of 489 patients with hypertension who were unresponsive to 25 mg of HCTZ treatment, the addition of once-daily aliskiren at 300 mg caused a significant reduction in SBP and DBP compared to the combination of HCTZ and the placebo. In the same study the BP-lowering effects of the HCTZ/aldiskiren combination were similar to those of HCTZ/irbesartan and HCTZ/amlodipine combination treatments, with a higher incidence of peripheral edema observed with HCTZ/amlodipine.\textsuperscript{97}

It was also found that combination therapy in obese hypertensive patients with HCTZ and aliskiren was effective in lowering BP.\textsuperscript{98} The BP-lowering effects were greater than with HCTZ used alone.

The antihypertensive effects of aliskiren in combination with amlodipine were assessed in 762 patients with mild to moderate hypertension.\textsuperscript{99} In this 6 week study, all patients started treatment with amlodipine 5 mg. Patients who had inadequate BP at this dose were randomized to receive aliskiren 150 mg plus amlodipine 5 mg, or a double dose of amlodipine. After 6 weeks, patients taking the aliskiren/amlodipine combination had significant reductions in mean sitting SBP and mean sitting DBP compared to those patients taking low dose amlodipine alone (11.0/8.5 mmHg and 5.0/4.8 mmHg respectively). The effects on BP were similar when comparing combination therapy to a double dose of amlodipine. Patients on high dose amlodipine had an 11.2% rate of edema versus 2.1% in the aliskiren/amlodipine group and 3.4% in the low dose amlodipine group.

Recently the results of the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial were reported.\textsuperscript{100} This was a double-blind, randomized trial in which patients with type 2 diabetes, hypertension, and proteinuria who were already receiving losartan 100 mg and other antihypertensive therapy to reach an optimal BP goal were randomly assigned to receive aliskiren (250 mg daily) for 3 months followed by an increase in dosage to 300 mg daily for another 3 months, in addition to losartan. A reduction in albuminuria was seen with the combination treatment. Concern is still raised regarding the potential for hyperkalemia when using 2 drugs which influence the RAS, especially in patients with diminished renal function.\textsuperscript{101a}

The hypertrophy-reducing effects of aliskiren 300 mg, losartan 100 mg and their combination were evaluated over 9 months in 465 patients with LV hypertrophy and hypertension (Aliskiren in Left Ventricular Hypertrophy [ALLAY] trial).\textsuperscript{102} Aliskiren was found to be as effective as losartan in promoting LV mass reduction measured by cardiovascular magnetic resonance imaging. The reduction in LV mass with the combination of aliskiren plus losartan was not significantly different from that with losartan monotherapy, independent of BP lowering.

### Effects of Aliskiren on Components of the Renin-Angiotensin-Aldosterone System

In a study by Nussberger and associates, increasing doses of aliskiren significantly inhibited the RAS in a dose-dependent manner.\textsuperscript{103} Eighteen healthy male volunteers were subjected to a randomized, parallel group, double-blind, 3-way crossover protocol consisting of 3 treatment periods of 8 days, separated by washout periods of 6 days. Each volunteer received 2 dose levels of aliskiren (low before high; 40 and 80 mg/day or 160 and 640 mg/day) and randomized placebo or 20 mg/day of enalapril. On day 1, all doses of aliskiren maximally reduced Ang II levels within 1 hour of dosing, whereas enalapril maximally reduced Ang II only after 6 hours. Reduction in Ang II levels was maintained for up to 6 hours on day one and also on day 8 with all doses of aliskiren, except for the 40 mg/day dose. The percent reduction of Ang II levels versus baseline with aliskiren at doses of 160 mg (56%) or 640 mg (76%) were similar or greater than that achieved with 20 mg of enalapril (57%). As expected, the percent inhibition of PRA and Ang I with aliskiren reflected changes in Ang II levels.

Treatment with enalapril resulted in > 15 fold increase in the PRA and Ang I levels on day one and even greater on day 8. On day 1, plasma aldosterone was decreased after 3 hours following dosing with only the 80, 160, and 640 mg doses of aliskiren and also with enalapril. Reduction in plasma aldosterone lasted up to 6 hours with
enalapril and up to 24 hours with the highest dose of aliskiren, effects that were significantly attenuated by the eighth day of dosing. On day 1, a trend toward natriuresis was observed with all doses of aliskiren in comparison to pretreatment levels of sodium excretion, yet a statistically significant natriuretic effect was only observed with 640 mg aliskiren (+91%) and 20 mg enalapril (+54%). On day 8, however, the enhancement of natriuresis was no longer present with urinary sodium returning to pretreatment values. Urinary potassium excretion was not affected with any of the tested doses.

Adverse Effects and Drug–Drug Interactions

Generally, aliskiren at all doses and with the various combination therapies was shown to be well tolerated in all the reported studies. Common reported adverse effects included fatigue, headache, dizziness, and diarrhea. In 1 study, the proportion of patients reporting headache was 2.4%, 6.2%, and 4.6% with 150, 300, and 600 mg of aliskiren, respectively, compared with 5.3% of patients treated with the placebo and 3.0% of patients treated with 150 mg of irbesartan. No reports of orthostasis or increased heart rate as a result of treatment with aliskiren or with its combination with other agents were presented in the above clinical trials. Dose-related gastrointestinal adverse effects that include diarrhea, abdominal pain, dyspepsia and gastroesophageal reflux have occurred in 2% of patients. Cough, angioedema, and edema of the face, hands, and whole body are rare. The drug has no effect on cardiac repolarization and conduction.

Studies looking at the effects of aliskiren on plasma potassium levels have shown a low frequency (1.1%) of hyperkalemia (> 5.5 meQ/L) that is comparable to the placebo. When aliskiren was combined with an ACE inhibitor in diabetic patients, the incidence of hyperkalemia was found to be 5-fold higher (5.5%), which may be further potentiated with the concomitant use of potassium-sparing agents.

Daily oral doses of 150 mg of aliskiren had no effect on the pharmacokinetics or pharmacodynamics of 25 mg of warfarin in healthy adults. Furthermore, single oral doses of aliskiren 150 mg showed no evidence of clinically important pharmacokinetic interactions with standard doses of lovastatin, amlopidine, valsartan, ramipril, atenolol, celecoxib, cimetidine, and digoxin. Concurrent use of aliskiren with furosemide will reduce furosemide levels. Concurrent use of aliskiren with ketoconazole, a strong CYP3A4 inhibitor, was associated with an 80% increase in the serum concentration of aliskiren.

Clinical Use

The recommended oral dose of aliskiren for the treatment of hypertension is 150 mg once daily. The dose may be increased to 300 mg once daily if the BP is not adequately controlled. The effect of a given dose of aliskiren is usually seen by 2 weeks. Doses above 300 mg achieve no additional BP control but will increase the rate of diarrhea. No dosage adjustment is necessary in the elderly or in patients with hepatic or renal impairment. Black patients tend to have smaller reductions in BP than whites and Asians, which is also seen with all drugs that affect the RAS. Aliskiren should not be taken with a high-fat meal, which will decrease drug absorption. Similar to ACE inhibitors and ARBs, aliskiren should not be used during pregnancy. Whether aliskiren has similar or more favorable effects than other inhibitors of the RAS has not been determined.

Aliskiren has been used in combination with other antihypertensive agents to increase BP-lowering efficacy. Based on clinical trial experiences, a product combining aliskiren and hydrochlorothiazide (HCTZ) is now available in doses of 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg; a product containing aliskiren and valsartan is available in doses of 150/160 mg and 300/320 mg. This formulation (Valturna) is the first combination drug using different inhibitors of the renin-angiotensin-aldosterone system.

Conclusion and Future Development

There has been a long search to find a direct renin inhibitor compound that would be clinically useful and orally active in patients with hypertension. Aliskiren is the first in a unique class of highly selective, non-peptide, orally active human renin inhibitors that is approved as a treatment for systemic hypertension. Other direct renin inhibitors are being evaluated in clinical trials.

Previous animal studies with aliskiren have demonstrated dose-dependent reductions in both BP and components of the RAS with significant end-organ injury prevention. Clinical trials using aliskiren in patients with hypertension have shown the drug to be effective and safe in lowering BP and enhancing the suppression of the RAS both as monotherapy and when used in combination with HCTZ, amlopidine, and other inhibitors of the RAS, such as valsartan. Aliskiren may ultimately play a significant protective and therapeutic role in patients with diabetic vascular disease, atherosclerotic disease, and HF given the proven beneficial effects seen with ACE inhibitors and ARB therapy in these disease states.

Clinical trials are now in progress evaluating the efficacy and safety of aliskiren in patients with HF. Results from the Aliskiren Observation of Heart Failure Treatment (ALOFT) have shown that aliskiren, when added to an ACE inhibitor or ARB, had additional favorable effects on neurohormonal indices (brain natriuretic peptide, NT-proBNP, and urinary aldosterone) and was well tolerated.
A clinical trial is also in progress evaluating aliskiren and placebo in patients with acute MI with an ejection fraction <45% to assess the effects of therapy on ventricular remodeling (Aliskiren Study in Post-MI Patients to Reduce Remodeling [ASPIRE]).\textsuperscript{116} In addition, aliskiren is being compared to placebo in congestive heart failure patients hospitalized for an episode of acute decompensated heart failure regarding the effects of therapy on death and heart failure rehospitalizations (Aliskiren Trial on Acute Heart Failure Outcomes [ASTRONAUT]).\textsuperscript{117} A study is in progress comparing enalapril to aliskiren in patients with chronic heart failure regarding effects on cardiovascular deaths and hospitalizations (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure [ATMOSPHERE]).\textsuperscript{118} One study in progress is evaluating the effects of aliskiren compared to valsartan on NT-pro type natriuretic peptide levels (Aliskiren and Valsartan to Reduce NT-proB-Type Natriuretic Peptide via Renin-Angiotensin-Aldosterone Blockade (AVANTGARDE-TIMI43)).\textsuperscript{119} Finally, a morbidity and mortality study is being done evaluating aliskiren versus placebo in patients with type 2 diabetes and pre-existing cardiovascular and/or renal disease (Aliskiren Trial in Type 2 Diabetic Nephropathy [ALTITUDE]).\textsuperscript{120}

\textit{Note: References for this chapter can be found here: www.cvpc3.com}
Modern diuretic therapy grew out of 2 apparently unrelated endeavors in the 1930s: (1) the development of sulfanilamide, the first effective antibacterial drug, and (2) the discovery of the enzyme carbonic anhydrase. Clinical experience with sulfanilamide showed that this drug increased urine flow as well as sodium (Na+) and potassium (K+) excretion. The recognition that sulfanilamide inhibited carbonic anhydrase fueled attempts to synthesize compounds that might be more specific inhibitors of carbonic anhydrase. One such compound was acetazolamide. Unfortunately, the diuretic effect of acetazolamide was self-limited, lasting but a few days. One consequence of the search for inhibitors of carbonic anhydrase, however, was the discovery of a series of potent diuretic compounds with greater long-term effectiveness. The prototype of these diuretics was chlorothiazide, which became available in 1958 and ushered in the modern era of diuretic therapy, initially for the treatment of edematous states and shortly thereafter for the treatment of hypertension.1

Diuretics remain important therapeutic tools. First, they are capable of reducing blood pressure (BP), while simultaneously decreasing the morbidity and mortality that occurs in the inadequately treated hypertensive state. Diuretics are currently recommended by the Joint National Commission on Detection, Evaluation, and Treatment of Hypertension of the National High Blood Pressure Education Program (JNC) as first-line therapy for the treatment of hypertension.2 In addition, they remain an important element of the treatment regimen for heart failure (HF) in that they improve the congestive symptomatology, which characterizes the more advanced stages of HF.3,4 This chapter reviews the mechanism of action of the various diuretic classes and the physiologic adaptations that accompany their use and establishes the basis for their use in the treatment of hypertension and HF. In addition, comments are provided on commonly encountered side effects with diuretics.

Individual Classes of Diuretics

The predominant site(s) of action of various diuretic classes along the nephron are depicted in Figure 11-1. The range of diuretic classes have both inter- and intraclass differences in pharmacokinetics and, in most instances, pharmacodynamic responses dependent on both the nature and extent of underlying disease (Table 11-1).5

Carbonic Anhydrase Inhibitors

The administration of a carbonic anhydrase inhibitor ordinarily results in a brisk alkaline diuresis. By inhibiting carbonic anhydrase, these compounds decrease the generation of intracellular H+, which is a prerequisite for the absorption of Na+, therein lies their primary diuretic effect.6 Although carbonic anhydrase inhibitors work at the proximal tubule level, where the bulk of Na+ reabsorption occurs, their final diuretic effect is typically rather modest, being blunted by reabsorption more in more distal nephron segments.7,8 Acetazolamide is currently the only carbonic anhydrase inhibitor employed primarily for its diuretic action; others are used topically for treatment of glaucoma. Acetazolamide is readily absorbed and is eliminated by tubular secretion. Its use is limited by its transient action and by the fact that prolonged use results in a metabolic acidosis, amongst other adverse effects. Acetazolamide (250 to 500 mg daily) can be carefully used in patients with HF who have developed metabolic alkalosis from thiazide or loop diuretic use and who cannot tolerate the volume load associated with the Cl– repletion required for correction of the alkalemic state. Topiramate, an
anticonvulsant, inhibits carbonic anhydrase and is associated with the development of metabolic acidosis. Patients with a history of renal calculi or known renal tubular acidosis should not receive topiramate.9

Osmotic Diuretics

Mannitol is a polysaccharide diuretic given intravenously that is freely eliminated by glomerular filtration. Mannitol is poorly reabsorbed along the length of the nephron and thereby exerts a dose-dependent osmotic effect. This osmotic effect traps water and solutes in the tubular fluid, thus increasing Na+ and water excretion. The half-life for plasma clearance of mannitol depends on the level of renal function but usually is between 30 and 60 minutes; thus, its diuretic properties are very transient. Because mannitol also expands extracellular volume and can precipitate pulmonary edema in patients with HF, it should be cautiously used in these patients if at all. Moreover, excessive mannitol administration, particularly when the glomerular filtration rate (GFR) is reduced, can cause diuretic-related depletions of NaCl, hyperkalemia, and/or acute renal failure.10-12 The latter is dose-dependent, relates to afferent arteriolar vasoconstriction, and typically corrects with the systemic elimination of mannitol as may be accomplished with hemodialysis.

Loop Diuretics

Loop diuretics act predominately at the apical membrane in the thick ascending limb of the loop of Henle where they compete with chloride for binding to the Na+/K+2Cl− co-transporter, thereby inhibiting Na+ and Cl− reabsorption.12 Besides this primary action, loop diuretics also have a variety of other effects on other nephron segments. Loop diuretics reduce Na+ reabsorption in the proximal tubule by weakly inhibiting carbonic anhydrase and through poorly defined mechanisms independent of carbonic anhydrase inhibition.13 Loop diuretics also have effects in the distal tubule,14 descending limb of the loop of Henle,15 and collecting duct.16

Although the action of loop diuretics in these other nephron segments is quantitatively minor, as compared with their effects in the thick ascending limb, these actions serve to blunt the expected increase in more distal reabsorption, which is triggered with the use of these potent diuretics. Other clinically important effects of loop diuretics include an impairment in both free water excretion during water loading and free water absorption during dehydration, a 30% increase in fractional calcium (Ca2+) excretion,17 a substantial increase in magnesium (Mg2+) excretion,18 and a transient increase followed by a decrease in urate excretion.19

In addition to their effects on water and electrolyte excretion, loop diuretics modify renal prostaglandin synthesis, particularly that of prostaglandin E2 (PGE2).20 The increased angiotensin-II generation following the administration of loop diuretics coupled with the increased synthesis of vasodilatory PGE2 probably accounts for the marked redistribution of renal blood flow from the inner to the outer cortex of the kidney.20 Despite these alterations in renal blood flow distribution, both total renal blood flow and GFR are preserved after loop diuretic administration to normal subjects.

Loop diuretics in clinical use include furosemide, bumetanide, torsemide, and ethacrynic acid. The latter is almost exclusively reserved for patients with significant sulfa allergies in that it is the only loop diuretic that is not a sulfa congener.21 The loop diuretics are highly protein-bound; therefore, they are minimally filtered at the glomerulus. They typically access the tubular lumen through secretion via an organic anion transporter localized to the proximal tubule. The urinary diuretic concentration best represents the fraction of drug delivered to the medullary thick ascending limb and significantly correlates with the natriuretic response following diuretic administration.5,22

Furosemide remains the most widely used diuretic in this class.23 Furosemide is somewhat erratically absorbed with an absolute bioavailability of 49% ± 17% and a range of 12% to 112%.24 The coefficients of variation for absorption for different furosemide products varies from 25% to 43%; thus, switching from one formulation to another will not likely result in a better and more predictable patient response to furosemide.24 Furosemide is an organic anion compound that is highly bound to albumin in
Diuretic Therapy in Cardiovascular Disease

Table 11-1. Pharmacokinetics of Diuretics

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Oral Bioavailability (%)</th>
<th>Normal Subjects</th>
<th>Renal Insufficiency (hrs)</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>10–100</td>
<td>1.5–2</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>80–100</td>
<td>1</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Torsemide</td>
<td>80–100</td>
<td>3–4</td>
<td>4–5</td>
<td>6</td>
</tr>
<tr>
<td><strong>Thiazide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>ND</td>
<td>2–5</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>64</td>
<td>24–55</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>30–50</td>
<td>1.5</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>65–75</td>
<td>2.5</td>
<td>Increased</td>
<td>ND</td>
</tr>
<tr>
<td>Hydroflumethiazide</td>
<td>73</td>
<td>6–25</td>
<td>ND</td>
<td>6–28</td>
</tr>
<tr>
<td>Indapamide</td>
<td>93</td>
<td>15–25</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Polythiazide</td>
<td>ND</td>
<td>26</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Trichlormethiazide</td>
<td>ND</td>
<td>1–4</td>
<td>5–10</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Distal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>?</td>
<td>17–26</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>Triamterene</td>
<td>&gt;80</td>
<td>2–5</td>
<td>Prolonged</td>
<td>ND</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>?</td>
<td>1.5</td>
<td>No change</td>
<td>ND</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>69</td>
<td>4–6</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = not determined.

Adapted with permission from Brater DC. Diuretic therapy. N Engl J Med. 1998;339:387. Copyright © 1998 Massachusetts Medical Society. All rights reserved.

plasma, which gains entry to the tubular lumen through a probenecid-sensitive proximal tubular secretory mechanism.25 Furosemide protein binding may be influenced by accumulated uremic toxins and/or fatty acids, although this is of poorly defined clinical significance.26 Secretion of furosemide as well as other loop diuretics may be impaired by the presence of elevated levels of endogenous organic acids such as those seen in chronic kidney disease (CKD), and by other drugs that share the same transporter such as salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs). Following an oral dose of furosemide to normal subjects, the onset of action is within 30 to 60 minutes; peak effect occurs within 2 hours, and its duration of action is approximately 6 hours. The relationship between renal furosemide excretion and its natriuretic effect is best described by a sigmoidal-shaped dose-response curve (Figure 11-2).27 This same pharmacokinetic-pharmacodynamic relationship based on urinary diuretic delivery applies to the other loop diuretics as well.28 Alterations in this normal dose-response relationship can occur in a variety of pathophysiologic states such as HF29 and volume depletion.29 The NSAID indomethacin also alters this relationship through its inhibition of prostaglandin synthesis.29 This relationship appears not to be distorted by increased amounts of urinary protein as is seen in the nephrotic syndrome; thus urinary protein binding of loop diuretics is not a major mechanism for the diuretic resistance of the nephrotic syndrome.31

Bumetanide is 40 times more potent than furosemide and, like the other loop diuretics, is available in both oral and intravenous forms. In normal subjects, the bioavailability of bumetanide is 80%, and the onset of diuretic effect occurs within 30 minutes, with a peak effect within 1 hour. The duration of action of oral bumetanide is between 3 and 6 hours and its half-life is between 1 and 3.5 hours.32 In healthy subjects, 60% of bumetanide is excreted unchanged in the urine; and the remaining drug is hepatically metabolized via the cytochrome P450 pathway. Because of this extrarenal metabolism, bumetanide does not accumulate in renal failure, although renal disease does modify the time course of its tubular delivery.33 In contrast, in patients with hepatic disease, the plasma half-life of bumetanide is prolonged sufficiently so that more drug ultimately reaches tubular fluid.34

Torsemide is a loop diuretic that is both rapidly absorbed and 80% to 90% bioavailable. Maximal Na+ excretion occurs within the first 2 hours after either its
intravenous or oral administration. Only 20% of the drug is excreted unchanged in the urine with the remaining 80% undergoing hepatic metabolism.\(^3\) In healthy subjects, the half-life of torsemide is 3.3 hours, but it is prolonged to 8 hours in cirrhotic patients.\(^3\) When selecting an oral agent in patients with HF, oral torsemide may be especially advantageous because its absorption remains intact and is much less variable than is the case with oral furosemide.\(^3\) In fact, torsemide disposition in HF patients is comparable to that of normal subjects. Compared with furosemide-treated patients, torsemide-treated patients with HF are less likely to be readmitted for HF decompensation and are generally less fatigued.\(^3\) The pharmacodynamic response to torsemide in the patient with HF, decompensated or not, demonstrates a shift of the dose-response relationship downward and to the right.

### Thiazides

The major site of action of the thiazide diuretics is the early distal convoluted tubule where they inhibit the coupled reabsorption of Na\(^+\) and Cl\(^-\).\(^3\) The water-soluble thiazides such as hydrochlorothiazide (HCTZ) also inhibit carbonic anhydrase and, at high doses, further increase net Na\(^+\) excretion by this mechanism.\(^4\) Thiazides also inhibit NaCl and fluid reabsorption in the medullary collecting duct.\(^5\) In addition to these effects on Na\(^+\) excretion, the thiazides also impair urinary-diluting capacity without affecting urinary-concentrating mechanisms,\(^6\) reduce Ca\(^++\) and urate excretion,\(^7,\) and increase Mg \(^++\) excretion.\(^8\) The most widely prescribed drug in this diuretic class is HCTZ, although chlorthalidone has also been shown to be useful in clinical trials. HCTZ is well absorbed with an absolute bioavailability of 71%. The onset of diuresis with HCTZ generally occurs within 2 hours, peaks between 3 and 6 hours, and continues for as long as 12 hours.\(^9\) The half-life of HCTZ is prolonged in patients with decompensated HF and/or renal insufficiency.\(^10\) Large doses of thiazide diuretics in the order of 100 to 200 mg/d will initiate a diuresis in patients with CKD, although the magnitude of the diuretic response will be a function of the GFR and thereby the filtered Na\(^+\) load.\(^11\)

Metolazone is a quinazoline diuretic and is similar to the thiazides both in structure and locus of action.\(^12\) Although its major site of action is in the distal tubule, metolazone has a minor inhibitory effect on proximal Na\(^+\) reabsorption through a carbonic anhydrase-independent mechanism.\(^13\) Metolazone is also lipid-soluble and has a longer duration of action and thereby accesses the tubular lumen for longer periods of time during states of renal insufficiency, unlike the thiazides.\(^14\) These unique pharmacologic features likely account for the enhanced natriuretic efficacy of metolazone and its effectiveness in diuretic-resistant states when given together with a loop diuretic. Metolazone is available in different formulations, with the Zaroxolyn product being absorbed particularly slowly and erratically. In the instance of metolazone “not working,” the unpredictability of metolazone absorption should be as much a consideration as the severity of the underlying illness.\(^15\)

### Distal Potassium-Sparing Diuretics

Potassium-sparing diuretics can be divided into 2 distinct classes: (1) competitive antagonists of aldosterone, such as spironolactone, and (2) those that do not interact with aldosterone receptors, such as amiloride and triamterene. These agents all act on the principal cells in the late distal convoluted tubule, the initial connecting tubule, and the cortical collecting duct, where they inhibit active Na\(^+\) reabsorption. The inhibition of Na\(^+\) entry into the cell causes a reduction in the activity of the basolateral Na\(^+\), K\(^-\)-ATPase, which, in turn, reduces intracellular K\(^+\) concentration. The resulting fall in the electrochemical gradient for K\(^+\) and H\(^+\) reduces the subsequent secretion of each of these cations.\(^16\) Because these drugs are only mildly natriuretic, their clinical value at a renal level rests in their ability to reduce the excretion of K\(^+\), especially when distal fluid delivery is increased by more proximally acting diuretics or in states of aldosteronism.\(^17\) Each of these agents also reduces Ca\(^++\) and Mg\(^++\) excretion.\(^18\) Spironolactone is a lipid-soluble K\(^-\)-sparing diuretic that is readily absorbed with a prominent food effect, which substantially increases its absorption. Spironolactone is extensively protein-bound with upwards to a 20-hour half-life; however, it is metabolized to 2 active metabolites, canrenone and 7-alpha-thiomethylspironolactone with half-life values in the 24-hour range.
The onset of spironolactone effect can be quite varied, in part, relating to the prevailing aldosterone status of a patient.\textsuperscript{55,57} Spironolactone is the preferred K\textsuperscript+-sparking diuretic in CKD in that its site of action is on the basolateral cell membrane and, therefore, access to this location is independent of GFR; however, its tendency to cause hyperkalemia in renal failure patients limits its use.

Eplerenone is another K\textsuperscript+-sparking diuretic, which, like spironolactone, is an aldosterone receptor antagonist. However, as compared with spironolactone, it is more selective for the aldosterone receptor with a much lower affinity for androgen and progesterone receptors. The molecular structure of eplerenone replaces the 17\textalpha thiocacetyl group of spironolactone with a carboxymethyl group, which results in selectivity for the aldosterone receptor over steroid receptors.\textsuperscript{58} Eplerenone is metabolized by CYP3A4 to inactive metabolites. Eplerenone effect.\textsuperscript{60} The mg-for-mg BP-lowering effect of eplerenone requires twice daily dosing for an optimal BP-lowering effect.\textsuperscript{61,62}

Amiloride is poorly absorbed and is actively secreted by organic cation transporters into the tubular lumen, where it then works as a direct inhibitor of the epithelial Na\textsuperscript+ channel at the apical membrane of collecting duct cells.\textsuperscript{63} It has a duration of action of about 18 hours and is generally well tolerated. Amiloride can be used as a substitute for spironolactone in patients with aldosteronism.\textsuperscript{64} Triamterene, on the other hand, is well absorbed and is hydroxylated to active metabolites. The half-life of triamterene and its metabolites ranges from 3 to 5 hours.\textsuperscript{65} It also depends on active cationic secretion to gain access to its site of action. Triamterene accumulates in cirrhotic patients owing to a reduction in hydroxylation and biliary secretion.\textsuperscript{66} Both triamterene and amiloride accumulate in renal-failure patients\textsuperscript{67} and are associated with worsening of renal function, particularly when given with NSAIDs.\textsuperscript{68}

Adaptation to Diuretic Therapy

Diuretic-induced inhibition of Na\textsuperscript+ reabsorption in 1 nephron segment elicits important adaptations in other nephron segments, which not only limits their antihypertensive and fluid-depleting actions but also contributes to the development of adverse effects. Although a portion of this resistance to diuretic effect is a normal consequence of diuretic use, disease-state related diuretic resistance is often encountered in patients with clinical disorders such as HF, cirrhosis and/or proteinuric renal failure. An understanding of the process of adaptation to diuretic therapy is necessary if this effect is to be minimized and adverse-effects limited.

The initial dose of a diuretic normally produces a brisk diuresis, which is quickly followed by a new equilibrium state in which daily fluid and electrolyte excretion either matches or is less than intake with body weight stabilizing. In nondematous patients given either a thiazide or a loop diuretic, this adaptation or braking phenomenon occurs within 1 to 2 days and limits net weight loss to 1 to 2 kg.\textsuperscript{29}

This braking phenomenon has been clearly demonstrated in normal subjects given a loop diuretic, such as furosemide or bumetanide.\textsuperscript{68,71} Furosemide administered to subjects ingesting a high-salt diet (270 mmol/24 h) produced an initial brisk natriuresis, which resulted in a negative Na\textsuperscript+ balance over the ensuing 6 hours. This was followed by an 18-hour period when Na\textsuperscript+ excretion was reduced to levels well below the prescribed Na\textsuperscript+ intake, resulting in a positive Na\textsuperscript+ balance. This postdiuresis Na\textsuperscript+ retention matched the initial natriuresis with the result at the end of the day being ending a neutral Na\textsuperscript+ balance state and no weight loss. After 3 successive days of furosemide administration, a similar pattern of Na\textsuperscript+ loss and retention was demonstrated each day. In fact, this same result is repeated after even a month of furosemide administration.\textsuperscript{21} However, if salt intake is kept very low, Na\textsuperscript+ balance can remain negative after a single dose of furosemide, even though the initial natriuresis is, to a degree, blunted.

The mechanistic basis for the braking phenomenon is quite complex. The relationship between natriuresis and furosemide excretion rate is shifted to the right in those subjects receiving a low-salt diet, which denotes a blunting of the tubular responsiveness to the diuretic (see Figure 10-2).\textsuperscript{69,71} The importance of extra-cellular fluid (ECF) volume depletion in postdiuretic Na\textsuperscript+ retention has been clearly shown, although there is an ECF volume-independent component to the Na\textsuperscript+ retention.\textsuperscript{72} This ECF volume-independent component appears to be unrelated to aldosterone, as spironolactone therapy, has little effect on the Na\textsuperscript+ retention.\textsuperscript{21} Using lithium (Li\textsuperscript+) as a marker of proximal Na\textsuperscript+ handling, Na\textsuperscript+ retention has been ascribed to a reduced delivery of Na\textsuperscript+ from the proximal tubule and an increase in the fractional reabsorption of Na\textsuperscript+ in the distal tubule.\textsuperscript{73} Structural hypertrophy in the distal nephron has also been demonstrated in rats receiving prolonged infusions of loop diuretics.\textsuperscript{74,75} These structural changes are associated with increased distal nephron Na\textsuperscript+ and Cl\textsuperscript− absorption and K\textsuperscript+ secretion,
phenomena that are both aldosterone independent. These nephron structural adaptations may contribute to postdiuretic Na⁺ retention and to diuretic tolerance in humans, and could explain the Na⁺ retention that can persist for up to 2 weeks after diuretic therapy is discontinued.

**Neurohumoral Response to Diuretics**

An immediate (within minutes) increase in plasma renin activity (PRA) and plasma aldosterone concentrations occurs in response to a diuretic dose that is independent of volume depletion or sympathetic nervous system (SNS) activation. This rise in PRA is caused by inhibition of NaCl reabsorption at the macula densa in conjunction with loop-diuretic stimulation of renal prostacyclin release. This first-wave of neurohumoral effects, although transient, increases afterload and for a short period of time may limit the effectiveness of a loop diuretic. Following this initial rise in PRA, diuretics cause a more sustained increase in PRA and aldosterone due to stimulation from an increase in SNS activity (β-agonism) and a fall in ECF volume.

Diuretics also increase the renal production of prostaglandins, which is the probable explanation for the reduction of preload and the decrease in ventricular filling pressures that occur within 5 to 15 min of loop diuretic administration. Inhibition of prostaglandin synthesis with nonsteroidal anti-inflammatory drugs diminishes the natriuretic response with all classes of diuretics. Although the SNS is stimulated by loop diuretics, as determined by increases in plasma catecholamine concentrations and an increase in heart rate, α₁-receptor blockade with prazosin does not improve the natriuretic effect of furosemide. Neurohumoral activation by diuretics remains an important consideration in the overall effectiveness of diuretics in the treatment of hypertension and HF.

**Diuretics in Hypertension**

Hypertension (HTN) is loosely defined by a systolic blood pressure (SBP) ≥140 mm Hg and/or a diastolic blood pressure (DBP) ≥90 mm Hg and is one of the most common disorders in the United States, with about 75 million people aged 20 years or older affected. What constitutes hypertension is dependent on the definition applied, and if you add to this figure those patients with borderline or pre-HTN, this number grows considerably larger. Both cardiovascular and cerebrovascular events, CKD, and all-cause mortality increase in a continuous fashion with increases in SBP and/or DBP. Systolic BP is more predictive of morbidity and mortality than is DBP. Diuretics are currently recommended by the JNC-7 as first-line therapy for the treatment of hypertension. This position was adopted based on a number of outcome studies that used diuretics or beta-blockers and that reported therapy-related reductions in stroke and cardiovascular endpoints. All JNC documents dating to the original JNC I—published in 1977—have advocated a similar position favoring the initial use of diuretics in the management of hypertension.

**Mechanism of Action**

The exact means by which diuretics lower BP is not known, although these agents have been used for more than 50 years. The effect of diuretics on BP may be separated into 3 sequential phases: acute, subacute, and chronic (Figure 11-3), which correspond to periods of roughly 1 to 2 weeks, several weeks, and several months, respectively. In the acute phase of response to diuretics, the predominant effect of these agents is to reduce ECF volume and thereby decrease cardiac output. The initial response to diuretic therapy in a patient receiving a “no added salt” diet (100 to 150 mmol/d) is a negative Na⁺ balance of from 100 to 300 mmol, which occurs in the first 2 to 4 days of treatment. Plasma Na⁺ concentrations remain normal, and the loss of body Na⁺ translates into a 1 to 2 L decrease in ECF volume. Direct measurement of ECF volume of hypertensive patients treated with diuretics show a 12% decrease. There is a similar reduction.
in plasma volume, which suggests that the acute volume loss arises proportionally from both the plasma and interstitial compartments. This decrease in plasma volume reduces venous return and diminishes cardiac output, thereby producing the initial vasodepressor response. The change in plasma volume variably stimulates both the SNS and the renin-angiotensin-aldosterone (RAA) axes. The degree to which these systems are activated may govern the magnitude of the acute BP decrease observed with a diuretic. It has also been shown in hypertensive patients that diuretics can restore nocturnal BP decline in a manner similar to Na+ restriction, which suggests that the kidneys and Na+ balance have a definable role in the circadian rhythm of BP.

Over time, these effects on volume and cardiac output lessen in importance, although BP remains lowered. During the first few weeks of treatment, plasma volume returns to slightly less than pretreatment levels, despite the continued administration of a diuretic. Thus, the chronic vasodepressor effect of diuretics is less so one of persistent volume reduction than it is one coupled to a long-term reduction in total peripheral resistance (TPR). The subacute phase of BP reduction with diuretics reflects a transitional period during which both of these factors contribute. There is no straightforward explanation for the drop in TPR that accompanies long-term diuretic use. The decrease in TPR during prolonged therapy has been attributed to several factors, including changes in the ionic content of vascular smooth-muscle cells, altered ion gradients across smooth-muscle cells, and changes in membrane-bound ATPase activity. The ability of diuretics to reduce BP seems to be critically linked to the functional treatment of hypertension. The chronic vasodepressor effect of diuretics is less so one of persistent volume reduction than it is one coupled to a long-term reduction in total peripheral resistance (TPR).

Another consideration in the ability of a diuretic to reduce BP over the long term relates to the natriuretic pattern of diuretics. For example, when long-term therapeutic responses to HCTZ and furosemide are compared in hypertensive patients, SBP and DBP are more consistently reduced with HCTZ. One explanation for this difference is the pattern of diuresis with each agent. The natriuretic pattern with a thiazide diuretic (compound-dependent) is fairly prolonged but modest at best, whereas a loop diuretic produces a brisk early diuretic response that then rapidly falls off. The latter pattern is often accompanied by a significant postdiuretic period of Na+ and water (H2O) retention; thus, the result of short-acting loop diuretic therapy can often be no net volume loss. This period of antinatriuresis is of less consequence with the relatively less potent thiazide-type diuretics. In the end, a thiazide-type diuretic may be able to maintain a mild state of volume contraction more efficiently than a loop diuretic.

An exception to this may be found with the response to the more long-acting loop diuretic torsemide; in addition, small doses of this compound may cause significant BP reduction, a vasodepressor process that seems to be independent of the observed degree of diuresis.

Diuretics in Clinical Trials

By the mid 1990s, evidence about the effects of BP-lowering regimens, mainly based on diuretics and β-blockers, was available from a series of randomized controlled clinical trials involving close to 50,000 hypertensive patients. Systematic overviews and/or meta-analyses of these trials showed that reductions in BP of about 10 to 12 mm Hg systolic and 5 to 6 mm Hg diastolic conferred relative risk reductions in stroke risk of 38% and a risk of coronary heart disease (CHD) of 16% within just a few years of starting therapy. The size of these effects was similar in major subgroups of trials and patients, and seemed to be largely independent of differences in disease event rates amongst study patients. The few studies that directly compared diuretics and beta-blockers detected no clear differences in the risk of stroke or coronary artery disease (CAD). However, it was shown in elderly patients with hypertension that first-line diuretic therapy reduced cerebrovascular events, CAD, cardiovascular and all-cause mortality, in contrast to first-line treatment with β-blockers that only reduced the odds for cerebrovascular events with scant effect on cardiovascular events and all-cause mortality. As the issue of the position of β-blockers in the treatment hierarchy has heated up over the last 10 years, the β-blocker used most often, atenolol, has become more so the topic than the drug class itself.
In 1995, many studies of BP-lowering drugs were identified as planned or ongoing. Most of these trials had been designed to detect large differences in relative risk and had insufficient power to detect small to moderate differences between the studied regimens. To maximize the information acquired by these and future trials, a collaborative program of prospectively designed overviews was developed. The first publication of these overviews occurred in 2000.120 Overviews of trials comparing angiotensin-converting enzyme (ACE)-inhibitor-based regimens with diuretic or β-blocker-based regimens in hypertensive patients provide little evidence that the benefits of ACE inhibitors are any different than those conferred by diuretics or beta-blockers (Figure 11-4).124-126 Overviews of trials comparing calcium channel blockers (CCBs) with diuretic- or β-blocker-based regimens provide some evidence of differences in the effects of the 2 regimens on cause-specific outcomes with the risk for stroke being significantly less with CCBs than with diuretics (Figure 11-5). There was no evidence of differences between the treatment effects of CCB regimens whether they were based on dihydropyridine or nondihydropyridine agents.125,127,128 These meta-analyses also show that there is no real difference in outcomes comparing diuretic-related regimens to other drug classes based on age and gender.129,130

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized clinical outcome trial of antihypertensive and lipid-lowering therapy in a diverse population (including substantial numbers of women and minorities) of 33,357 high-risk hypertensives aged 55 years or older with a planned mean follow-up of between 4 to 8 yrs. This trial compared 3 classes of antihypertensive therapy, the α-blocker doxazosin, the CCB amlodipine, and the ACE inhibitor lisinopril to the thiazide-type diuretic chlorthalidone. The study was terminated for the doxazosin arm of the study approximately 2 years early because of its inferiority to chlorthalidone with regard to 2 combined endpoints: (1) coronary revascularization and angina pectoris and (2) the development of HF.131

The primary outcome in ALLHAT132 was combined fatal CHD or nonfatal MI, analyzed by intent-to-treat. Secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization, HF, and peripheral arterial disease). The results indicated that mean follow-up was 4.9 years. There was no difference between treatments relative to the primary outcome as well as all-cause mortality. For amlodipine versus chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% versus 7.7%; RR, 1.38; 95% confidence interval, 1.25-1.52). For lisinopril versus chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% versus 30.9%; RR, 1.10; 95% confidence interval, 1.05-1.16); stroke (6.3% versus 5.6%; RR, 1.15; 95% confidence interval, 1.02-1.30); and HF (8.7% versus 7.7%; RR, 1.19; 95% confidence interval, 1.07-1.31). The opinion expressed by the authors of this study was that thiazide-type diuretics were superior in preventing one or more major forms of cardiovascular disease and are less expensive; therefore, they should be preferred for first-step antihypertensive therapy.132,133

Regression of Left Ventricular Hypertrophy with Diuretic Therapy

An increased left ventricular (LV) mass has been recognized as a powerful independent risk factor for cardiovascular morbidity.134,135 Antihypertensive therapy, with the exception of direct vasodilators, is effective in regressing LV hypertrophy (LVH).135,136 In 1991, Moser and Setaro compiled an overview of all studies evaluating LVH regression in diuretic-treated hypertensive patients, which supported the efficacy of diuretics in regressing LV mass.137 Two meta-analyses have been undertaken specifically looking at LVH regression with different antihypertensive agents.138,139 Using echocardiography, Dahlöf et al analyzed 109 studies comprising 2,357 patients.138 Diuretics were associated with an 11.3% reduction in LV mass; however, this was primarily due to a reduction in LV volume as has been shown in other studies.140 Alternatively, the reduction of LV mass associated with ACE inhibitors was 15%, β-blockers 8%, and CCBs blockers 8.5% with structural changes largely reflected by a reversal of posterior and intraventricular septal thickness. Another analysis of 39 trials of diuretics, β-blockers, CCBs, and ACE inhibitors showed that LV mass was importantly related to the treatment-induced decline in BP and, in particular, SBP. Reductions in LV mass of 13%, 9%, 6%, and 7% occurred with ACE inhibitors, CCBs, β-blockers, and diuretics, respectively.139 Accordingly, diuretics are comparable to most other drug classes in their ability to regress LV mass.141-142 A significant reduction in LV mass with antihypertensive therapy has not yet been shown in prospective randomized trials to be specifically related to reduced cardiovascular morbidity and mortality; moreover, the degree to which BP is reduced with the chosen therapy is an important determinant of the extent to which LV mass regresses.143

Patient Populations Responsive to Diuretics

When used alone in the nonedematous Stage 1 hypertensive patient, thiazide diuretics are as efficacious as most other classes of drugs.144 Although it is imprudent to offer...
Diuretic Therapy in Cardiovascular Disease

**Figure 11-4.** Comparisons of ACE-inhibitor-based therapy with diuretic-based or β-blocker-based therapy. ACE-I = ACE inhibitor; p homog = p value from χ² test for homogeneity.


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**Figure 11-5.** Comparisons of calcium-antagonist-based therapy with diuretic-based or β-blocker-based therapy. DHP = dihydropyridine; NHP = nondihydropyridine; p homog = p value from χ² test for homogeneity.

universal recommendations about antihypertensive care on the basis of race alone, in clinical practice this is still routinely done. That said, black and elderly hypertensives typically respond better to diuretics than do nonblack and younger patients.\textsuperscript{130,144,145} The same can be said for other salt-sensitive forms of HTN, such as that seen in the patient with diabetes and HTN and/or CKD.

**Elderly**

Five studies emphasizing diuretic therapy were specifically performed in the elderly hypertensive (age > 60 years): the Systolic Hypertension in Elderly Program (SHEP),\textsuperscript{114} the Swedish Trial in Old Patients (STOP),\textsuperscript{115} the Medical Research Council Trial in the treatment of older adults (MRC-2),\textsuperscript{116} the European Working party on High Blood Pressure in the Elderly (EWPHE),\textsuperscript{117} and the trial of Coope and Warrender.\textsuperscript{145} Significant reductions in stroke similar to that observed in younger patients and greater benefits in terms of protection from MI and HF were demonstrated in these older patients. In addition, diuretics have been shown to improve the quality of life as assessed by exercise capacity but may increase the likelihood of sexual dysfunction.\textsuperscript{146,147}

Four clinical trials, with a total of 34,676 patients, have compared diuretics with \( \beta \)-blockers: the International Primary Intervention Prevention Study in Hypertension (IPPPSH),\textsuperscript{148} Heart Attack Primary Prevention in Hypertension Research Group (HAPPHY),\textsuperscript{149} Medical Research Council (MRC) and MRC-2.\textsuperscript{115} These 2 drug classes were comparable with regard to the incidence of stroke. With regards to MI, 2 studies favored either diuretic or \( \beta \)-blockers over the other although the between class differences were inconsequential.

Three multicenter prospective clinical trials have been specifically performed in the elderly: the SHEP,\textsuperscript{114} STOP,\textsuperscript{115} and MRC-2 trials.\textsuperscript{116} All 3 trials found significant reductions in cerebrovascular and cardiovascular morbidity and mortality associated with diuretic and/or \( \beta \)-blocker therapy. To highlight one of these trials, the SHEP was a double-blind, placebo-controlled trial comprised of 4,736 men and women with isolated systolic hypertension (ISH) who were older than 60 years of age.\textsuperscript{114,150} Patients were randomized to receive a low-dose of the diuretic chlorthalidone (12.5-25.0 mg/day) as initial therapy; the \( \beta \)-blocker atenolol (25-50 mg/day) and reserpine (0.05-0.10 mg/d) were added as needed to reach goal BP. At the end of the 5-year follow-up period, 46% of the subjects had adequate BP control using only a low dose of chlorthalidone. Another 23% of patients were controlled with the addition of atenolol. Outcomes included a statistically significant 36% reduction in strokes and nonstatistically significant reductions in MI of 27% and overall mortality of 13%. Absolute risk reduction with active treatment compared with placebo was twice as great for diabetic versus non-diabetic patients. Results of these trials clearly establish the benefit of low-dose diuretics and/or \( \beta \)-blockers for the treatment of ISH in the elderly and have been the basis for current treatment recommendations advocating diuretic therapy in uncomplicated forms of hypertension.\textsuperscript{151-151b}

**Blacks**

In black patients, hypertension is more prevalent at a younger age, is usually more severe, and is associated with a greater incidence of cardiac, central nervous system, and renal complications than occur in white patients.\textsuperscript{152-158} Although the pathogenesis of hypertension has not been clearly defined, the majority of blacks fall into the low-renin category. This low-renin status cannot be explained by volume expansion alone, because no consistent relationship between these 2 factors has been found in this population.\textsuperscript{155} In addition, the INTERSALT study, a multicenter, cross-sectional study that evaluated the relationship between electrolytes and BP, was unable to correlate excessive salt intake as a major contributing factor to the development of hypertension in blacks.\textsuperscript{154} Although not fully resolved as of yet there appears to be an emerging role for potassium intake in lowering daytime BP and in converting nocturnal nondipping BP patterns to a dipping characterization in normotensive and hypertensive blacks.\textsuperscript{156,157} In a number of clinical trials, black patients have responded very well to thiazide-type diuretics.\textsuperscript{158,160} It has been reported that between 40% and 67% of young black patients and between 58% and 80% of older blacks respond to monotherapy with diuretics.\textsuperscript{159} As a rule, diuretics are more effective than \( \beta \)-blockers, ACE inhibitors, or angiotensin receptor blockers (ARBs) in blacks.\textsuperscript{158-162} However, when diuretics are added to any of these antihypertensive drug classes in black patients, their efficacy is substantially improved.\textsuperscript{159-161,163}

In a number of trials, diuretic therapy has been associated with reductions in morbidity and mortality in blacks. Black patients made up approximately half of the study participants in the Veterans Administration Cooperative Study and the Hypertension Detection and Follow-Up Program (HDFP), both of which were diuretic-based studies.\textsuperscript{111,112} In the Veterans Administration Cooperative Study, diuretic treatment was associated with a reduction in morbid events from 26% to 10% in black patients.\textsuperscript{111} In the HDFP study, there was an 18.5% mortality reduction for black men and a 27.8% mortality reduction for black women.\textsuperscript{112} However, the ability of diuretics to delay or prevent renal dysfunction in hypertensive blacks was put into question by the Multiple Risk Factor Intervention Trial (MRFIT), which did not show a benefit in this regard;\textsuperscript{164} however, more recent data from ALLHAT suggest an equally positive renal protective effects for chlorthalidone in hypertensive blacks when compared to amlodipine and lisinopril.\textsuperscript{165}
General Considerations

Diuretics are likely to find their greatest use as “sensitizing” agents. Their primary modes of sensitization derive from volume depletion and related neurohumoral activation. In this regard, even subtle degrees of volume contraction or RAA-axis activation, as produced by low-dose thiazide-type diuretics, can enhance the effect of co-administered antihypertensive compounds.166,167 This additive effect has rekindled interest in the use of fixed-dose combination antihypertensive therapy in the primary management of essential hypertension (see Chapter 21, New Aspects of Combination Therapy: Focus on Hypertension).168 The concept of using 2 drugs at low doses for BP control is not necessarily of recent vintage. It has, however, gathered new support because it is increasingly evident that most patients who receive such treatment not only achieve their target BP pressures but do so with a minimum of adverse effects.168,169

The dose-response relationship for the antihypertensive effect of diuretics has been fully characterized over the past 2 decades. In the process, many of the supposed negative attributes of diuretics have been shown to be much less common than was first thought. In the early days of diuretic use, doses were unnecessarily high. At that time, the concept “if a little is good, a lot is better” was embedded in clinical practice. It was soon recognized, however, that the dose-response relationship for BP reduction with a thiazide-type diuretic, such as HCTZ, flattened beyond a dosage of 25 mg/d. Much of the negative biochemical and metabolic experience with diuretics occurred with the very high dosages (100 to 200 mg/d) routinely used in the early days of their use. When it was found that the BP reduction with HCTZ was similar whether the dosage was 12.5 or 25 to 100 mg/d, diuretics once again became an attractive treatment option.132,170

As practice patterns shifted to a low-dose strategy for thiazide-type diuretics, it was soon apparent that the frequency of the metabolically negative adverse effects had dramatically diminished: thus, such entities as hypokalemia, hypomagnesemia, glucose intolerance, and hypercholesterolemia are much less common with low-dose diuretics.166,170 When the strong end-organ protection data for diuretics are combined with the fact that these agents produce few adverse effects at low doses, a compelling argument can be made for the use of diuretics as initial therapy for most persons with uncomplicated mild to moderate hypertension.170

Diuretics in HF

Diuretics remain a necessary component of the treatment of HF, a condition that is extremely common with an estimated 670,000 new cases diagnosed each year in the United States. The prevalence of HF is steadily increasing as the United States population ages and patients with HF survive longer. HF is the leading discharge diagnosis in persons older than 65 years of age; thus, this disease has an enormous economic impact, estimated at $37.2 billion in 2008 by the American Heart Association.

Until the middle 1970s, the treatment of HF was limited to dietary Na+ restriction, diuretics, and digitalis. Since then, the therapeutic options have changed dramatically, and a very clear survival benefit derives from use of therapies such as ACE inhibitors, ARBs, and β-blockers. Diuretics are important components of the treatment of both acute decompensated and chronic HF. Unfortunately, the pharmacokinetics and pharmacodynamics of diuretics are altered in the setting of HF, which complicates their use particularly when orally administered. The following section briefly reviews the pathophysiology of HF and highlights mechanisms of diuretic resistance and strategies to overcome this resistance.

Pathophysiology of HF

All forms of HF are marked by systolic and/or diastolic dysfunction. Systolic dysfunction is characterized by dilatation of the LV cavity and a gradual reduction in ejection fraction. The preserved systolic function form of HF is characterized by a normal or small left ventricular cavity with a thickened ventricular wall and a normal to increased ejection fraction. Systolic dysfunction is most commonly caused by ischemic disease or idiopathic cardiomyopathies.171 The preserved systolic function form of HF is most commonly seen in the elderly and in those patient with a history of hypertension. These 2 forms of HF often coexist and either one may predominate in any one particular patient. HF is frequently a dynamic process best exemplified by patients with poorly controlled hypertension in whom systolic function is preserved early in the course of the disease only to be followed by systolic dysfunction if left untreated.172

The hemodynamic derangements associated with HF provoke a complex array of biologic responses. Systemic neurohumoral activation cause significant effects on preload, afterload, and heart rate and lead to many of the symptoms associated with HF. Activation of biologic systems within the myocardium also plays a significant role in the remodeling of the failing ventricle(s) and vasculature. It is now felt that this remodeling process plays a central role in the pathophysiology of congestive heart failure (CHF).173,174

Myocardial remodeling is characterized by a progressive change in the geometry of the ventricular chamber.172 At the molecular level, it is associated with hypertrophy and apoptosis of myocytes, side-by-side slippage of myocytes, regression to a molecular phenotype characterized by the expression of fetal genes and proteins, and altera-
tions in the quantity and composition of extracellular matrix. Many of these alterations can be induced by exposure of myocardial cells to mechanical stress, angiotensin-II, norepinephrine, endothelin, inflammatory cytokines, and reactive oxygen species. From a clinical perspective, agents such as ACE inhibitors or β-blockers that reverse this remodeling process show the greatest benefits in the treatment of HF.

Hemodynamic alterations that accompany HF result in systemic vasoconstriction and therein increase in LV afterload. This increase in afterload causes further reductions in systolic function, increases pulmonary vascular tone, elevates pulmonary venous pressure, and, eventually, LV failure. The increased vascular tone in HF reflects the activation of neurohumoral systems, especially the SNS and the RAA axes. Attenuation of endothelium-dependent vasodilatation and increases in endothelin production may also contribute to the systemic and pulmonary vasoconstriction. Arterial vasodilators, particularly ACE inhibitors and ARBs, increase stroke volume and cardiac output with a somewhat variable reduction in systemic BP and are the “backbone” of therapy for HF.

As already mentioned, neurohumoral activation is a consistent finding in patients with HF. Elevated SNS activity is reflected by increased sympathetic nerve traffic and increased levels of urinary and plasma catecholamines. These alterations are reflected in an attenuation in the contractile and chronotropic responses to β-adrenergic stimulation. The SNS nervous system appears to be activated even in patients with asymptomatic disease and may contribute to the progression of HF.

The renin-angiotensin system (RAS) is also activated in HF patients, as evidenced by increased plasma concentrations of renin, angiotensin-II, and aldosterone. It has also been recognized that tissue components of the RAS are independently activated and contribute to myocardial and vascular remodeling. The increased angiotensin-II levels in HF also have renal implications, effecting glomerular hemodynamics and Na+ reabsorption. In states of mildly reduced renal perfusion, such as HF, angiotensin-II is important in maintaining glomerular filtration by its effect on efferent arteriolar tone. In severe HF, however, angiotensin-II concentrations become markedly elevated, causing afferent arteriolar constriction and glomerular mesangial cell contraction, both of which contribute to a further reduction in the glomerular filtration. Sodium reabsorption is increased both by a direct effect of angiotensin-II on proximal tubular Na+ reabsorption and through stimulation of aldosterone wherein distal Na+ reabsorption increases. Although diuretics are important in countering this excessive Na+ retention, they also further stimulate angiotensin-II production and should typically be combined with agents that interfere with the RAS. Although ACE inhibitors have a major impact on the symptomatic relief and progression of HF, the exact mechanism behind their beneficial effect remains hard to pin down (see Chapter 9, The Renin-Angiotensin Axis: Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers). ACE inhibitors also inhibit the degradation of bradykinin, which stimulates nitric oxide, an important mediator of a number of endothelial functions. It is not clear to what extent the positive effects of ACE inhibitors reflect a reduction in angiotensin-II levels, an increase in bradykinin levels, or both. At the tissue level, angiotensin-II can also be generated by non-ACE pathways; thus its production is not completely inhibited by ACE inhibitors. Angiotensin receptor blockers, a class of drug that also has beneficial effects in HF and are without a meaningful effect on bradykinin have yet to refine the thinking on this issue.

Circulating levels of endothelin, arginine vasopressin, and atrial natriuretic peptide are also commonly elevated in patients with HF. Levels of endothelin correlate with pulmonary vascular resistance in HF. Arginine vasopressin is stimulated despite the presence of a low serum Na+ and plasma osmolality in many HF patients. Ar- ginine vasopressin contributes to both the hyponatremia and possibly the increased afterload in advanced state HF. Atrial natriuretic peptide is a renal vasodilator that acts as a counter-regulatory factor opposing the actions of several vasoconstrictors. Endothelin-receptor inhibitors, arginine vasopressin-receptor antagonists, and brain natriuretic peptide have been carefully studied in HF, but as yet have not been shown to offer substantive benefit to the HF patient already receiving standard-of-care therapy.

Clinical Use of Diuretics in HF

Diuretics are useful in the long-term management of chronic stable HF patients who demonstrate a pattern of continuing weight gain (volume excess) despite adherence to a low Na+ diet. They are also useful in patients who experience acute decompensated HF, in which case intravenous loop diuretics are viewed as critical components of the treatment plan. Intravenous loop diuretics can rapidly improve the symptom profile of the patient with decompensated HF, but they also can be associated with hemodynamic deterioration. In a study of 15 patients with severe chronic HF, intravenous furosemide (1.3 +/- 0.6 (SD) mg/kg body weight) led to an abrupt increase in systemic vascular resistance and mean arterial pressure, and to a decrease in pump function as marked by an increase in LV filling pressures. This deleterious effect reversed itself over 2 hours, coinciding with, but not necessarily relating to, the onset of diuresis. This phenomenon of acute decompensation is likely dose-dependent; thus, caution needs to be exercised in acutely decompen-
sated HF as to the amount of intravenous furosemide administered. In patients with compensated HF and severe edema, loop diuretics can be important add-on therapy to ACE inhibitors. In a study of 13 patients with severe edema secondary to HF, furosemide therapy increased stroke volume owing to a reduction in systemic vascular resistance and consequently afterload. In a double-blind study comparing a loop diuretic or cardiac glycoside with a placebo, symptoms and pulmonary capillary wedge pressure were improved to a similar extent by both drug classes. However, patients treated with diuretics were more likely to become volume-contracted with symptoms such as orthostatic hypotension and weakness and show biochemical evidence of prerenal azotemia. Therefore, salt-depleting therapy requires an ongoing assessment of effective blood volume and adjustments in dietary salt intake and/or diuretic dose to maintain filling pressures sufficient to optimize cardiac performance.

Mild HF often responds to dietary salt restriction (50 to 100 mmol/d) and/or low doses of a thiazide-type diuretic. As HF worsens, the GFR also decreases and patients become less responsive to conventional doses of a thiazide-type diuretic, which usually occurs as the GFR falls below 30-mL/min (plasma creatinine concentration of 2 to 4 mg/dL). Larger and more frequent dosing of loop diuretics together with more rigorous control of dietary Na+ intake may then be called for as the disease progresses.

Factors Influencing Diuretic Efficacy

Alterations in Pharmacokinetics

HF modifies both diuretic absorption and the time course and extent of its renal elimination. Although diuretic pharmacokinetics usually go unaltered in mild HF, with severe HF, major abnormalities occur. Although the absolute absorption of furosemide and bumetanide is normal in HF patients, the time required to reach peak serum diuretic concentrations after oral dosing is significantly delayed. The delayed absorption can reduce the peak diuretic concentrations in plasma and urine, thus diminishing diuretic tubular delivery and thereby efficacy. Impaired drug absorption is thought to be related to reduced gastric and intestinal motility, an edematous bowel wall, and/or HF-related decreased splanchnic blood flow.

As renal plasma flow declines in HF, so will the delivery of furosemide or other loop diuretics to their site of action in the loop of Henle. The secretion of furosemide is reduced when the GFR falls below 30-mL/min because of the accumulation of endogenous organic acids that compete with furosemide for secretion by proximal tubular organic anion transporters. At this level of renal insufficiency, loop diuretics must be administered in higher doses in order to circumvent these secretion-limiting factors.

Alterations in Pharmacodynamics

The relationship between natriuresis and excretion of loop diuretics is not altered in mild HF, but the dose-response curve is shifted rightward in more advanced HF (Figure 11-6). The factors behind this shift in diuretic responsiveness are numerous, including structural adaptations that occur in the distal nephron, as well as excessive activation of the RAS and SNS. ACE inhibitors can sometimes reestablish a diuresis in resistant HF patients by inhibiting the generation of angiotensin-II and thereby favorably altering afterload and/or renal blood flow. Conversely, if the BP drop is excessive with an ACE inhibitor, the diuretic response can be attenuated.

Diuretic Dosing in HF

Because of alterations in diuretic pharmacokinetics and pharmacodynamics, patients with HF often appear to be resistant to diuretics. The first step in evaluating an HF patient for diuretic resistance is to assess the level of dietary Na+ and fluid intake. At steady state, dietary Na+ intake can be assessed from the measurement of 24-hour Na+ excretion. Patients ingesting a high- Na+ diet will overwhelm the capacity of the diuretic to produce a net diuresis and weight loss. If this is the case, a diettian may be essential to instructing the patient as to how best to
reduce daily Na+ intake to < 100 mmol/d. Before labeling the patient as truly diuretic resistant, it is also important to assure that the patient is adherent with his or her diuretic dosing (usually twice a day dosing is necessary) and that the patient is not taking medication that interferes with the action of diuretics, such as an NSAID. Once these factors are eliminated from consideration, changes in diuretic doses or route of administration and diuretic combinations should be considered as therapy options.

In HF patients refractory to standard furosemide doses, high-dose therapy may prove efficacious. Daily doses of between 500 and 2000 mg of intravenous furosemide were administered to 20 patients with HF and refractory edema. With this regimen, a diuresis was established, body weight was reduced, and the HF class was improved. Similar studies have reported improved furosemide efficacy in refractory HF where high doses of oral furosemide were employed. When moderate to severe renal impairment is present in decompensated HF, a brief trial of high-dose furosemide is reasonable. Gerlag and Van Meijel treated patients with renal insufficiency (mean GFR, 32 mL/min) and refractory HF with high-dose oral and intravenous furosemide over a 4-week period. Patients experienced a mean reduction in weight of 11.1 kg and an improvement in New York Heart Association (NYHA) classification. Such high diuretic doses can be viewed as a marker of the severity of the underlying HF and therein provide some measure of prognosis.

A loop diuretic administered as an infusion is another method of improving the response in an HF patient with diuretic resistance. In a randomized crossover study comparing continuous infusion versus bolus bumetanide in patients with severe renal insufficiency (mean GFR, 17 mL/min), Rudy et al observed a greater net Na+ excretion during continuous infusion despite comparable total 14-h drug excretion. The rate of urinary bumetanide excretion remained constant when infused. With intermittent administration, peak bumetanide excretion was observed within the first 2 hours and tapered thereafter. In a similar study employing furosemide, a continuous intravenous infusion of furosemide (loading dose of 30 to 40 mg followed by infusion at a rate of 2.5 to 3.3 mg/h for 48 hours) was compared to an intermittent intravenous bolus administration (30 to 40 mg every 8 hours for 48 hours) in patients with NYHA class III and class IV HF. A significantly greater diuresis and natriuresis was observed using continuous furosemide infusion as compared with intermittent administration; this was accomplished at a lower peak furosemide concentration. When continuously infused, the pattern of furosemide delivery produced more efficient drug utilization. In a study examining the cost of care for 17 elderly patients with class IV HF, a continuous intravenous furosemide infusion resulted in a diuresis of between 9 and 20 L over an average of 3.5 days. The length of stay for these patients was on average 2.3 days shorter when compared to a contemporary group of class III and class IV HF patients who were managed with conventional dosing of furosemide, and resulted in significant cost savings.

Diuretic combinations can be used in HF patients otherwise refractory to loop diuretics alone. Because of structural adaptation occurring in the distal nephron with prolonged loop diuretic therapy, the combination of a distal-acting diuretic and a loop diuretic is particularly effective in such patients. The combination of bumetanide and metolazone (a thiazide-type diuretic) produces an additive, if not synergistic, diuretic effect. During prolonged furosemide therapy, the responsiveness to a thiazide is considerably augmented. Numerous reports have demonstrated a profound diuresis (several liters daily) accompanied by clinical improvement, with the addition of metolazone to a loop diuretic (usually furosemide) in HF patients previously resistant to loop diuretic therapy alone. Metolazone is particularly effective because its duration of action is prolonged, it is lipophilic, and it remains effective in states of renal impairment. Spironolactone has also been used in combination with loop diuretics and has been followed by an improvement in diuretic response in HF patients. Above and beyond the known diuretic properties of spironolactone, it was recently shown that, as an aldosterone-receptor antagonist, spironolactone blocks a wide-range of deleterious tissue-based effects attributable to aldosterone, which include augmentation of vascular and myocardial fibrosis. Accordingly, spironolactone, and more recently eplerenone, are increasingly advocated as adjunct therapy in HF.

This therapeutic recommendation is a byproduct of the Randomized Aldactone Evaluation Study (RALES), the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). In the RALES trial, spironolactone (25 mg/d) was shown to reduce the risk of all-cause mortality in NYHA Class IV HF patients treated with standard ACE inhibitor and diuretic therapy. In EPHESUS, eplerenone (50 mg/d) added to optimal medical therapy substantially reduced morbidity and mortality among patients with acute MI complicated by left ventricular dysfunction and HF. In the EMPHASIS-HF trial, eplerenone 25 to 50 mg/d was shown to reduce the risk of the primary endpoint, cardiovascular death or HF hospitalization, in patients with NYHA class II HF treated with standard therapy when compared to the placebo-treated patients receiving standard therapy. It was demonstrated that aldosterone levels may often be elevated ("aldosterone escape") in HF
patients despite the use of ACE inhibitors. Increasingly, diuretic combinations, including loop and distal tubular diuretics, as well as aldosterone receptor antagonists, are routinely used in patients with HF.

**Other Pharmacologic Approaches to Diuresis**

Other approaches to diuresis include the use of dopamine agonists (see Chapter 26, Selective and Nonselective Dopamine Receptor Agonists), vasopressin antagonists (see Chapter 28, Vasopressin and Vasopressin Receptor Antagonists), adenosine antagonists (see Chapter 37, Cardiovascular Drugs in Development), natriuretic peptides (see Chapter 27, Natriuretic Peptides: Nesiritide), and neutral endopeptidase inhibitors (see Chapter 37) either given alone under select circumstances or administered together with a loop diuretic.

**Adverse Effects of Diuretics**

**Hyponatremia**

Hyponatremia is a potentially serious complication of diuretic therapy. Elderly females treated with thiazide diuretics are most commonly affected, and the condition is usually seen within the first 2 weeks of therapy. Elderly females seem to exhibit an exaggerated natriuretic response to a thiazide diuretic yet have a diminished capacity to excrete free H₂O. These individuals also may have a low solute intake, which further diminishes their capacity for free H₂O elimination.

Thiazide diuretics are more likely to cause hyponatremia than are loop diuretics because they increase Na⁺ excretion and prevent maximal urine dilution while preserving the kidney’s innate concentrating capacity. Loop diuretics inhibit Na⁺ transport in the renal medulla and prevent the generation of a maximal osmotic gradient and actually can be used in hyponatremic subjects to increase free H₂O clearance. HF-related hyponatremia is more often a consequence of prominent neurohumoral activation than a consequence of diuretic use per se, although diuretic use undoubtedly contributes to its development.

Mild asymptomatic hyponatremia can be treated by withholding diuretics, restricting free H₂O intake, and correcting serum K⁺ values if hypokalemia exists. Severe, symptomatic hyponatremia complicated by seizures is an emergency requiring intensive therapy, although steps should be taken to avoid rapid or overcorrection of the hyponatremia, because central pontine myelinolysis has occurred under these circumstances. The risks of ongoing hyponatremia must be weighed against those of too rapid a correction, and current recommendations are that plasma Na⁺ should be corrected by no more than 12 to 20 mmol/L in the first 24 hours (0.5-1.0 mmol/L/hr). This area, however, remains extremely controversial.

**Hypokalemia and Hyperkalemia**

Hypokalemia is a common finding in patients treated with loop and/or thiazide diuretics. During the first week of therapy with a thiazide diuretic, plasma K⁺ in subjects not taking K⁺ supplements falls by an average of 0.6 mmol/L as compared with 0.3 mmol/L in those taking furosemide. However, it is unusual for serum K⁺ values to settle < 3.0 mmol/L in diuretic-treated outpatients, apart from a high dietary Na⁺ intake and/or when a long-acting diuretic is being given (as is the case with chlorothalidone). Mechanisms that contribute to hypokalemia during thiazide or loop diuretic use include augmented flow-dependent K⁺ secretion in the distal nephron, a fall in luminal Cl⁻ concentration in the distal tubule, metabolic alkalosis, and/or stimulation of aldosterone and/or vasopressin release, both of which promote distal K⁺ secretion (Figure 11-7).

Although mild degrees of diuretic-induced hypokalemia can be associated with increased ventricular ectopy, the clinical significance of diuretic-induced hypokalemia is argued. The Multiple Risk Factor Intervention Trial (MRFIT) found a significant inverse relationship between the serum K⁺ concentration and the frequency of premature ventricular contractions (PVCs). This relationship, however, has not been observed in all trials, possibly because of the short duration of many of these trials. In the MRC study involving 324 patients with mild hypertension, 287 of whom underwent ambulatory electrocardiogram monitoring, diuretic use was not asso-
uated with an increased frequency of PVCs after 8 weeks of therapy, whereas after 24 months there was a significant difference in PVCs in those patients receiving diuretics as compared with those receiving a placebo (20% versus 9%). These PVCs were significantly correlated with the serum K+ concentration. Patients with LVH, HF, or myocardial ischemia are at a particularly high risk of developing lethal ventricular arrhythmias in the setting of K+ depletion.

Despite a sometimes monotonous level of concern about cardiovascular risk (rather than benefit) with diuretic therapy, in part, due to associated electrolyte abnormalities, several clinical trials, including the Systolic Hypertension in the Elderly Program, Swedish Trial in Old Patients with Hypertension, and MRC have shown that low-dose diuretic therapy reduces cardiovascular risk event rates by 20% to 25%. Perhaps the use of lower doses of thiazides or combination therapy with a K+-sparring diuretic explains these favorable results as compared with earlier trials, such as MRFIT, in which higher doses of diuretics were employed and PVCs were more frequent. Those subjects who developed hypokalemia in the SHEP trial did not secure the treatment benefits on cardiovascular events as well as stroke recognized in similarly-treated, but normokalemic patients, with ISH.

Comparative effects on sudden cardiac death (SCD) of different doses and combinations of diuretics have been reported. The risk of SCD among patients receiving combined thiazide and K+-sparing diuretic therapy was lower than that found in patients treated with thiazides alone (odds ratio 0.3:1). Compared with low-dose thiazide therapy (25 mg/d), intermediate-dose thiazide therapy (50 mg/d) was associated with a moderate increase in the risk of SCD (odds ratio 1.7:1) and high-dose (100 mg/d) was associated with an even greater increase in risk (odds ratio 3.6:1). In contrast with K+-sparring diuretics, the addition of K+ supplements to thiazide therapy had little effect on the risk of SCD (odds ratio 0.9:1). Among patients receiving only 1 antihypertensive medication, the risk of SCD was not higher with diuretic treatment than with β-blockers (odds ratio 1:1). Serum K+ concentrations < 3 mmol/L occur infrequently with thiazide diuretics, and when found, are more common with loop diuretics or carbonic anhydrase inhibitors. Profound hypokalemia with serum K+ concentrations < 2.5 mmol/L can lead to diffuse muscle weakness, including diaphragmatic paralysis, rhabdomyolysis, and acute renal failure.

Potassium-sparing diuretics (such as triamterene and amiloride) and aldosterone-receptor antagonists (such as spironolactone and eplerenone) are often used for their ability to conserve K+ when it might otherwise be lost with thiazide and loop diuretic therapy. In certain instances, significant enough K+ retention occurs so as to result in hyperkalemia. Hyperkalemia with K+-sparing diuretics is usually encountered in patients with an existing reduction in their GFR (when also given K+ supplements or salt substitutes), individuals who develop acute-on-chronic renal failure, those on an ACE inhibitor/ARB and/or an NSAID, or in other situations that predispose to hyperkalemia, such as metabolic acidosis, hyporeninemic hypoaldosteronism, or heparin therapy (including subcutaneous heparin regimens).

**Hypomagnesemia**

Loop diuretics inhibit Mg++ reabsorption in the loop of Henle, a site where approximately 30% of the filtered load of Mg++ is reabsorbed. Potassium-sparing diuretics, including spironolactone, diminish the increase in Mg++ excretion that accompanies thiazide or loop diuretic use. Prolonged therapy with thiazides and loop diuretics reduces plasma Mg++ concentration by an average of 5% to 10%, although patients occasionally develop severe hypomagnesemia. Cellular Mg++ depletion occurs in 20% to 50% of patients during thiazide therapy and can be present despite a normal serum Mg++ concentration. This complication is more common in the elderly and in those patients receiving prolonged, high-dose diuretic therapy. Hypomagnesemia often coexists with diuretic-induced hyponatremia and hypokalemia, disorders that cannot be fully reversed until the underlying Mg++ deficit is corrected. In one study, 41% of patients with hypokalemia were also found to have low serum Mg concentrations. Two studies report hypomagnesemia in 19% to 37% of HF patients treated with loop diuretics. The data regarding the association of hypomagnesemia with an increased prevalence of ventricular premature contractions, SCD, and overall cardiovascular survival are conflicting, and a definite causal relationship is lacking. Associated symptoms of hypomagnesemia include depression, muscle weakness, refractory hypokalemia, hypocalcemia, and atrial/ventricular arrhythmias. Many of these abnormalities and, in particular, refractory hypokalemia and hypocalcemia, correct promptly with Mg administration.

**Acid-Base Changes**

Mild metabolic alkalosis is a common feature of thiazide diuretic therapy, particularly at higher doses. Severe metabolic alkalosis is much less frequent and, when it occurs, it is in association with loop diuretic use. The generation of a metabolic alkalosis with diuretic therapy is primarily due to contraction of the extracellular fluid space caused by urinary losses of a relatively HCO3-free fluid. Diuretic-induced metabolic alkalosis is best managed by administration of K+ and/or Na+ chloride, although Na+ chloride administration may be impractical in already volume-expanded patients (such as those with HF).
such cases, a K+-sparing diuretic or a carbonic anhydrase inhibitor, such as acetazolamide, may be considered. Metabolic alkalosis also impairs the natriuretic response to loop diuretics and may play a role in the diuretic resistance occasionally found in the HF patient. All K+-sparing diuretics can cause hyperkalemic metabolic acidosis, which in elderly patients, or in those with renal impairment or HF, can reach a life-threatening level.

**Metabolic Abnormalities**

**Hyperglycemia**

Prolonged thiazide diuretic therapy impairs glucose tolerance and occasionally precipitates diabetes mellitus. Hyperglycemia and glucose intolerance have been linked to diuretic-induced hypokalemia, which inhibits insulin secretion by β cells. These aberrations are compounded by increases in SNS activity, which decreases peripheral glucose utilization. In addition, it has been shown that the development of new-onset diabetes mellitus associated with short-term exposure to HCTZ and atenolol was more common in those with abdominal obesity. The link between thiazide diuretic use and the onset of diabetes has been one not without debate. Many of the studies purporting to establish this relationship were compromised by small numbers of patients, relatively limited follow-up periods, varying definitions of new-onset diabetes, inadequate comparison groups, selection criteria that limited the generalizability of the findings, and study designs that precluded interclass comparisons amongst antihypertensive drug classes.

Diuretic-associated glucose intolerance appears to be dose-related, less common with loop diuretics, and in many instances reversible on withdrawal of the agent, although the data on reversibility in HCTZ-treated patients appear conflicting; thus, long-term thiazide therapy can be viewed as causing only small changes, if any at all, in fasting serum glucose concentration, an effect that might be reversed with the concomitant use of K+-sparring diuretics. Other drug classes, such as ACE inhibitors and ARBs, are associated with a lesser incidence of new-onset diabetes. It remains to be determined the extent to which either of these drug classes reduces the diabetogenic potential of thiazide-type diuretics.

**Hyperlipidemia**

Short-term thiazide diuretic therapy can dose-dependently elevate serum total cholesterol levels, modestly increase low-density lipoprotein cholesterol levels, and raise triglyceride levels, while minimally changing high-density lipoprotein cholesterol concentrations. These lipid effects have been reported to be more apparent in blacks, males, diabetics, and nonresponders to diuretic therapy. In nonresponders to diuretic therapy, the observed increase in lipid values likely relates to the higher diuretic doses used (or required) in such patients. All diuretics, including loop diuretics, cause these lipid changes, with the possible exception of indapamide. The mechanisms of diuretic-induced dyslipidemia remain uncertain, but have been related to insulin resistance and/or reflex activation of the RAS and SNS in response to volume depletion. Supporting this latter notion is the fact that doses of diuretics, which are low enough so as not to activate the SNS, do not increase lipid values; in contrast, higher diuretic doses are more apt to be associated with reflex SNS activation. Long-term clinical trials differ from short-term studies in that cholesterol levels are little changed from baseline after one year of diuretic therapy. Moreover, data from the HDFP indicate that diuretic-treated hypertensive subjects with baseline cholesterol values of > 250 mg/dL experience a decline in cholesterol levels from the second to the fifth year of treatment. Finally, in diuretic-treated SHEP patients, CV outcomes were similar in patients with cholesterol levels < 200 mg/dL and > 280 mg/d; thus, whatever lipid changes that do occur with diuretics are not only short-term, but also are probably of limited clinical significance.

**Hyperuricemia**

Thiazide diuretic therapy increases serum urate concentrations by as much as 35%, an effect related to decreased renal clearance of urate and one that is most prominent in those with the highest pretherapy urate clearance values. Decreased urate clearance may be linked to increased reabsorption secondary to diuretic-related extracellular fluid volume depletion and/or competition for tubular secretion, since both thiazide diuretics and urate undergo tubular secretion by the same organic anion transporter pathway. Diuretic-related hyperuricemia is dose-dependent and is important for 2 reasons: (1) as a precipitant of gout, and (2) relative to its effect on cardiovascular event rate.

First, diuretic-related hyperuricemia does not typically precipitate a gouty attack unless the patient has an underlying gouty tendency or serum urate concentrations routinely exceed 12 s/dL. To this end, in the MRC trial, patients receiving high-dose thiazide diuretics had significantly more withdrawals for gout than did placebo-treated patients (4.4 versus 0.1/1000 patient years). Second, in the SHEP trial, those with a serum uric acid increase ≥ 0.06 mmol/L (median change) in the active treatment group had a similar risk of coronary events as the placebo group, suggesting that diuretic-related hyperuricemia offsets the positive cardiovascular benefits otherwise seen with diuretic therapy—a difference that was not explained by BP effects.

Allopurinol should not be routinely started (as often is the case) for asymptomatic diuretic-related hyperurice-
mia. If a gouty attack occurs in a diuretic-treated patient, the diuretic in use should be temporarily discontinued. Often, a diuretic can be restarted at a lower and sometimes still effective dose. In the process, careful attention should be paid to avoidance of excessive volume contraction. In the patient with preexisting gout and with a need for diuretic therapy, xanthine oxidase inhibitor, allopurinol or febuxostat, can be considered. However, allopurinol (a renally cleared compound) should be used cautiously (dose-adjusted according to level of renal function) in patients receiving a thiazide-type diuretic, since allopurinol hypersensitivity reactions are more common with this combination. A final consideration is what steps to take in a patient with diuretic-related hyperuricemia who is intolerant of allopurinol. In such subjects, febuxostat as an alternative, better-tolerated xanthine oxidase inhibitor can be used and/or the ARB losartan, which is a uricosuric compound, can be safely given with its producing a 1mg/dL reduction in serum uric acid without risk of acute urate nephropathy and/or uric acid stones.

Osteoporosis
Loop diuretic use in older subjects can increase urinary calcium secretion, leading to bone loss. Recently it was shown that the use of loop diuretics in older patients was associated with increase rates of hip bone loss.

Other Adverse Effects

Impotence
Adverse effects of thiazide and thiazide-like diuretics on male sexual function, including decreased libido, erectile dysfunction, and difficult ejaculation, have been reported in several studies with an incidence that varies from 3% to 32%. As an example, in the MRC trial in which 15,000 hypertensive subjects received either placebo, thiazide (bendroflumazide), or a β blocker (propranolol) for 5 years, impotence was 22-fold and 4-fold higher in those receiving bendroflumazide, compared with placebo or a β blocker, respectively. In this trial, impotence was the most frequent reason for withdrawal from antihypertensive therapy. Another smaller trial reported on by Chang et al also found a higher frequency of decreased libido, difficulty in gaining and sustaining an erection, and trouble ejaculating in thiazide-treated patients. Multivariate analysis suggested that these findings were not mediated by either low-serum K⁺ or by the observed fall in BP.

In a study by Wassertheil-Smoller et al, problems with sexual interest, erection, and orgasm were greater among men receiving chlorthalidone compared with those given placebo or atenolol. Of note in this trial, weight loss corrected the problem of chlorthalidone-induced sexual dysfunction. Also, use of a diuretic in combination with other antihypertensive agents has been associated with a higher incidence of sexual dysfunction symptoms than with the use of a diuretic alone. The mechanism by which thiazides affect erectile function or libido is unclear, although it has been suggested that these drugs yield a direct effect on vascular smooth muscle cells and/or decrease the response to catecholamines; however, patients with diuretic-related impotence can respond to sildenafil without any additional drop in BP.

Impotence and decreased libido are the more frequent sexual adverse effects with spironolactone. Gynecomastia, another fairly frequent complication of spironolactone therapy, may be associated with mastodynia and is typically bilateral. One study reported that 91 (13%) of 699 men prescribed spironolactone, alone or in association with another antihypertensive treatment, developed dose-related gynecomastia that was reversible. At daily doses of ≤50 mg, the incidence of gynecomastia was 6.9%; at daily doses of ≥150 mg, the incidence was 52.2%. The sexual adverse effects of spironolactone have been attributed to endocrine dysfunction; spironolactone is structurally similar to the sex hormones and inhibits the binding of dihydrotestosterone to androgen receptors, thus producing an increased clearance of testosterone. Eplerenone is another aldosterone-receptor antagonist which is more selective than spironolactone and is devoid of the sexual adverse effects seen with spironolactone.

Ototoxicity
The association of ototoxicity and loop diuretics is well established. Loop diuretics are direct inhibitors of the Na⁺/K⁺/2Cl⁻ cotransport system, which also exist in the marginal and dark cells of the stria vascularis, which are responsible for endolymph secretion; thus, the ototoxicity of these agents may be indirect, due to changes in ionic composition and fluid volume within the endolymph. Loop diuretic-induced ototoxicity usually occurs within 20 minutes of infusion and is typically reversible, although permanent deafness has been reported. Ototoxicity has been seen with ethacrynic acid, furosemide, and bumetanide with both intravenous and oral administration. The frequency appears to be higher with furosemide than with bumetanide. Patients with renal failure and those receiving concomitant aminoglycoside therapy are at greatest risk of developing ototoxicity.

Ototoxicity is clearly related to both the rate of infusion and to peak serum concentrations. Heidland and Wigand conducted audiometric studies during the infusion of furosemide at a constant rate of 25 mg/min and reported reversible hearing loss in two-thirds of patients. Fries and colleagues found no hearing loss in renal-failure patients receiving between 500 and 1000 mg over 6 hours. Plasma levels of furosemide greater than 50 μg/mL are associated with a greater incidence of auditory disturbances, and Brown and colleagues found patients
Diuretic Therapy in Cardiovascular Disease

Diuretics have been a mainstay in the treatment of various cardiovascular disorders and are first-line therapies in the management of patients with CHF and with systemic HTN. The dosage of each agent is important in maximizing clinical benefit while reducing the risk of adverse effects.

Note: References for this chapter can be found here: www.cvptct3.com
Magnesium, Potassium, and Calcium as Cardiovascular Disease Therapies

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Both deficiency states and abnormalities in the metabolism of the electrolytes magnesium, potassium, and calcium have been considered as etiologic factors in systemic hypertension, ischemic heart disease, heart failure (HF), chronic kidney disease, stroke, atherosclerosis, diabetes mellitus, asthma, and/or a variety of arrhythmias. In a wide range of experimental models, either deficit replacement and/or simple supplementation of these cationic substances have been shown to both prevent and treat these cardiovascular maladies. In this chapter, magnesium (Mg), potassium (K), and calcium (Ca) are discussed as potential therapies for cardiovascular disease (CVD).

Magnesium

Magnesium is the second most common intracellular cation in the human body (see Chapter 30, Alternative and Complementary Medicine for Preventing and Treating Cardiovascular Disease), second only to K, with a free cytosolic concentration approximating 0.5 mmol/L. Magnesium is also the fourth most abundant cation in the body. Magnesium is distributed in 3 major body compartments: approximately 65% in the mineral phase of bone, about 34% in muscle, and 1% in plasma and interstitial fluid. Unlike plasma Ca, which is 40% protein-bound, only ~20% of plasma Mg is protein-bound. Consequently, changes in plasma protein concentrations have less overall effect on total plasma Mg than on total plasma calcium. Magnesium is a cofactor in more than 300 different enzymatic reactions in the body and is of particular relevance to those enzymes that rely on nucleotides as cofactors or substrates. This is because, as a rule, it is not the free nucleotide but its Mg complex that is the actual cofactor or substrate. Magnesium is a critical factor for many cell membrane functions, including the gating of Ca ion channels, mimicking many of the effects of calcium-channel blockade. Magnesium is a necessary cofactor for any biochemical reaction involving adenosine triphosphate (ATP) and is essential for the proper functioning of the sodium (Na)-K and Ca ATPase pumps, which are essential to the maintenance of a normal resting membrane potential. Intracellular Mg deficiency can adversely affect myocardial membrane potential, which then serves as a prompt for atrial and ventricular arrhythmias. Deficiency states or abnormalities in Mg metabolism also play important roles in ischemic heart disease, HF, sudden cardiac death (SCD), diabetes mellitus, pre-eclampsia-eclampsia, and hypertension.

Cardiovascular Effects of Mg

The Mg ion has numerous properties that could theoretically benefit the CV system. Mg modulates the contraction and tone of vascular smooth muscle cells, thus reducing systemic vascular resistance and thereby decreasing blood pressure (BP). Magnesium also dilates coronary and cerebral arteries and is effective in the relief of coronary vasospasm. Magnesium slows heart rate, preserves mitochondrial function and high-energy phosphate levels, and serves as an antiarrhythmic. In addition, Mg possesses both antiplatelet and anticoagulant properties and antiatherosclerotic properties and the ability to improve endothelial function; it also has a retardant effect for the formation of free oxygen radicals. Various Mg deficiency states or metabolic abnormalities can adversely affect CV function, as outlined in Figure 12-1.

Role of Magnesium in Ischemic Heart Disease and Myocardial Infarction

For many years Mg deficiency has been loosely tied to both ischemic heart disease and myocardial infarction.
in patients with MI in several small studies, and an early Mg administration was found to have beneficial effects acute MI in humans date back to as early as the 1950s. Disease associations have been demonstrated in chronic ischemic heart coronary artery disease (CAD), such as diabetes mellitus, hypertension, and hyperlipidemia. A series of basic science studies have since demonstrated that acute ischemia is, in fact, associated with a dramatic increase in the efflux of Mg from the injured myocyte as well an increase in cellular Ca and Na content. Moreover, low myocardial Mg concentrations have been demonstrated in chronic ischemic heart disease. In addition, Mg deficiency has been etiologically involved with many of the established risk factors for coronary artery disease (CAD), such as diabetes mellitus, hypertension, and hyperlipidemia.

Studies in animal models of ischemia and infarction have suggested a beneficial role for Mg. It has been theorized that Mg protects against reperfusion injury by limiting cellular Ca overload. Reports of the use of Mg in acute MI in humans date back to as early as the 1950s. Mg administration was found to have beneficial effects in patients with MI in several small studies, and an early overview on this topic suggested that the morbidity and mortality rate was lower with Mg therapy.

The beneficial effects of intravenous (IV) Mg sulfate (MgSO	extsubscript{4}, 8 mmol over 5 minutes followed by 65 mmol over 24 hours) have failed to demonstrate a significant difference in cardiac arrhythmias compared to a placebo. Left ventricular ejection fraction 72 hour and 1 to 2 months after admission and in-house survival rates were higher in patients who received MgSO	extsubscript{4}. Similarly, a beneficial effect of Mg therapy has been reported in patients with unstable angina pectoris undergoing bypass grafting.

The use of Mg in the preoperative and early postoperative periods is also highly effective in reducing the incidence of atrial fibrillation after elective coronary artery bypass grafting; other studies, though, have been unable to confirm these cardioprotective effects. For example, MgSO	extsubscript{4} given intravenously before, during, and after reperfusion neither decreased myocardial damage
as gauged by an infarct-zone wall motion score index at 30 days nor improved short-term clinical outcome in patients with acute MI treated with direct angioplasty.43

The discrepancy in the results of these studies has dampened the enthusiasm for routine use of Mg in the management of patients with acute MI. The disparate results between these 2 large clinical trials (LIMIT-2 and ISIS-4) remain puzzling. However, the ISIS-4 trial was not specifically designed to test the hypothesis that Mg might limit reperfusion injury, and the time factor in which Mg is given needs to be further clarified. It is also important to determine whether those patients with Mg deficiency are the ones who benefit or whether Mg should be used as a true cardioprotective agent in the non-Mg-deficient individual. At this time, Mg administration cannot be recommended as routine treatment in the management of acute MI.32,44 The most recent of the periodically updated American College of Cardiology/American Heart Association guidelines for the treatment of patients with acute MI that comments on IV Mg therapy states that it should be used only to correct documented Mg deficiency and for the treatment of the torsades de pointes–type of ventricular tachycardia.45 Also, a recent Cochrane Database Review on this topic found that it is unlikely that Mg, even when used in doses > 75-mmol, is beneficial in reducing mortality both in patients treated early and in patients treated late, and in patients already receiving thrombolytic therapy. This review also noted that Mg treatment may reduce the incidence of ventricular fibrillation, ventricular tachycardia, and severe arrhythmias needing treatment, but it may increase the incidence of flushing, bradycardia, and significant hypotension.46

Mg in Diabetes and Congestive Heart Failure
Mg deficiency occurs in association with various medical disorders but is particularly common in diabetes mellitus,1,47-51 CHF,14,52,53 and following diuretic use.54 Recognition of K+ deficiency and/or its correction follows fairly standard guidelines in these conditions; alternatively, the circumstances are much different for Mg, since serum Mg values reflect total body stores poorly.1 Potassium repletion in a hypokalemic patient can prove particularly difficult unless an underlying Mg deficiency is first corrected.51 Hypocalcemia is another common sequela to hypomagnesemia and can prove resistant to treatment owing to hypomagnesemia-related defects in parathyroid release and/or action.55 This form of hypocalcemia responds to small amounts of supplemental Mg but can redevelop unless full repletion of the underlying Mg deficit is accomplished.56 The incidence of diuretic-related hypocalcemia and/or hypomagnesemia in either HF and/or hypertension can be considerably lessened by using potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs).57

Excessive glycosuria is the main cause of Mg deficiency in diabetes mellitus, and its severity is inversely correlated with the level of glycemic control.50 Fat and protein mobilization during acute hyperglycemia-associated metabolic decompensation, among other factors, also plays a role in diabetes-associated hypomagnesemia. Hypomagnesemia can be both a cause and effect of hyperglycemia and is associated with insulin resistance.49,58,59 The prevalence and severity of Mg deficiency can be influenced by other conditions, particularly HF14,52,53 and diuretic use.51,54 In these cases, multiple electrolyte imbalances can evolve simultaneously, predicting poor patient survival.40 Hypokalemia is coupled with a poor prognosis, hypokalemia with increased ventricular dysrhythmias, and hypomagnesemia with arrhythmias and the aforementioned refractory hypokalemia and/or hypocalcemia.52 However, Mg deficiency has yet to be established as an independent risk factor for sudden cardiac death (SCD) or all-cause mortality in such conditions even as it increases the frequency of certain forms of ventricular ectopic activity.61,61a

Arrhythmias
There is an inverse correlation between myocardial irritability and serum Mg concentrations, which is well illustrated in patients with HF.62,63 For example, 0.2 mEq/kg of MgSO4 given over one hour to HF patients reduced ectopic beats in a 6-hour post-dosing monitoring period,62 and MgCl given as a 10-minute bolus (0.3 mEq/kg) followed by a 24-hour maintenance infusion (0.08 mEq/kg/h) also reduced the hourly rate of ectopic beats. Noteworthy was the fact that Mg concentrations 30 minutes and 24 hours after the bolus were 3.6 ± 0.1 and 4.2 ± 0.1 mg/dL, respectively, which is outside the physiologic range for this cation. Oral Mg replacement (15.8 mmol MgCl/day for 6 weeks) has also reduced ventricular irritability during the chronic HF treatment despite the fact that serum Mg changed insignificantly (0.87 ± 0.07 to 0.92 ± 0.05 mmol/L).64 The risk from hypomagnesemia is particularly high in individuals concurrently receiving digitalis, as this association has an additive effect on arrhythmia development.55,66

As previously stated, Mg is an essential cofactor for the Na-K-ATPase enzyme. Mg deficiency limits the function of this enzyme, which, in turn, lowers intracellular K concentrations. As a consequence of this, the resting membrane potential becomes less negative, thereby lowering its threshold for the development of arrhythmias.67-69 In addition to its effect on the Na-K-ATPase pump, Mg has been shown to have significant effects on the several different types of K channels known to exist within cardiac cells.70 Experimental studies in animals offer ample support for the theory that Mg increases cellular resistance to the development of arrhythmias. For example, Mg infusion has been shown to raise the threshold for both
ventricular premature contractions and the induction of ventricular fibrillation in normal denervated (heart-lung preparations) and whole-animal digitalis-treated hearts.\textsuperscript{71-72} Moreover, considerable evidence exists linking Mg deficiency with an increased incidence of both supraventricular and ventricular arrhythmias.\textsuperscript{73,76}

Evidence of the salutary effects of IV Mg in treating both supraventricular and ventricular tachyarrhythmias has been available for many years.\textsuperscript{12,68-69} In addition, numerous anecdotal reports have been published attesting to the utility of Mg in cases of refractory ventricular arrhythmias, although most of these cases were probably associated with Mg deficiency. Interestingly, K-sparing diuretics, compounds that also exhibit Mg-sparing effects, do not carry the same increased risk for SCD observed with non-K-sparing diuretics.\textsuperscript{77} Despite these observations and the theoretical benefits of Mg with regard to the development of arrhythmias, there has been no controlled study designed to evaluate the efficacy of Mg as an antiarrhythmic agent in the treatment of ventricular arrhythmias. Furthermore, it is unclear whether the potential effectiveness of Mg in these situations represents a pharmacologic effect of Mg or whether it merely reflects the benefits of correcting an underlying deficiency state. Whatever its potential role in the management of ventricular fibrillation,\textsuperscript{79,79} supraventricular arrhythmias,\textsuperscript{40} and “run-of-the-mill” ventricular arrhythmias, Mg clearly has a time-honored and proven place in the treatment of ventricular arrhythmias associated with digoxin toxicity.\textsuperscript{85,80,81}

Magnesium in Hypertension

A number of studies have observed some form of hypomagnesemia (serum and/or tissue) in hypertensive patients with significant inverse correlations between Mg concentration and BP.\textsuperscript{4,8,82,83} Dietary Mg appears to be of some importance to this relationship. Epidemiologic studies have linked hypertension and hypertensive heart diseases, as well as ischemic heart disease, with “soft water,” low in Mg, and protection from CV disease with “hard water,” high in Mg,\textsuperscript{3} with an inverse relationship between dietary Mg and the level of BP.\textsuperscript{84-86} This reduction in serum or tissue Mg might be enough to induce peripheral vasoconstriction and thereby raise BP, although the exact mechanism triggering this change in vascular tone remains unknown.\textsuperscript{4,8,82,84-87}

The therapeutic value of Mg in the treatment of hypertension was suggested as early as 1925, when Mg infusions were found to be effective in treating malignant hypertension. Considering the inexpensive nature of Mg and the fact that it is easy to handle, Mg is often considered a theoretically useful adjunctive if not primary treatment modality for hypertension. However, this has not proven to be the case in most patients, although successful drug therapy of hypertension appears to be associated with elevations in the levels of erythrocyte-free Mg.\textsuperscript{88} Ingestion of foodstuffs with a high content of Mg may have an effect on BP, though Mg-enriched diets also typically contain significant amounts of the vasodepressor cations K and Ca.\textsuperscript{93,96} Mg supplementation, however, has not been found to affect BP in a primary prevention of hypertensive study in 698 healthy adults with high normal diastolic BP (80 to 89 mm Hg) treated for 6 months with 360 mg of Mg diglycine.\textsuperscript{91}

However, the results of studies where Mg was used to treat hypertension have demonstrated conflicting results regarding BP reduction.\textsuperscript{92-97} Methodologic issues and heterogeneity of study populations may explain much of the inconsistency in treatment results.\textsuperscript{9} Nevertheless, Mg supplementation may more consistently be of benefit in certain patient subsets, including blacks, obese patients, those with insulin resistance, patients with hypertriglyceridemia, those with severe or malignant forms of hypertension, situations wherein Mg was supplemented long term, and/or hypertensive patients receiving thiazide diuretics.\textsuperscript{85,86} Also, in many forms of secondary hypertension as well as in preeclampsia, Mg is effective in modestly reducing BP.\textsuperscript{99,100} Taken together, these data suggest that Mg is at best weakly hypotensive and unpredictably so. The use of Mg supplementation with diuretics, especially long-acting thiazide diuretics, is advisable to prevent intracellular Mg and K depletion.\textsuperscript{101}

Magnesium in Stroke

Magnesium exhibits a range of neuronal and vascular actions that may ameliorate ischemic central nervous system (CNS) insults, including stroke.\textsuperscript{102-104} Significant neuroprotection with Mg has been observed in different models of focal cerebral ischemia, with infarct volume reduction from 25% to 61%.\textsuperscript{103} Maximal neuroprotection is evident at readily attainable serum concentrations, and neuroprotection is still seen when administration is delayed up to 6 hours and in some cases 24 hours after the onset of ischemia.\textsuperscript{100} Several small trials have reported a reduced incidence of death or dependence with administration of Mg, but confidence intervals are wide, and more definitive data from ongoing large trials are needed before specific recommendations can be made for the use of Mg in the patient with an acute stroke.

Clinical Use of Magnesium

There is a high incidence of Mg deficiency in hospitalized patients, particularly in those with other conditions that may aggravate Mg deficiency, such as poor nutrition and multisystem disorders.\textsuperscript{107} This is particularly important in patients receiving treatment with a myriad of medications, such as diuretics\textsuperscript{14} and aminoglycoside antibiotics,\textsuperscript{108} which increase urinary losses of Mg (Table 12-1).
Difficulty in establishing the diagnosis of Mg deficiency is due to the lack of reliable laboratory tests and the minimal or often absent clinical manifestations accompanying this disturbance. When present, clinical manifestations are quite nonspecific and confined to subtle mental changes or neuromuscular irritability. Tetany, one of the most striking and better-known manifestations of hypomagnesemia, is only rarely seen; instead, less specific signs such as tremors, muscle twitching, bizarre movements, focal seizures, generalized convulsions, delirium, or coma are more common findings. Magnesium deficiency should be suspected when other electrolyte abnormalities coexist since it tends to cluster with abnormalities such as hypocalcemia and hypokalemia. Electrocardiographic (ECG) changes, such as prolongation of the QT and PR intervals, widening of the QRS complex, ST-segment depression, and low T waves as well as supraventricular and ventricular tachyarrhythmias, should also raise the index of suspicion for Mg deficiency.

Once hypomagnesemia is suspected, the measurement of serum Mg concentration continues to be the most routine test used for detection of hypomagnesemia. While a low level is helpful and is typically indicative of low intracellular stores, normal serum Mg values can still be observed in the face of significant body deficiencies of Mg; thus, serum Mg determinations are an unreliable measure of total body Mg balance. Intracellular Mg measurements, as well as other technologies, are available, but remain clinically impractical. A more practical measure of Mg balance is the “Mg loading test,” which at the same time is both therapeutic and diagnostic. This test consists of the parenteral administration of MgSO₄ and a time-wise assessment of urinary Mg retention, which can be accomplished on an outpatient basis in as short a time as one hour. Individuals in a state of normal Mg balance eliminate at least 75% of an administered load. This approach is recommended in all patients with a high index of suspicion for hypomagnesemia, particularly in those with ischemic heart disease or cardiac arrhythmias.

Repletion of an Mg deficit should occur cautiously in anuric individuals and in those with significant renal impairment. In mild deficiency states, Mg balance can often be reestablished by simply eliminating the causative factors and allowing the Mg content in a normal diet to repair the deficit. Parenteral Mg administration, however, is the most effective way to correct a hypomagnesemic state and should be the route used when replacement is necessary during medical emergencies. Total body deficits of Mg in the depleted patient are typically in the order of 1 to 2 mEq/kg of body weight. A recommended repletion regimen is 2 g of MgSO₄ (16.3 mEq) given intravenously over 30 min, followed by a constant infusion rate providing between 32 and 64 mEq/day until the deficit is presumed corrected. A variety of oral Mg salts are available for clinical use (Table 12-2). Mg oxide is commonly

### Table 12-1. Causes of Hypomagnesemia

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<tr>
<th>Gastrointestinal tract losses</th>
<th>Excessive renal excretion</th>
<th>Drug-induced</th>
<th>Nutritional deficiencies</th>
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<th>Redistribution</th>
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<tbody>
<tr>
<td>Chronic diarrhea</td>
<td>Recovery phase of acute kidney injury</td>
<td>(acetazolamide, alcohol, aminoglycosides, amphotericin B, carbenicillin, thiazide-type and loop diuretics, cisplatin, digoxin, mannitol, methotrexate, pentamidine, panitumumab, cetuximab, calcineurin inhibitors, theophylline)</td>
<td>Malnutrition</td>
<td>Hyperaldosteronism</td>
<td>Insulin treatment for diabetic ketoacidosis</td>
<td></td>
</tr>
<tr>
<td>Malabsorption syndromes</td>
<td>Renal tubular acidosis</td>
<td>Magnesium-free enteral or parenteral feedings</td>
<td>Magnesium-free enteral or parenteral feedings</td>
<td>Hyperparathyroidism</td>
<td>High-catecholamine states</td>
<td></td>
</tr>
<tr>
<td>Chronic laxative abuse</td>
<td>Post-obstructive diuresis</td>
<td>Long-term alcohol abuse</td>
<td>Hyperthyroidism</td>
<td>Diabetes mellitus</td>
<td>Major trauma or stress</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Primary renal tubular magnesium wasting</td>
<td></td>
<td></td>
<td>Ketoacidosis (diabetic, alcoholic)</td>
<td>Hungry-bone syndrome</td>
<td></td>
</tr>
<tr>
<td>Specific malabsorption of magnesium</td>
<td>Drug-induced</td>
<td></td>
<td></td>
<td>Hypoparathyroidism</td>
<td>Multiple mechanisms</td>
<td></td>
</tr>
<tr>
<td>Prolonged nasogastric suctioning</td>
<td>Nutritional deficiencies</td>
<td></td>
<td></td>
<td>Syndrome of inappropriate secretion of antidiuretic hormone</td>
<td>Chronic alcoholism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td>Barter's syndrome</td>
<td>Alcohol withdrawal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Redistribution</td>
<td></td>
<td></td>
<td></td>
<td>Major burns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple mechanisms</td>
<td></td>
<td></td>
<td></td>
<td>Liquid protein diet</td>
<td></td>
</tr>
</tbody>
</table>

employed, but this salt form is poorly soluble and acts as a cathartic, thereby decreasing absorption and potentially increasing stool Mg losses. Mg gluconate is the preferred salt form for oral therapy, as this agent possesses a high degree of solubility and does not cause diarrhea. Mg carbonate is poorly soluble and does not appear to be as effective in reversing hypomagnesemia as the gluconate salt. Oral Mg is not recommended for therapy during acute situations, since the high doses necessary almost always cause significant diarrhea. The intramuscular route for Mg administration is a useful but painful means of delivery and should be avoided as long as adequate IV access is available.115

Conclusion (Mg)

Deficiency states or abnormalities in Mg metabolism play important roles in ischemic heart disease, HF, SCD, diabetes mellitus, preeclampsia and eclampsia, and various forms of hypertension.38,116 How best to use Mg in these conditions, either individually or collectively, remains a work in progress. Of similar importance is the effect of diuretic therapy on Mg balance and the difficulty in accurately identifying the presence and degree of a deficiency state. Therefore, presumptive therapy in patients at risk for Mg deficiency-related cardiac complications should be considered.

Potassium

Potassium has a diverse relationship with CV disease.117-117b This includes issues as varied as its dietary intake, such deficiency states as may occur with diuretic therapy, and finally the consideration of specific K membrane channels, which have an important play in CV actions. For example, a relationship between a high dietary intake of K and a reduced risk of CV disease has been suggested by both animal experiments and clinical investigations.118–123 Conversely, diuretic-induced hypokalemia, once present, carries an increased CV risk.122,123 Finally, drugs affecting membrane K channels have also been shown to favorably impact a variety of CV conditions.121

Cardiovascular Effects of Potassium

Potassium in Systemic Hypertension

In experimental animals prone to CV events, high dietary K+ appears to protect against the development of stroke, cardiac hypertrophy, and/or systemic hypertension.125-128 Observational population studies have shown a direct correlation between arterial BP levels and dietary and/or urinary Na/K ratios and an inverse relationship with urinary K.128-131 Urinary Na/K is typically more strongly correlated with BP and CV disease than either Na or K excretion alone.126,132 The negative relationship between K intake and BP is more sharply defined for hypertensives than normotensives and for those with a family history of hypertension.133 In particular, hypertension is more strongly associated with lower K excretion, as relates to both a decreased intake and other factors, in black adults than in white adults with similar Na intake.134,135 Potassium has multiple potential vasodepressor effects in humans that support its use as a BP-lowering substance126,136,137 (Table 12-3). Potassium supplementation in humans has a natriuretic action even in the presence of elevated aldosterone and can decrease cardiac output.126,138,139 Potassium can also increase kallikrein excre-
have observed reductions in 24-hour BP of 6/3 mm Hg intake of K.143,144 This phenomenon is age-independent in is particularly prominent in patients with a low dietary subjects with hypertension.144-146 Fotherby and Potter that similar observations have also been made in elderly hypertensive patients on either a normal or a high Na diet. It is still not known for how long the BP-lowering effect of K is maintained. In diuretic-treated patients who become hypokalemic, K supplementation can correct the deficiency while at the same time further reducing BP.149 Rather than recommending K supplements for the entire population of hypertensive patients or more particularly for those patients at risk for developing hypertension, biological markers need to be identified that might predict a response to K supplementation.

As an example of how this issue is approached on a national basis, the 2009 Canadian Hypertension Education Program Guidelines state that supplementation of K, Ca, and Mg is not recommended for the prevention or treatment of hypertension.

**Potassium in Stroke**

A protective effect of K intake on risk of stroke has been recognized for a number of years, dating to the initial report by Khaw and Barrett-Connor.151 More recently, in the National Health Professionals Study, K intake was also shown to relate inversely to the risk of all forms of stroke.152 This finding was further corroborated in a review by Fang et al of the first National Health and Nutrition Examination Survey (NHANES-I), although the inverse association between K intake and stroke mortality was detected only in black men and hypertensive males in this study.153 The study by Fang et al examined stroke mortality only and did not adjust for dietary factors that might confound the risk relationship between K and stroke—such as dietary intake of fiber, calcium, or vitamin C—which may explain its ethnicity- and gender-related findings.153 As regards the relationship between K intake and stroke, Bazzano et al evaluated data from the NHANES-I Epidemiologic Follow-Up Study and also identified an independent association between low dietary K intake and an increased risk of stroke.123 The relationship between decreased K intake and stroke occurrence is as of yet not mechanistically resolved. It is possible, though not definitively proven, that the

### Table 12-3. Proposed Mechanisms of Blood Pressure Reduction with Potassium

1. Direct natriuretic effect and conversion of salt-sensitive hypertension to salt-resistant hypertension
2. Increased renal kallikrein and eicosanoid production
3. Increased nitric oxide (increased vasodilatory response to acetylcholine)
4. Attenuation of sympathetic activity
5. Decreased amount and effect of PRA and blunted rise in PRA following K+-related natriuresis
6. Direct arterial effect—enhanced activity of Na⁺K⁺-ATPase
7. Enhanced vascular compliance
8. Conversion of non-dipping to dipping nocturnal blood pressure status
9. Genetic inheritability of response
10. Decreased production of reactive oxygen species

PRA = plasma renin activity.

reduction in BP that accompanies a high K intake, and/or a more primary effect in slowing the atherosclerotic process may be important factors in the positive effects of this nutritional factor; however, recent findings in male smokers suggesting that a high Mg intake, more so than a high K intake, may play a role in the primary prevention of cerebral infarction requires that nutritional intake and stroke rate be looked at in a comprehensive manner. Of note, the Food and Drug Administration has approved a health claim that "diets containing foods that are good sources of K and low in sodium may reduce the risk of high BP and stroke."

Potassium in the Prevention of Atherosclerosis

It is currently believed that the development of the atherosclerotic lesion is initiated by the oxidation of low-density lipoproteins (LDLs) within the intimal layer of arteries. Oxidized LDLs are then phagocytized by macrophages and monocytes, leading to the development of the lipid-laden foam cell, which is the prototypic cell of atherosclerosis. These foam cells lead to the formation of the fatty streak, the first microscopically visible element of the atherosclerotic plaque. Fatty streaks are of no clinical significance. In fact, many of them disappear spontaneously. However, certain of the fatty streaks progress into true atherosclerotic, fibrofatty plaques. Thereafter, endothelial cell injury occurs, leading to endothelial cell dysfunction. Subsequently, hemodynamic stress and/or induction of an inflammatory state triggers the release of platelet-derived growth factor from platelets and/or macrophages, which facilitates the transition of a fatty streak to a fibrous plaque. Ultimately, the transformation, proliferation and migration of subintimal smooth muscle cells leads to the development of the atherosclerotic lesion, with its well-described consequences.

Recent data suggest that the protective effect of K on the atherosclerotic process may relate to its effect on the function of those cells involved in lesion formation as described above (Figure 12-2). Increases in K have been shown in vitro to inhibit the formation of free radicals from both vascular endothelial cells and macrophages. This inhibitory effect on free radical formation could lead to a significant reduction in lesion formation in individuals with a high K intake. Indeed, studies in animals have demonstrated reduced cholesterol content in the aorta of rats given large amounts of K.

In addition to its effect on free radical formation, an increase in K intake has been shown to inhibit proliferation of vascular smooth muscle cells and to inhibit both platelet aggregation and arterial thrombosis. Thus, through a variety of mechanisms, a high K intake could, at least theoretically, slow both the initiation and progression of the atherosclerotic lesion as well as the occurrence of thrombosis in the atherosclerotic vessel wall. By these actions, small elevations of K related to high levels of dietary intake could account for the apparent protection against CV diseases of atherosclerotic origin observed in primitive cultures with diets rich in K and low in Na. In contrast to the experiences described above, studies show that elevated K were associated with a higher prevalence of documented CAD and CV mortality.

Electrophysiologic Effects of Potassium

Hypokalemia

Hypokalemia reduces the rate of repolarization of the cardiac cell, leading to a prolongation of the recovery time. In addition, hypokalemia causes the slope of phase 3 of the transmembrane action potential to become less steep. As a result, there is an increase in the interval during which the difference between the transmembrane potential and the threshold potential is small. Consequently, the period of increased excitability is prolonged and the appearance of ectopic atrial and/or ventricular beats is facilitated. A decrease in the extracellular K concentration increases the difference in K concentration across the cell membrane and tends to hyperpolarize the cell during diastole.

Hypokalemia produces a flattening or inversion of the T wave with concomitant prominence of the U wave on
the ECG. This generally occurs without any significant change in the QT interval, although if the T wave fuses with the U wave, the QT interval may prove difficult to measure. When hypokalemia is severe, the QRS complex may widen slightly in a diffuse manner. The ECG pattern of hypokalemia can be quite non-specific, and a similar pattern may be seen following the administration of digitalis, antiarrhythmic agents, or phenothiazines; the pattern may appear also in patients with ventricular hypertrophy or bradycardia.

**Potassium Supplementation**

**General Considerations**

Potassium in its various forms may be administered for multiple reasons. First, in diuretic-treated patients, it is given to replace a total body deficit, which may be as much as 300 to 400 mEq with a serum K value of 2.0-2.5 mmol/L. Such replacement may be followed by a lower rate of CV events as has been observed in a wide-range of diuretic-treated patients. Second, K may be given in a temporizing fashion to patients with hypokalemia attributable to transcellular shifts of K, wherein there is no total body deficit but a perceived need to treat a low serum K value. This is not uncommonly the case in patients with high endogenous levels of catecholamines and, in particular, the beta agonist epinephrine, or in those receiving exogenous beta, agonists, such as formoterol, where there is a suggestion that there is a higher mortality rate. This may be a particular issue with long-acting beta, agonists, such as asthmatics or postcode patients. This may be a particular issue with long-acting beta, agonists, such as asthmatics or postcode patients. Additionally, subjects with salt-sensitive hypertension may see a beneficial BP response to K supplementation. Furthermore, dietary K may be as effective as supplementation, although the data in this regard are not nearly as abundant. Finally, some investigators have proposed that the small elevations of serum K concentration related to high levels of dietary K intake might be enough to inhibit free radical formation, smooth muscle proliferation, and thrombus formation. In this way, the rate of progression to atherosclerotic lesions may be slowed and thrombosis in atherosclerotic vessels diminished. The issues surrounding K replacement in clinical practice have recently been carefully articulated.

**Oral Potassium Therapy**

If a patient consumes a diet that is deficient in K-rich foods (ie, fruits and vegetables), dietary alterations may be sufficient to correct their hypokalemia. Such dietary modifications can provide 40 to 60 mEq/day of K although generally in the form of K citrate or acetate, which is somewhat less effective than K chloride in correcting diuretic-induced hypokalemia. Salt substitutes provide another economical alternative to prescription K+ supplements, although their bitter taste may dissuade patients from their continuous use. They contain 7 to 14 mEq K/g (5 g equals approximately one teaspoon). Potassium supplements are usually given as K chloride, available in either liquid or tablet formulations, although there are other forms as well (Table 12-4). The most common adverse effect of K supplements is gastric irritation. The non-chloride-containing K supplements provide an alternative for those unable to tolerate the K chloride preparations or in whom K depletion occurs in the setting of metabolic acidosis. As severe hyperkalemia can occur as a consequence of oral supplementation, serum K levels should always be monitored during long-term therapy.

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**Table 12-4: Oral Potassium Formulations**

<table>
<thead>
<tr>
<th>Supplements</th>
<th>Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled-release microencapsulated tablets</td>
<td>Disintegrate better in the stomach than encapsulated microparticles; less adherent and less cohesive</td>
</tr>
<tr>
<td>Encapsulated controlled-release microencapsulated particles</td>
<td>Fewer gastric erosions than wax-matrix tablets</td>
</tr>
<tr>
<td>K+ chloride elixir</td>
<td>Inexpensive, tastes bad, poor adherence; few erosions, immediate effect</td>
</tr>
<tr>
<td>K+ chloride (effervescent tablets) for solution</td>
<td>Convenient, more expensive than elixir, immediate effect</td>
</tr>
<tr>
<td>Wax-matrix extended-release tablets</td>
<td>Easier to swallow, more gastrointestinal tract erosions compared with microencapsulated formulations</td>
</tr>
</tbody>
</table>

* Other K+ formulations: K+ gluconate, K+ citrate, K+ acetate, and K+ carbonate, for use in hyperchloremia and hypokalemia. All K+ formulations are readily absorbed.

Adapted with permission from Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: A contemporary review by the National Council on potassium in Clinical Practice. *Arch Intern Med.* 2000;160:2429. Copyright © 1996 American Medical Association. All rights reserved.
an ACE inhibitor, ARB, and, most importantly, an aldosterone receptor antagonist such as spironolactone.\textsuperscript{173}

**Intravenous Potassium Therapy**

Potassium can be administered intravenously in patients with severe hypokalemia and in those hospitalized and unable to tolerate oral preparations. A detailed discussion of the approximation of a K deficit is beyond the scope of this chapter, although in the absence of an independent factor causing transcellular K shifts, the magnitude of the deficit in body stores of K correlates with the degree of hypokalemia. However, in the absence of ECG changes and with a K level > than 2.5 mEq/L, K\textsuperscript+ can generally be safely administered at a rate of up to 10 mEq/h in concentrations as high as 30 mEq/L. However, higher concentrations (200 mmol/L) and rates of delivery (20 mmol/h) have been shown to be well tolerated.\textsuperscript{174,175} Maximum daily administration should rarely exceed 100 to 200 mEq. If the serum K\textsuperscript+ level is under 2 mEq/L and is associated with either ECG changes and/or neuromuscular symptoms, K can be administered intravenously at a rate of 40 mEq/h and at concentrations as high as 60 mEq/L. This should be accompanied by continuous ECG monitoring as well as measurement of serum K levels every few hours. In cases of life-threatening hypokalemia, K should initially be given in glucose-free solutions, as glucose may further lower K by prompting insulin-mediated transcellular shifts of K.\textsuperscript{176}

**Conclusion (K)**

Exogenous K has traditionally been used as a replacement in hypokalemia related to systemic illness and drug use.\textsuperscript{177,178} Not uncommonly, Mg must be given together with K to successfully correct hypokalemia if significant hypomagnesemia coexists. Recent evidence is mounting that K could be used to prevent and/or treat a range of CV diseases, such as hypertension and atherosclerosis, with favorable effects on morbidity and mortality.\textsuperscript{117,177,179}

**Calcium**

Abnormalities in Ca homeostasis, like those in Mg and K, appear to play an important role in the pathogenesis of CV disease.\textsuperscript{82,180}

**Cardiovascular Effects of Calcium**

**Calcium in Systemic Hypertension**

Calcium metabolism is linked closely to the regulation of systemic BP, and Ca supplementation has been proposed as a treatment for systemic hypertension, even though data on the association between dietary Ca intake and BP have been at best inconsistent.\textsuperscript{181} Increased cytosolic concentrations of free Ca found within vascular smooth muscle cells are thought to be responsible for the increased contractility of vessels characteristic of hypertension.\textsuperscript{82} In animal models, acute intracellular Ca\textsuperscript{2+} overload of vascular smooth muscle cells can spark hypercontractility.\textsuperscript{82} Hypertension can then develop if a general increase in systemic arteriolar tone ushers in a rise in peripheral resistance. Furthermore, with progressive elevation of intracellular Ca, the structural integrity of both arterial and arteriolar walls is compromised. Thus, in various animal models, Ca overload initiates lesions of an arteriosclerotic character.\textsuperscript{82,182} The increased concentrations of free Ca within vascular smooth muscle cells could be secondary to alterations in Ca entry, binding, or extrusion from the cells.\textsuperscript{82,180} Studies on human cells have shown changes related to all three of these potential mechanisms. Beyond the probability that an increased intracellular Ca is involved in the pathogenesis of hypertension, there are other recognized relationships between Ca and hypertension.\textsuperscript{183} These include the relationship between serum Ca levels and BP,\textsuperscript{82} the effect of dietary and supplemental Ca on BP, obesity,\textsuperscript{184} and the renal excretion of Ca and/or endogenous parathyroid hormone (PTH) in patients with hypertension.\textsuperscript{98,183}

**Serum Calcium and Hypertension**

Hypertension is more common in the presence of hypercalcemia and, in many but not all studies, there appears to be a direct relationship between the total serum Ca level and BP.\textsuperscript{183} However, the relationship between serum ionized Ca and BP does not appear to be as strong. Nevertheless, there are sufficient data to suggest a vasoconstrictive effect of increasing extracellular Ca levels, presumably by a stimulation of catecholamine release and/or a direct vascular effect.\textsuperscript{185}

**Increased Renal Excretion of Calcium**

Compared with normotensive subjects, hypertensive individuals excrete more Ca both under basal circumstances\textsuperscript{186} and during Na loading.\textsuperscript{187} This may be due to the increase in Ca excretion known to occur following intravascular volume expansion and a resultant rise in Na excretion. Alternatively, it may be secondary to a decreased binding of Ca to kidney cells.\textsuperscript{183} Whatever the precise mechanism, it is known that patients with volume-expanded forms of hypertension excrete Ca in excess.\textsuperscript{183}

**Increased Levels of Parathyroid Hormone (PTH)**

Hypertensive patients tend to have increased levels of plasma PTH, most likely as a homeostatic response to their urinary Ca leak.\textsuperscript{180} Although not nearly as high as those seen with primary hyperparathyroidism, these elevated PTH levels could exert a pressor effect and thereby cause or contribute to hypertension and increased
mortality, a finding that is particularly prominent in women.188-190

Observational Studies and Clinical Trials with Calcium Supplements

There have been numerous reports on observational studies of Ca intake and hypertension, with the majority demonstrating an inverse relationship between dietary Ca’ intake and the level of BPB.198,199,200 However, clinical trials of Ca supplementation (1–2 g/day for up to 4 years) have been less consistent in this regard, with only approximately two-thirds of such studies demonstrating any beneficial effect of supplemental Ca on BP pressure.193,193-194 The rationale for supplemental Ca therapy is based on the assumption that PTH levels are elevated in response to low levels of ionized Ca, resulting from the hypercalciuria seen in some forms of volume-expanded hypertension.199 Additional Ca, by raising plasma calcium, would tend to suppress PTH and thereby lower BP. Indeed, in selected populations of hypertensives characterized by either increased urinary Ca excretion, low ionized Ca, or increased PTH levels, Ca supplements often cause a decrease in BP, albeit one that may not be clinically significant. Increased Ca intake also acts to increase Na excretion in the urine and may lower BP by this mechanism.199 However, in unselected populations of hypertensives, most clinical studies have shown little or no effect of Ca supplementation on BP.193,193,194 Furthermore, even those patients with lower serum Ca and higher PTH levels who may benefit from calcium supplementation may do so with the potential risk of developing kidney stones in a dose-dependent manner, although the risk of calcium oxalate stone formation does not increase significantly in postmenopausal women with osteoporosis given calcium carbonate.195 In contrast, studies in pregnant women have shown that Ca supplementation can provide important reductions in both systolic and diastolic BP and can reduce their risk of developing preeclampsia.196,197

In summary, based on the available data, Ca supplementation or an increased intake of Ca through enriched foods cannot be routinely recommended as a treatment for the general hypertensive population or for the prevention of hypertension. Individual patients, such as pregnant women,198 may benefit from this approach, but there are currently no screening methods for identifying those patients in the general population who would benefit the most from Ca supplementation.

Calcium and Myocardial Contractility

Calcium is of fundamental importance to the process of myocardial contraction.199 The initial event is activation of Na channels, resulting in rapid Na influx and membrane depolarization. As a consequence, voltage-gated, dihydropyridine-sensitive sarcolemmal Ca channels are opened, allowing an influx of Ca into the myocyte. There is a close proximity between sarcolemmal Ca channels and Ca channels of the sarcoplasmic reticulum, which is pertinent in that Ca then stimulates the junctional sarcoplasmic reticulum to release Ca via a ryanodine-sensitive calcium-release channel. The sum of the released Ca represents a substantial increase in the free intracellular Ca, which then diffuses into the myofibrils to combine with troponin. Troponin, in its Ca-free state, inhibits the interaction of myosin and actin. With the rise in intracellular Ca, troponin is bound to Ca, and this inhibition disappears. Actin then combines with myosin, leading to the split of ATP by a Ca-dependent ATPase. The energy that is released from this process is then transformed into mechanical work leading to the interaction of actin and myosin filaments and the resultant shortening of myofibrils.199

Recently, there has been much interest in the cellular abnormalities of Ca homeostasis in the failing human heart. Studies of animal models and myocardium from patients with HF have demonstrated abnormalities of cytosolic Ca handling, myofilament Ca sensitivity, and myocyte energetics. Many of these metabolic abnormalities have been shown to be the result of alterations in the activity or number of myocyte enzymes and transport channels that are important in excitation-contraction coupling.200 While a great deal of research work remains to be done in this area, it is becoming evident that cardiac dysfunction is intimately associated with Ca handling abnormalities in cardiac cells.201 A discussion of agents used to increase Ca at the myosin-actin interaction sites and Ca sensitivity at those sites for the treatment of HF is provided in Chapter 13, Inotropic Agents. Calcium supplementation itself has been poorly studied as a possible treatment for HF.

Calcium Use in Cardiac Arrest

As described above, Ca plays an essential role in excitation-contraction coupling,199 and for many years intravenous calcium chloride was administered in cardiac resuscitation efforts in patients with bradyasystolic arrest.202 It is no longer used for this indication, since no survival benefit has been observed with its use,203,204 and there is evidence that Ca may induce cerebral vaso-spasm205,206 and impact the extent of reperfusion injury in the heart and brain.207 However, when cardiac arrest occurs as a consequence of hyperkalemia, IV Ca is warranted in that it antagonizes the membrane effect of K.

Calcium Use with Arrhythmias

Intravenous Ca can slow the heart rate and has been used to treat tachycardias. The drug must be used cautiously, however, in patients receiving digoxin because it can precipitate digitalis toxicity and ventricular arrhythmias related to afterdepolarization. Afterdepolarizations are membrane potential voltage oscillations that are
dependent on a preceding action potential. There are 2 types of afterdepolarizations: (1) Early afterdepolarizations occur during phase 2 or 3 of the action potential, whereas delayed afterdepolarizations occur after the resting membrane potential has been reestablished (phase 4). (2) Delayed afterdepolarizations have been shown in vitro to occur in the setting of digitalis toxicity or catecholamine excess as well as in hypertrophied myocardium and in Purkinje cells after MI. Delayed afterdepolarizations appear to result from the oscillatory release of Ca ions from sarcoplasmic reticulum during conditions of Ca overload. The clinical significance of delayed afterdepolarization and triggered activity is not completely clear, but this mechanism has been etiologically invoked to explain at least some ventricular arrhythmias. Decreases in extracellular Ca concentration can increase the action potential duration, resulting from an increase in duration and a decrease in amplitude of phase 2 of the cardiac action potential. Hypocalcemia may cause a clinically insignificant decrease in the QRS duration; cardiac arrhythmias are uncommon. Intravenous calcium has been used to treat intoxications from Ca-channel blockers (see Chapter 8, Calcium Channel Blockers) complicated by bradyarrhythmia and hypotension.

Clinical Use of Calcium

A number of Ca salts are available (Table 12-5). Each has a different amount of elemental Ca per administered gram. Calcium supplements are generally administered in conjunction with meals 2 to 3 times daily. The solubility of the various Ca salts is quite varied. For example, calcium carbonate, although attractive as a therapy in that it is 40% elemental Ca by weight, is poorly absorbed, which limits its utility. Calcium citrate and gluconate are Ca salts, which tend to be better absorbed. In cases where hypocalcemia persists despite adequate oral calcium supplementation, a vitamin D supplement may be required to enhance Ca absorption. Intravenous Ca is available as several different salts including calcium chloride (27.2 mg/mL), Ca gluceptate (18 mg/mL), and Ca gluconate (9 mg/mL). Calcium chloride is the preferred formulation because it produces more predictable levels of ionized Ca in plasma, though it can be quite venotoxic and should be used carefully whenever adequate vascular access is in question.

### Table 12-5. Available Forms of Calcium

<table>
<thead>
<tr>
<th>Calcium Salt</th>
<th>Calcium(%)</th>
<th>Calcium (mEq/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium acetate</td>
<td>25</td>
<td>12.5</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>21</td>
<td>10.5</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>6.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Calcium gluconate, dibasic</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>13</td>
<td>6.5</td>
</tr>
<tr>
<td>Calcium phosphate, dibasic</td>
<td>23</td>
<td>11.5</td>
</tr>
<tr>
<td>Calcium phosphate, tribasic</td>
<td>39</td>
<td>19.5</td>
</tr>
</tbody>
</table>


Note: References for this chapter can be found here: www.cvpet3.com

**Conclusion (Ca)**

Except for specific situations, such as Ca entry blocker overdose, pregnancy, and hypocalcemia, Ca is not recommended for the prevention and treatment of CVD. There are recent data to suggest that Ca supplementation could increase the risk of CVD. Dietary Ca intake, however, should be maintained for the purpose of general health maintenance particularly as relates to the issue of osteoporosis.
The life expectancy of patients with congestive heart failure (CHF) is shortened or at best unchanged by long-term exposure to currently available positive inotropic agents. All positive inotropic agents currently available enhance myocardial contractility by increasing intracellular Ca²⁺ concentration. Rising intracellular Ca²⁺ promotes afterpotential depolarizations and, thereby, ventricular arrhythmia and sudden death. Accordingly, the use of positive inotropic agents for the treatment of CHF is not as widespread as in the past and is now limited to specific indications. Moreover, cardiac glycosides, the only oral inotropic agents, are now administered at doses that mostly reverse the autonomic dysfunction associated with CHF and minimally affect myocardial contractility. The low doses of cardiac glycosides that are now routinely recommended are most likely responsible for their neutral effect on mortality. The use of intravenous inotropic agents such as dobutamine and milrinone is limited to patients who, despite optimal manipulation of cardiac-loading conditions, are in a low-cardiac-output state in the absence of severe functional mitral regurgitation. In the presence of severe functional mitral regurgitation, further manipulations of loading conditions can improve forward cardiac output without the risk of triggering ventricular arrhythmia that often plagues positive inotropic therapy. Currently, the use of dobutamine is reserved for patients with severely decompensated CHF who are not improved by intravenous administration of loop diuretics and natriuretic peptides in addition to optimal oral doses of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), nitrates, and digoxin and not concomitantly treated with beta-blocking agents. The aim of short-term dobutamine therapy is to achieve an improvement in left ventricular (LV) performance that is sustained after discontinuation of therapy. The mechanisms that mediate the sustained improvement in LV performance are not fully elucidated but appear to be predominantly related to reversal of peripheral abnormalities and not to sustained increase in myocardial contractility. The metabolic cost of enhancing myocardial contractility with dobutamine leads to a twofold increase in myocardial blood flow in experimental preparations of heart failure (HF). When the presence of severe coronary artery disease hinders the required increase in myocardial blood flow, dobutamine may promote myocardial ischemia and loss of cardiac myocytes, as evidenced by a rising level of troponin I.

Long-term administration of dobutamine is routinely used as a bridge to transplantation in patients who develop a low-output syndrome while awaiting cardiac transplantation. The use of lower doses of dobutamine than those previously administered seems to have reduced the likelihood that the initial improvement in LV performance attenuates with time, a phenomenon referred to as tachyphylaxis.

The indications and aim of short-term administration of milrinone are similar to those of dobutamine (Table 13-1). The metabolic cost of enhancing myocardial contractility with milrinone is offset by the concomitant decrease in LV wall tension that results from its substantial vasodilating properties. Thus, milrinone is the preferred positive inotropic agent in patients with decompensated CHF who exhibit clinical or laboratory evidence of active myocardial ischemia or in patients with known critical coronary artery obstructions. Since milrinone acts downstream from the beta-adrenergic receptors, it is also the preferred inotropic agent for patients with decompensated CHF who are receiving beta-adrenergic blockade. Last, in view of its arteriolar- and venous-relaxing properties, milrinone is preferable to dobutamine in patients with decompensated CHF and severe pulmonary hypertension.
Digitalis Glycosides

Digitalis glycosides have had a long and venerable history in the treatment of CHF. In 1785, William Withering reported on his use of the digitalis leaf as a purported diuretic agent to treat anasarca, presumably due to CHF. Indeed, the major effects of digitalis were thought to be on the kidneys, although important effects on heart rate were noted. Only in the latter part of the nineteenth century did it become apparent that there was a direct action of digitalis glycosides to increase cardiac contractility, while in the earlier part of the twentieth century its effects on the peripheral circulation and the autonomic nervous system were noted.

Pharmacologic Action

Digitalis glycosides have important effects on multiple systems in addition to augmenting myocardial contractility. Electrophysiologically, digitalis glycosides speed conduction in the atrium while inhibiting conduction through the atrioventricular (AV) node. In normal circulation, digitalis glycosides also produce generalized arteriolar vasoconstriction; they also affect the central nervous system (CNS) by enhancing parasympathetic tone and reducing sympathetic nervous system activation. Digitalis sensitizes baroreflexes to decrease efferent sympathetic activity, which acts to reduce sinus node activity and thus reduce heart rate. The increase in baroreflex sensitization also increases parasympathetic tone, while central vagal nuclei are also stimulated. The broad enhancement of parasympathetic activity with digitalis glycosides contributes to slow the heart rate and to control supraventricular arrhythmias. As discussed below, in the failing state of circulation, the effects of sympathetic withdrawal may be dominant so as to reduce arterial vascular resistance, while in the normal circulation, arterial vasoconstriction may be dominant. Integration of these various actions adds to the inotropic activity of digitalis glycosides and their therapeutic usefulness.

The action of digitalis glycosides to increase contractility and alter the electrophysiology of heart muscle occurs through inhibition of the enzyme Na⁺ K⁺-ATPase on the surface membrane of myocardial cells, which results in an increase in the amount of Ca²⁺ to activate contraction. The Na⁺ K⁺-ATPase is an energy-requiring “sodium pump,” which extrudes 3 Na⁺ ions that enter the cell during depolarization in exchange for 2 potassium ions, thus creating an electrical current and a negative resting potential. Contraction is brought about by an action potential that depolarizes the surface membrane of the cell. This action potential is created by a rapid inward current of Na⁺ into the cell that opens Ca²⁺ channels, permitting Ca²⁺ to enter the cell. This, in turn, releases substantially more Ca²⁺ from stores in the sarcoplasmic reticulum within the cell and thereby activates the contractile mechanism by binding to a component of the troponin-tropomyosin system, which had been maintaining the resting state. With Ca²⁺ bound to troponin, actin and myosin can interact to produce force and shortening. The greater the amount of activating Ca²⁺, the greater the force and shortening. When Ca²⁺ is released from troponin and taken up by the sarcoplasmic reticulum, relaxation occurs. The relatively small amount of Ca²⁺ that enters the cell with activation is ultimately removed by an electrogenic Na⁺-Ca²⁺ exchange, which extrudes 1...
Ca²⁺ for 3 Na⁺ ions. When intracellular Na⁺ is increased, less exchange occurs and the net amount of intracellular Ca²⁺ is increased. Thus, by inhibiting the Na⁺ K⁺-ATPase, digitalis glycosides produce a decrease in intracellular K⁺ and an increase in intracellular Na⁺, which increases intracellular Ca²⁺ (Figure 13-1).¹⁵,¹⁶

In general, the main pathway by which all inotropic agents, including digitalis glycosides, increase contractility is by increasing the amount of Ca²⁺ available for activation.¹⁷ This is the case in the normal as well as the failing myocardium. In the failing heart, there appears to be a decrease in the Ca²⁺ released into the cytosol with activation.¹⁸,¹⁹ The inotropic effects of digitalis glycosides are apparently due to an increase in intracellular Ca²⁺ that augments Ca²⁺ stores in the sarcoplasmic reticulum, resulting in a subsequent increase in the extent of myocyte activation.

The electrophysiologic actions of digitalis glycosides are complex, since they are intimately related to autonomic actions as well as K⁺ effects and also the type of cardiac tissue affected.²⁰ In pacemaker cells in the atria, there is little effect except for increased automaticity at toxic levels. In the sinoatrial node and AV conduction system, the refractory period is prolonged. At toxic levels, conduction block can be produced through decreasing resting potential, which results in slowed conduction.²⁰ At toxic levels of glycoside, the Purkinje system may become autonomous due to decreased resting potentials. All of these effects are magnified by decreased extracellular K⁺ so that toxicity is enhanced by a low serum K⁺ and reduced by an increased K⁺.²⁰

At therapeutic levels, the effects of digitalis glycosides reflect the direct electrophysiologic actions of the drug and the indirect actions of neurohormonal stimuli. In the atria, increased parasympathetic tone depresses the refractory period, which overrides the direct digitalis effect to prolong the refractory period. Increased parasympathetic stimulation may reduce automatismo through hyperpolarization of pacemaker cells, while sinus node activity, which is not affected directly by digitalis, is reduced through both increased parasympathetic and decreased sympathetic tone.¹⁵

Toxic levels of digitalis glycosides tend to exaggerate the parasympathetic augmentation, which may actually lead to atrial arrhythmias. Sympathetic activity may increase at toxic levels,²¹ which, added to the direct actions of digitalis glycosides, can potentially result in life-threatening ventricular tachyarrhythmias.

In addition to effects on heart muscle to increase contractility and on vascular smooth muscle to increase contraction, digitalis glycosides exert significant actions on the autonomic nervous system, and these effects may provide a major part of purported beneficial actions,¹³,²²,²³ including both stimulation and inhibition; effects may vary with the dose of drug and underlying state of disease. In addition, short- and long-term effects may differ and alter ultimate efficacy. Relatively low doses of digitalis glycosides increase parasympathetic tone through apparent increased sensitivity of the efferent limb of both ventricular and arterial baroreceptors.¹³ Increased sensitivity of arterial baroreceptors enhances efferent parasympathetic activity while leading to withdrawal of reflex sympathetic tone,²² resulting in sinus bradycardia as well as arterial and venous dilatation. This indirect effect is opposite to the direct effect of glycosides to produce smooth muscle vasoconstriction. Added effects of this sympathetic withdrawal include increased renal blood flow, renin release inhibition, and decreased antidiuretic hormone release.²⁴ Release of acetylcholine by vagal fibers is also thought to inhibit norepinephrine release from nerve endings as well as to reduce beta-receptor responses.²²

The overall effects of digitalis glycoside in the healthy individual are the result of the sum of its actions on the heart, the circulation, and the CNS, so that it is difficult to differentiate direct from indirect effects of glycosides in many instances. Digitalis glycosides increase myocardial contractility directly in both the normal and failing heart, although the effects are relatively greater in the latter situation. However, hemodynamic results differ. In the

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Figure 13-1. Diagram of various inotropic sites of action on and within the cardiac cell. While catecholamines act at cell surface receptors, agents such as amrinone and milrinone (PDE III inhibitors) act within the cell to augment adenylic cyclase. Calcium sensitizers increase Ca²⁺ sensitivity of troponin (Tn) in the contractile system itself.

absence of CHF, where both sympathetic and parasympathetic tone are minimal, digitalis glycosides increase peripheral arterial resistance directly, with a concomitant modest increase in arterial pressure accompanied by a shift in blood volume to the splanchnic bed, with a decline in venous return and cardiac output. In contrast, in CHF with withdrawal of elevated sympathetic nerve activity and increased parasympathetic tone, a fall in peripheral arterial resistance occurs with an increase in cardiac output. In terms of the heart, a decrease in ventricular-filling pressure also occurs while stroke volume increases. These effects are increased by enhancing parasympathetic tone in the failing circulation, which may mimic some of the beneficial effects of beta blockers and unloading agents, as noted elsewhere.

Whether the effects of digitalis glycosides are always beneficial, and if so, at what dose, remains controversial. Studies in the elderly and in patients with myocardial infarction (MI) have demonstrated an increased threat of digitalis toxicity without careful monitoring. However, in the presence of severe failure (New York Heart Association (NYHA) class III), withdrawal of digoxin has resulted in substantial and rapid clinical deterioration despite concomitant therapy, including ACE inhibitors and diuretics. When used in mild CHF, digitalis glycosides have increased ejection fraction (EF), while ACE inhibitors were largely effective only in increasing exercise performance. These beneficial effects are observed whether the patients were in atrial fibrillation or in sinus rhythm. The placebo-controlled multicenter Digitalis Investigation Group (DIG) study sponsored by the National Institutes of Health, comprising more than 7,000 patients with CHF, showed that digoxin did not affect mortality but reduced hospitalization for HF when compared to the control group. Digoxin therapy was also shown to improve both ventricular function and patients’ symptoms.

Digitalis Preparations: Structure, Pharmacokinetics, and Metabolism

All cardiac glycosides contain a ring structure termed an aglycone, to which are attached up to 4 sugar molecules at the C3 position (Figure 13-2). The aglycone itself is formed by a steroid nucleus to which a beta unsaturated lactone ring is attached at the C17 position. Hydroxyl groups are generally found at C3 and C14, while a glucose moiety is generally attached through the C3 hydroxyl group. At present, digoxin and digitoxin are the glycosides that are used clinically; they differ structurally only by the presence in digoxin of a hydroxyl group in the C12 position. Cardiac activity, which correlates with the binding of drug to Na⁺ K⁺ -ATPase on the cell surface sarcolemma, depends on the unsaturated lactone ring, the hydroxyl at C14, and a cis configuration in carbons 8 to 17 in the aglycone ring. As the number of sugars on C3 is reduced, water-solubility increases, and hepatic metabolism rather than renal excretion is favored. Thus, digoxin is excreted primarily by the kidneys while digitoxin is metabolized in the liver. Digitoxin is 90% bioavailable, as compared to 60% for digoxin. A major difference between these agents is that digoxin is 25% protein-bound while digitoxin is 93% bound, such that the half-life of digoxin is 1.7 days and that of digitoxin is quite long at 7.0 days.

At present, digoxin and digitoxin are the only glycosides readily available in the United States, and digoxin is used in most instances. Digoxin has an onset of action from 30 minutes to 2 hours when given orally and 5 to 30 minutes when given intravenously. Peak action occurs in 6 to 8 hours when given orally and in 1 to 4 hours when given intravenously. The plasma half-life of digoxin is 32 to 48 hours, and 50% to 70% is renally cleared as an intact molecule. Renal impairment may delay excretion of digoxin, which may lead to its accumulation and the development of toxicity. Digitoxin has a much longer half-life of several days and is metabolized largely by the liver.

Clinical Use

A loading dose for both digoxin and digitoxin is necessary to reach a stable state rapidly, although with digoxin this is attained in 5 to 7 days with only a maintenance dose. While intravenous digoxin is available, the oral dosage is generally adequate except in urgent settings. The average loading dose of digoxin is 1.0 to 1.5 mg given in divided doses over 24 hours, with a maintenance dose of 0.125 to 0.25 mg a day. These doses are commonly halved in the elderly or in patients with renal insufficiency. The maintenance dose commonly needs adjustment in order to regulate resting heart rate in atrial fibrillation (between 55 and 70 beats per minute). In sinus rhythm, the dose is...
more uncertain, and a desired serum level of around 1.0 mg/mL should be sought.

As noted previously, the beneficial effects of augmented parasympathetic tone and sympathetic withdrawal may be obtained with relatively small doses of digitalis while not encountering potentials of toxicity.36,37 Thus, the issue of dosage of digoxin remains unsettled relative to the benefit sought.

Digitoxin requires a loading dose, since steady state on maintenance dosing is attained only after several weeks. The loading dose is about 1.0 mg in divided doses with maintenance of 0.1 to 0.15 mg a day. The advantage of digitoxin is its hepatic excretion in the presence of renal insufficiency and the lessened impact of poor patient adherence due to its much longer duration of action. Its disadvantage is the long time required for washout should toxicity occur or be suspected.

The serum level of digoxin can be affected by several other drugs.38 Cholestyramine, kaolin-pectin, neomycin, and bran can decrease digoxin absorption. Erythromycin, omeprazole, and tetracycline can increase digoxin absorption. Thyroxine can increase the volume of distribution of digoxin and enhance renal clearance. Quinidine increases serum digoxin levels, doubling levels in most patients over 1 to 2 days. The mechanism remains unclear, but if digoxin intake is not reduced, toxicity can occur. Verapamil reduces renal excretion and can increase serum digoxin levels by as much as 50% over a period of time. Amiodarone and propafenone appear to have a similar effect. With concurrent verapamil, amiodarone, and propafenone use, digoxin doses should be halved. Other antiarrhythmic agents do not exhibit interactions with digoxin.

Both thiazides and loop diuretics may lead to K+ depletion, which augments myocardial sensitivity to digitalis glycosides and leads to arrhythmias, often requiring oral K+ replacement or the use of K+-sparing diuretics such as amiloride. This may lead to arrhythmias of digoxin toxicity at even relatively low serum digoxin levels. Spironolactone and eplerenone, which inhibit the effects of aldosterone and thus serve to save K+, may also have an opposing effect to reduce renal clearance of digoxin, thus raising its serum level.38

In general, digoxin is used most commonly and thus is the focus of the remaining discussion.

**Digoxin in the Treatment of Congestive Heart Failure (CHF)**

As noted above, digoxin has its most beneficial hemodynamic actions when substantial ventricular depression is evident along with CHF. In this circumstance, it augments myocardial performance while reflexly reducing peripheral resistance.38 Slowing of the heart rate—whether via enhanced parasympathetic tone and reduced sympathetic activity to reduce sinus rate or via control of heart rate in atrial fibrillation (as discussed below)—will greatly benefit ventricular filling and reduce pulmonary congestion. Thus the actions of digitalis glycosides affect not only the performance of the depressed myocardium but have a central action to favorably alter the neurohumoral milieu that may impact adversely on the heart and circulation.39

In the treatment of CHF, digoxin is generally employed along with diuretics, beta blockers, and vasodilator agents.40 By reducing peripheral resistance, digoxin and peripheral vasodilators act in a complementary manner.41

In acute HF—characterized by acute pulmonary edema, severe limitations of cardiac output, and perhaps hypotension—more rapidly acting inotropic agents such as intravenous dobutamine or milrinone may be required along with loop diuretics, natriuretic peptides, and vasodilators. This situation may occur in the setting of rapid deterioration of the patient with CHF or following a large MI.42 In this circumstance, the main aim is to increase cardiac output and reduce filling pressure as a setting for longer-term stabilization.

While rapidly acting inotropic agents are being used, digitalization may be begun cautiously for its longer-term effects. In the setting of MI, the situation is more complex.44 Due to a fear that arrhythmias may be induced or oxygen consumption increased, which may be detrimental, digoxin is generally avoided in the first few days following the infarction; in the longer term, however, digitalization, especially if dosing is carefully controlled, may be of value along with other agents, especially ACE inhibitors. In the absence of clear CHF with only lower EF (NYHA class I–II), digitalis has had an apparent adverse effect on long-term mortality42 and should be avoided. For chronic CHF, digoxin is of use over the long term when administered in association with loop diuretics and ACE inhibitors. Benefits are most evident in patients with NYHA Class III or IV CHF. In this circumstance, the response of the circulation is characterized by a decrease in venous pressure and ventricular-filling pressure and an increase in cardiac output. Heart rate is slowed and EF tends to rise, while peripheral resistance falls with little or no change in arterial pressure. These salutary effects are attributed to a combination of augmented myocardial contractility and restoration of baroreceptor sensitivity, which results in enhanced parasympathetic and decreased sympathetic tone. Myocardial oxygen consumption tends to be reduced in HF due to a decrease in heart size and thus ventricular wall tension and a slowing of heart rate.

Earlier concepts supported the view that digoxin was of greatest benefit when atrial fibrillation was present and controlled. It is now clear that efficacy is also present when the patient with HF is in sinus rhythm.33 Withdrawal of
digoxin from such patients has led to rapid deterioration even when both diuretics and ACE inhibitors were used.28,43 While digoxin has been associated with an increase in EF, vasodilators have shown more significant increments in exercise performance.31 These considerations would justify the combined use of these agents. However, whereas the use of ACE inhibitors may well be indicated when the ejection is reduced but symptoms are limited (classes I and II), digoxin should probably be reserved for use with more overt symptoms (classes III and IV).

While digoxin can be given once a day without tolerance or tachyphylaxis, the dose is a matter of issue. In general, a serum level of 0.5 to 0.8 ng/mL is felt to be therapeutic.35 This level may vary from patient to patient, and clear dose-response relation has not been established. Indeed, some of the greatest benefits may be gained from lower doses (eg, 0.125 mg a day), which may induce the neurohumoral benefits of lower sympathetic and higher parasympathetic tone while reducing the incidence of possible toxic adverse effects, as discussed below. There appear to be no adverse effects from digoxin usage in terms of mortality in patients with CHF,24 and substantially increased morbidity is noted when the drug is withdrawn.28,29,32 Effects on mortality with digoxin are complicated by the fact that the nature and progression of the underlying process, which has led to failure in the first place, may well be the ultimate determinant of mortality. If morbidity is reduced substantially with digoxin, as demonstrated,24 a neutral effect on ultimate mortality, as has been demonstrated, would be acceptable. This was demonstrated in the DIG Study, which showed no effect on survival compared to the placebo; a reduction in hospitalizations; and a low incidence of digoxin toxicity.34

Digoxin has been of limited value in the treatment of right-sided HF, as may occur in cor pulmonale or left-to-right shunts. Digoxin also has limited value in the face of acute LV failure due to acute MI. After the first few days of an infarction have passed, longer-term digoxin use has been employed, as it would be in any form of chronic failure, but its effects on mortality have remained controversial. Nevertheless, since mortality may be increased by giving digoxin postinfarction, especially when clear evidence of HF is absent, its use is best reserved for those with overt CHF.

**Digitalis Toxicity**

Digoxin levels can be readily measured in the serum by immunologic techniques, and the therapeutic level is thought to be 1.0 to 2.0–ng/mL.45 Administration of other drugs may change the serum level by altering either absorption or elimination and may contribute to toxicity, as noted previously. For example, verapamil and quinidine may increase plasma levels. Drugs like spironolactone and canrenone can also falsely lower the measured concentration of digoxin.46

The signs and symptoms of digitalis toxicity have been amply described, although some may be very subtle.21,46–48 These include nausea and anorexia, which may lead to weight loss, fatigue, and visual disturbances. Psychiatric disturbances may occur less commonly; they may include delirium, hallucinations, or even seizures. Electrocardiographic alterations occur with variable degrees of AV block and ventricular ectopy. Sinus bradycardia, junctional rhythm, paroxysmal tachycardia with variable AV block, Wenckebach AV block, and ventricular tachycardia leading to ventricular fibrillation may be seen. Such arrhythmias are potentiated by hypokalemia as well as digitalis-mediated enhanced parasympathetic tone. They may be life-threatening in the presence of severe HF and should be avoided or controlled as much as possible.

The diagnosis of digitalis toxicity is suggested by signs and symptoms as well as electrocardiographic alterations and is supported by an elevated serum digoxin level.21,46–49 Certainty of the diagnosis may only be made with drug withdrawal accompanied by subsidence of these findings. With the therapeutic level of digoxin between 1.0 and 2.0 ng/mL, digitalis toxicity levels would be unlikely but not excluded; levels beyond 3.0 ng/mL would suggest toxicity, while levels below 1.5 ng/mL when not complicated by hypokalemia would suggest other problems. It is important to note that only steady-state serum drug concentrations show any correlation with cardiac glycoside toxicity. Thus, for example, in monitoring serum digoxin concentration, the samples should be collected at least 6 to 8 hours after drug administration.48 Nevertheless, there is considerable crossover between patients reflecting variable sensitivity, such that withdrawal of digoxin on suspicion is always advisable for treatment as well as diagnosis. This is especially true since some patients experience profound vagal responses with relatively small amounts of digoxin.

While withdrawal of digoxin and correction of hypokalemia as a potentiating cause may be adequate treatment of digitalis toxicity in most instances, a temporary pacemaker may be required for severe bradycardia or complete heart block. Lidocaine is useful to treat ventricular ectopy or ventricular tachycardia. Dilantin has also been used, while quinidine, which may displace digoxin from binding sites and thus raise serum digoxin levels further, should be avoided. Amiodarone and intravenous magnesium have also been successfully used for this purpose.

In the presence of massive digoxin overdosage, most commonly associated with suicide attempts, digitalis-specific antibodies (digoxin-specific Fab fragments) have been remarkably effective.21,51 In general, such an approach in the usual therapeutic setting is unnecessary.
but provides a backup to more conservative approaches, if they are not proceeding well, such as normalizing serum K+ and withholding digoxin.

Digoxin reduction should be considered and individualized in the elderly patient with renal insufficiency.52 Since electrical conversion is accompanied by ventricular arrhythmias, reduction of dosage 1 to 2 days before the procedure is advisable.

**Catecholamines**

In general, positive inotropism is based on enhancing the delivery of Ca2+ to the contractile system so as to increase force and shortening. Increasing Ca2+ in the serum will affect this transiently, while, as noted previously, digitals glycosides increase Ca2+ for activation by inhibiting sarcotomal Na+ K+-ATPase. Catecholamines increase activating Ca2+ via beta-adrenergic receptors and the adenylate cyclase system (Figure 13-1).

Beta receptors are located in the sarcolemma and comprise a complex structure that spans the membrane.53 The beta receptor is connected with G proteins (Figure 13-1) that either activate (Gs) or inhibit (Gi) a secondary system, adenylate cyclase, which, when activated by Gs, induces the formation of 3’,5’ cyclic adenosine-monophosphate (cAMP). cAMP, in turn, activates certain protein kinases, which lead to intracellular phosphorylation of proteins that enhance both the entry and removal of intracellular Ca2+. When more Ca2+ is provided to the troponin tropomyosin system, a greater interaction between actin and myosin occurs, increasing force and shortening. Increasing the rate of Ca2+ removal from the cytoplasm speeds the rate of relaxation.

In the normal heart, norepinephrine is synthesized and stored in sympathetic nerve endings that invest the entire heart, atria, conduction system, and ventricle.54 When activated, these nerve endings are depolarized and norepinephrine is released from granules in nerve endings into myocardial clefts containing beta-adrenergic receptors, which, when activated, turn on the sequence of events noted above. This not only enhances Ca2+ entry into the myocyte to augment contraction but also phosphorylates phospholamban, which enhances relaxation.55 Subsequently, most of the released norepinephrine is taken back up into the sympathetic nerve endings. Released norepinephrine is also inactivated by 2 enzymes, catechol-O-methyltransferase and monooamine oxidase, and the products are excreted largely by the kidneys.55

In very severe HF, stores of norepinephrine in the ventricle are largely depleted and the sympathetic nerve endings fail to take up norepinephrine normally.56 At the same time, circulating norepinephrine released from peripheral sympathetic nerve endings may be increased, especially in severe failure.57 In less severe HF, the decreased norepinephrine levels may reflect enhanced release due to increased sympathetic nerve activity.58

In both the normal and failing myocardium, activation of the adenylate cyclase system can augment contractility. Agents that do this may be divided into 2 categories. The first comprises the catecholamines (eg, norepinephrine, epinephrine) and their synthetic derivatives (eg, dobutamine, isoproterenol), which act via cell-surface adrenergic receptors.55 The second includes agents that inhibit the breakdown of cAMP by inhibition of phosphodiesterase (PDE) type III (eg, amrinone, milrinone, and enoximone).59 Newer agents, such as levosimendan, increase myofibrillar sensitivity to calcium by stabilizing calcium troponin binding, and others, such as istaroxime, upregulate sarcoplasmic reticulum calcium ATPase (SERCA), leading to enhanced calcium uptake by the sarcoplasmic reticulum during diastole and increased calcium release during systole further augmenting contraction.60,61

Catecholamines constitute an endogenous hormonal system exerting reflex control of the heart and circulation. Their effects depend on localized controlled neural release and receptor specificity in terms of action.

Dopamine is the naturally occurring precursor of both norepinephrine and epinephrine (Figure 13-3).62 While epinephrine is released from the adrenal medulla, norepinephrine is the primary mediator in the heart and peripheral circulation.55

The actions of both endogenous and exogenous catecholamines depend on their activation of specific alpha- and beta-adrenergic receptors (Table 13-2).55 Alpha
Table 13-2. Adrenergic Receptor Activity of Sympathomimetic Amines

<table>
<thead>
<tr>
<th></th>
<th>(\alpha_1)</th>
<th>(\beta_1)</th>
<th>(\beta_2)</th>
<th>Dopaminergic</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>&lt; 2 (\mu g/\text{kg/min})—vasodilation effects on peripheral dopaminergic receptors</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>Initiate with 8–12 (\mu g/\text{min}); maintain 2–4 (\mu g/\text{min})</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>continuous infusion at rate of 1–4 (\mu g/\text{min})</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>0.5–5 (\mu g/\text{min})</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>Start at 2–3 (\mu g/\text{kg/min}) and titrate upward</td>
</tr>
</tbody>
</table>

effectiveness trial of dopamine and norepinephrine in patients with shock, there were no significant differences between patients with shock who were treated with dopamine and those who were treated with norepinephrine. However, dopamine was associated with more cardiac arrhythmias and with a higher mortality rate among patients with cardiogenic shock.

Dobutamine (Figure 13-3) is a synthetic variant of the catecholamines whose structure has been altered to optimize hemodynamic response in the dog, characterized by an increase in cardiac output and a decrease in ventricular-filling pressure with little change in heart rate. Since arterial pressure also rises modestly, peripheral vascular resistance must of necessity fall. The positive inotropic activity of dobutamine is mediated by direct stimulation of beta1 adrenergic receptors in the myocardium (Tables 13-2 and 13-3).

It is unclear why heart rate does not increase concomitantly. The increased arterial pressure resulting from enhanced cardiac output may increase baroreceptor activity and thereby offset the rise in heart rate induced by beta-adrenergic stimulation. Given the capacity of dobutamine to increase cardiac output and reduce filling pressure without substantial heart rate change, dobutamine has been widely used to treat severe acute LV failure in the absence of profound hypotension, which is poorly responsive to diuretics, natriuretic peptides, and vasodilators, as may be seen following a very large MI or in the presence of severe hypotension, the beta1-stimulation of dobutamine may be harmful, and administration of an alpha1-stimulating alpha1-stimulating vasconstrictor such as norepinephrine or a higher dose of dopamine may also be necessary in order to increase arterial peripheral resistance.

Dobutamine infusion is generally begun at 2 μg/kg/min and titrated to optimize cardiac output while reducing LV filling pressure. Tachycardia is carefully avoided so as not to increase ischemia. The effects on myocardial oxygen consumption (MVO2) are complex. Enhanced contractility increases MVO2, while the resulting decrease in LV wall tension tends to reduce it. The net result is most often an increase in MVO2. However, a rise in systolic arterial pressure coupled to a reduction in LV-filling pressure may enhance myocardial perfusion in the absence of tachycardia. The major adverse effects of dobutamine are an excessive increase in heart rate with high rates of infusion and ventricular arrhythmias, both of which may mandate dose reduction and even drug discontinuation.

PDE Inhibitors and Other Agents

The adenylyl cyclase cAMP system can also be activated beyond the beta receptor. Hormones such as glucagon activate the system and can increase myocardial contractility.
Acute despite beta blockade. While useful in overcoming beta-adrenergic blockade if necessary, glucagon may induce gastric atony and nausea, which has limited its more generalized use.

Amrinone and milrinone (Figure 13-4) are prototypes of a class of cardiotonic agents that activate the adenylate cyclase system through inhibition of the enzyme that breaks down cAMP: PDE III. PDE III inhibitors decrease the breakdown of cAMP in the myocardium and increase cyclic guanidine monophosphate (cGMP) in vascular smooth muscle, resulting in an increase in myocardial contractility as well as arterial and venous vasodilatation. Other members of this class of drugs include enoximone. Presently, only amrinone and milrinone have been approved by the US Food and Drug Administration (FDA) for treatment of acute HF.

The mechanisms by which vasodilation occurs is not completely understood. Increased cAMP induces phosphorylation of myosin light-chain kinase, which decreases sensitivity to calcium and calmodulin. In the heart, inotropism may relate not only to increased cAMP-mediated calcium availability for contraction and increased rates of its removal for relaxation but also to increased sensitivity of the contractile system for calcium. Both amrinone and milrinone, which are available as intravenous agents, have substantial ability to augment cardiac output while reducing both right- and LV-filling pressures. The lowering of filling pressures is greater than that seen with dobutamine. Dilatation of the pulmonary vasculature is also a very useful therapeutic effect. Arterial pressure tends to be reduced while an increase in heart rate may occur. Since dobutamine increases cAMP and milrinone reduces its breakdown, the combination of these agents is substantially more potent than either agent alone. When either dobutamine or milrinone is utilized, ectopic activity may be increased, which requires careful supervision in their use.

PDE III inhibitors are also orally active and produce the same hemodynamic improvement as seen with intravenous use. However, in longer-term oral use, increased mortality was seen with the use of milrinone, especially in the presence of class IV HF. This increased mortality may have been due to the relatively short duration of action of this agent (1½ hours half-life) which leads to large peaks and valleys in dosing and concomitant arrhythmias. For the time being, this has vitiated clinical study of these agents, but more stringent control of the use of this class of agents as adjuncts to other agents may ultimately increase their value.

Milrinone

Intravenous milrinone therapy is commonly initiated with a bolus of 50 μg/kg, immediately followed by a continuous infusion at a rate of 0.375 to 0.75 μg/kg/min. Initiation of milrinone therapy with a loading bolus has the advantage of producing immediate hemodynamic improvement. However, the loading bolus may precipitate atrial or ventricular arrhythmias and/or systemic hypotension. In clinical conditions that do not require immediate improvement of LV performance, as in patients with decompensated CHF, initiating milrinone therapy without a bolus is preferable to avoid the risk of precipitating ventricular arrhythmias or hypotension. Whether or not a bolus is administered, IV milrinone produces identical hemodynamic improvement 2 hours after initiation of therapy. The IV bolus of milrinone is particularly useful to evaluate the reversibility of pulmonary hypertension in patients with severe CHF who are being screened for cardiac transplantation. The rapid onset of the direct relaxant effect of milrinone on the pulmonary vasculature is well suited to test pulmonary vascular reactivity. Milrinone decreases pulmonary vascular resistance by increasing cardiac output. In contrast to nitroprusside and nitric oxide, which also decrease pulmonary vascular resistance, milrinone does not affect the transpulmonary pressure gradient. The milrinone-induced increase in cardiac output presumably lowers pulmonary vascular resistance by recruiting accessory vessels in the pulmonary circulation as well as flow-mediated pulmonary vasodilatation.

Besides its positive inotropic action, milrinone substantially increases Ca ATPase activity in the sarcoplasmic reticulum (SR) and thereby LV relaxation in the canine pacing model of HF. Increased SERCA activity is due to a selective inhibition by milrinone of SR membrane-bound PDE III. Increased SERCA activity mediates the well-documented lusitropic action of milrinone. Of note, while the positive inotropic action of milrinone is limited by reduced cAMP and PDE levels in the failing cardiac myocyte, the lusitropic effect is completely preserved due to a compartmentalized modulation of cAMP in the failing heart.

The clinical effects of intermittent or long-term administration of milrinone in patients with severe CHF are controversial. Uncontrolled reports have suggested its usefulness in reducing the use of mechanical LV device
in patients awaiting cardiac transplantation. A recent controlled trial of intermittent administration of milrinone failed to document any clinical benefits. It is clear that not every patient with severe CHF is improved by long-term administration of milrinone. However, most HF/cardiac transplantation specialists have seen few patients who undoubtedly improved while receiving long-term milrinone therapy. Attempts have also been made to use milrinone to increase the tolerability of beta-blocker initiation by counteracting the myocardial depressant action of catecholamine withdrawal. Thus, this mode of therapy should be tailored to the individual response of patients and initiated only when other FDA-approved therapeutic modalities at the appropriate dosages have failed.

**Approaches Under Investigation**

**Other Positive Inotropic Agents Which Inhibit Type III PDE**

Enoximone is an imidazolone derivative that selectively inhibits the SR-associated type III PDE. Thus, the mechanisms of action of enoximone are similar to those of milrinone. However, the relative dose responses of the inotropic and vasodilating actions of enoximone and milrinone differ. At low doses, enoximone exhibits a more balanced inotropic and vasodilator effect than does milrinone. The therapeutic efficacy of enoximone at lower doses than those initially investigated was tested in 3 randomized, placebo-controlled trials in Europe and the United States. The use of low-level inotropic stimulation with enoximone to facilitate initiation of beta-adrenergic blockade in patients with tenuous CHF was studied in the ESSENTIAL study, but failed to demonstrate improvements in all-cause mortality or cardiovascular hospitalization, walk distance on 6-minute walk test, or symptomatic improvement compared with the placebo.

Vesnarinone, a noncatecholamine, nonglycosidic, orally-active 2(IH) quinolone derivative, is a mild inhibitor of type III PDE, but also affects numerous myocardial ion channels, resulting in the prolongation of the opening time of Na⁺ channels and a decrease in the delayed outward and inward rectifying K⁺ current (Figure 13-1). In vitro, it demonstrated significant effects on cytokine production which may theoretically account for some of its observed clinical benefits. Indeed, hemodynamic studies of vesnarinone in humans with CHF show very little effect on ventricular function. Initial placebo-controlled studies in patients with HF suggested a benefit in morbidity and mortality with a 60-mg dose although a subsequent large placebo-controlled, randomized trial of 30 and 60 mg vesnarinone was stopped due to increased mortality with the drug.

Other type III PDE inhibitors that have been under investigation include toborinone and olprinone.

**Calcium Channel Sensitizers**

Levosimendan has both positive inotropic and vasodilator properties and improves LV performance in patients with decompensated HF (Figure 13-5). It increases myocardial contractility via calcium sensitization through a calcium-dependent interaction with troponin. The calcium dependency of levosimendan prevents impairment of myofilament relaxation observed with calcium sensitizers that are calcium-independent. The vasodilator action of levosimendan is attributed to opening of the ATP-sensitive potassium channels. While levosimendan blocks the release of endothelin. While levosimendan is a potent and highly selective inhibitor of PDE III, this action does not contribute, at least at low doses, to its inotropic and vasodilator properties. In contrast to specific type III PDE inhibitors, such as milrinone or enoximone, the positive inotropic effect of levosimendan in cardiac tissue is not attenuated by disease.

In plasma, more than 95% of levosimendan is bound to plasma proteins. Approximately one-third of an IV bolus of levosimendan is excreted via the urine over 24 hours and one-third is excreted in feces over 72 hours. Levosimendan has 2 active metabolites, OR-1855 and OR-1896, that have inotropic, chronotropic, and vasodilator properties and a long duration of action. These metabolites are likely to prolong the hemodynamic effects of levosimendan after disappearance of the parent drug.

Several clinical trials with levosimendan conducted in central Europe and Russia involving patients with acute and CHF appeared promising. Hemodynamic effect of levosimendan was demonstrated with a dose-response relationship with increases in cardiac output and stroke volume, and decreases in pulmonary capillary wedge pressure. In a US study, 146 patients with NYHA class III or IV HF with an EF < 30% were randomized in a...
multicenter, double blind, placebo-controlled study. Intravenous levosimendan was bolused at 6 μg/kg followed by a continuous infusion started at a rate of 0.1 μg/kg/min. The rate was titrated up at hourly intervals over 4 hours to a maximum rate of 0.4 μg/kg/min and maintained at the maximal tolerated rate for an additional 2 hours. Levosimendan caused dose-dependent increases in stroke volume (28%) and cardiac index (39%) that were sustained from the completion of the titration to 6 hours, without a significant increase in heart rate. There was a dose-dependent decrease in pulmonary capillary wedge, right atrial, pulmonary arterial, and mean arterial pressures. On a qualitative level, levosimendan appeared to improve dyspnea and fatigue. In a continuation of the trial published separately, the investigators found that the hemodynamic effects of levosimendan were sustained with continuous infusion of up to 48 hours and that after terminating a 24-hour infusion, the hemodynamic effects were sustained for at least another 24 hours.105

The LIDO110,1145 study was an international, multicenter, double-blind, randomized study designed to compare the efficacy and safety of a 24-hour intravenous infusion of levosimendan and dobutamine in 203 patients with severe low output HF and to clinical outcomes at 31 days. An initial loading dose of levosimendan of 24 μg/kg was infused over 10 minutes, followed by a continuous infusion of 0.1 μg/kg/min for 24 hours. Dobutamine was infused for 24 hours at an initial dose of 5 μg/kg/min without a loading dose with an option to increase the dose if an inadequate response was seen. An adequate response was defined as an increase in cardiac output of at least 30%. The primary endpoint (proportion of patients with hemodynamic improvement as defined by cardiac index increase > 30% and decrease of ≥25% in pulmonary capillary wedge pressure at 24 hours) was achieved in 28% of levosimendan-treated patients and 15% of dobutamine-treated patients (P = .022). Clinical symptoms of dyspnea and fatigue improved to a greater, although nonsignificant, extent in the levosimendan group than in the dobutamine group. Termination of the infusion led to a rapid loss of the effects of dobutamine (<6 hours), but not those of levosimendan. In addition, there was a lower mortality in the levosimendan group at both 30 days (8% versus 17%; P = .049) and 6 months (26% versus 38%; P = .029).

A study conducted by RUSSLAN was a double-blind, placebo-controlled, randomized trial evaluating the safety and efficacy of levosimendan in 504 patients with unstable HF after acute MI.116 Patients receiving levosimendan experienced a lower risk of death and worsening HF than those administered placebo. Mortality was lower at 14 days with levosimendan compared with placebo (P = .031); at 180 days, there was still a difference that neared significance (P = .053). There were no differences among the groups with respect to changes in dyspnea or fatigue. In the worst-rank analysis, patients treated with levosimendan were judged to have experienced worsening dyspnea and fatigue less frequently.

More recent phase 3 studies, however, have demonstrated mixed results. REVIVE (Randomized multicenter evaluation of intravenous levosimendan efficacy versus placebo in the short term treatment of decompensated HF), a 600-patient trial, evaluated the effects of 24 hours of intravenous levosimendan in addition to standard therapy in patients with acute decompensated HF on short-term clinical outcomes.117,117a Over the first 5 days after initial treatment, improvement in clinical status was seen 33% more often as compared to placebo, and worsening HF or symptoms were seen 26% less often in patients receiving levosimendan (P = .015). The duration of hospitalization was shorter in the levosimendan group (7.0 days vs. 8.9 days, P = 0.006). However, there were more episodes of hypotension, atrial fibrillation, and ventricular ectopy as well as a nonsignificant increase in deaths at 14-90 days (15.1% in the levosimendan group vs. 11.6% in the placebo group).

The Survival of Patients with Acute Heart Failure in Need of Intravenous Support trial (SURVIVE) was a randomized trial comparing the effects of levosimendan and dobutamine in patients presenting with acute decompensated HF in need of intravenous inotropic support.118 Levosimendan was administered with a loading dose (12 μg/kg) followed by an infusion (0.2 μg/kg/min infusion for up to 23 additional hours). Brain natriuretic peptide was significantly decreased at 24 hours in the levosimendan-treated patients as compared to dobutamine-treated patients (-631 vs. -397 pg/mL respectively, P < .001). However, all-cause mortality over 180 days was similar in the levosimendan and dobutamine arms (26.1% vs. 27.9% respectively, P = 0.40). Similarly, there were no differences in cardiovascular mortality, hospitalization-free days, dyspnea, or global assessments over the 6 months of follow-up.

A similar agent, pimobendan, in addition to the calcium sensitization described above, has an additional effect of increasing levels of cAMP, due to the inhibitory effect of pimobendan on PDE III.119,120 Because its PDE inhibiting properties occur at concentrations that are similar to the concentrations at which calcium sensitization occurs, some of the calcium/contractility efficiency of pimobendan is offset by its PDE inhibition, which raises intracellular calcium. Pimobendan undergoes hepatic metabolism,121,122 yielding a metabolite, UD-CG212, that is 34 times more potent with plasma half-lives of 0.7 and 1.9 hours, respectively.123,124

Several short-term randomized, placebo-controlled trials of pimobendan in patients with HF demonstrated hemodynamic efficacy and functional status improve-
ment Sasayama et al randomized patients with NYHA class II-III HF treated with digoxin, diuretics, or ACE inhibitors, to placebo or pimobendan (1.25 or 2.5 mg twice daily) for 16 weeks. Pimobendan significantly increased quality of life score and exercise duration and prevented worsening of HF as compared to the placebo. Katz et al randomized 52 NYHA class III-IV HF patients treated with digoxin, diuretics, and ACE inhibitors to either 5 or 10 mg of pimobendan daily for 4 weeks. Hemodynamic assessment revealed a significant increase in cardiac index and decreases in pulmonary capillary wedge pressure and systemic vascular resistance 12 hours after administration of pimobendan and a significant increase in exercise duration at 4 weeks. Kubo et al randomized 198 ambulatory patients with NYHA class III-IV HF treated with digoxin, diuretics, and vasodilators to pimobendan 2.5 mg, 5 mg, or 10 mg daily or placebo for 12 weeks. Patients taking 5 or 10 mg of pimobendan demonstrated a statistically significant increase in exercise duration at 6 and 12 weeks and a significant decrease in HF hospitalizations. Quality-of-life questionnaire scores also improved at 6 and 12 weeks.

Two longer term clinical trials with pimobendan, however, had equivocal results. The Pimobendan in Congestive Heart Failure (PICO) trial was a multicenter, randomized, double-blind, placebo-controlled study of 317 patients with NYHA class II-III HF. The objective was to determine the effects of 2.5 mg and 5 mg of pimobendan daily, in addition to conventional therapy, on the exercise capacity of patients over a period of at least 24 weeks. The investigators found that compared to placebo, pimobendan improved exercise duration by 6% (p = 0.03 for the 2.5 mg group and P = 0.05 for the 5 mg group) but without improvement in quality of life, NYHA class, and with a trend towards an increase in mortality. The Effects of Pimobendan on Chronic Heart Failure (EPOCH) study randomized 276 NYHA class II-III HF patients and followed them for a period of 52 weeks. Patients were started on 1.25 mg of pimobendan twice daily and uptitrated to 2.5 mg twice daily if no clinical improvement was noted. The risk reduction for primary endpoint (HF death, sudden arrhythmic death, and hospitalization for worsening HF) was not statistically significant (P = .63). There was a statistically significant improvement in the number of pimobendan-treated patients who improved their NYHA functional class as compared to placebo (34.6% vs. 20.9%, respectively, P = .001) and a statistically significant increase in left-ventricular ejection fraction (LVEF) and decrease in atrial natriuretic peptide levels in the pimobendan-treated patients. Other studies have demonstrated beneficial effects of pimobendan on reducing neurohormonal (norepinephrine, atrial and brain natriuretic peptide) activation and on inhibiting the production of proinflammatory cytokines. Additional calcium-sensitizing drugs are in development, with some demonstrating promise in animal studies.

### Sodium Channel Modulators

Sodium-channel modulators (BDF 9198) are under investigation for HF. The sensitivity of the failing human myocardium to sodium-channel modulators is increased when compared with nonfailing myocardium, suggesting an alteration in sodium homeostasis in human HF.

### Sarcoplasmic Reticulum Calcium ATP-ase (SERCA) Agonists

SERCA, which mediates uptake of calcium into the SR during diastole, is downregulated in endstage HF myocytes, leading to impaired intracellular calcium cycling and worsening of both lusitropic and inotropic function. Several SERCA agonists are under study.

MCC-135 (Caldaret), studied in intravenous and oral formulations for the treatment of HF, improves calcium homeostasis by enhancing calcium uptake by the SR and inhibiting calcium overload in the myocardium across the sarcolemma, the latter seen with β-adrenergic agonists and PDE inhibitors. Satoh et al studied the effect of MCC-135 in rats with induced diabetic cardiomyopathy and failing ventricular muscle. MCC-135 increased SR calcium uptake and decreased calcium leakage into cardiac myocytes; it also demonstrated lusitropic effects by decreasing time-to-relaxation and time-to-peak tension. Animal studies have demonstrated a cardioprotective effect of Caldaret during ischemia reperfusion by protecting the myocyte against calcium overload through upregulation of SERCA, allowing for enhanced calcium clearance from within the myocyte leading to reduction in infarct size and improved LV function. In humans, several phase 2 trials with MCC-135 have been conducted. In the Caldaret in ST Elevation MI (CASTEMI) study, MCC-135 at a lower dose (57.5 mg), higher dose (172.5 mg), or placebo were administered intravenously over 45 minutes prior to primary percutaneous coronary intervention for ST-elevation MI, followed by a maintenance infusion for 24-48 hours. While there was no difference in early residual LV dysfunction post percutaneous coronary intervention, at 30 days there was a significant decrease in the incidence of LV dysfunction (LVEF ≤ 30%) in patients receiving low and high doses of Caldaret versus placebo (8.0%, 6.9% vs. 17.5%, P < .05 for the 2 comparisons). This difference was more pronounced in patients with anterior wall MI and Thrombolysis in MI grade 0/1 flow. The incidence of an LVEF ≤ 30% was significantly decreased between day 7 and day 30 in patients treated with the 2 doses of Caldaret and was unchanged in the placebo group. The most frequently reported adverse
events were hypotension, bradycardia, angina pectoris, headache, and vomiting; however, in the CASTEMI trial, these effects were equally frequent in both the MCC-135 and placebo groups.139

A similar SERCA agonist undergoing clinical studies is istaroxime (PST-2744).141 This compound inhibits the Na⁺-K⁺-ATPase pump, and also exhibits a stimulatory effect on the SR Ca²⁺ pump (Figure 13-6). Its metabolism is mainly hepatic, with a half-life ranging from 20-48 minutes in animal models.

In animal models at the highest nontoxic dose, contractility (as measured by dP/dt) increased 115% with PST-2744, as compared to 42% with digoxin.142 In a dog model of ischemia-induced LV dysfunction, PST-2744 increased contractility while heart rate, PR interval, and QT interval remained unchanged.143

In the HORIZON-HF trial, Gheorghiade et al examined the dose-dependent effects of PST-2744 on hemodynamics, echocardiographic parameters, and neurohormonal levels in NYHA Class III HF patients.144 At multiple doses, PST-2744 (0.5 - 1.5 μg/kg/min) led to significant decreases in pulmonary capillary wedge pressure and increases in stroke, work index, and systolic blood pressure. There were no effects on right atrial pressure, diastolic blood pressure, mean arterial pressure, or heart rate with any dose. Among the echocardiographic parameters, there was a significant decrease in LV end-systolic volume and end-diastolic volume and a significant increase in deceleration time at the higher doses. There were no significant changes in brain natriuretic peptide, plasma renin activity, aldosterone, blood urea nitrogen, and creatinine. On the electrocardiogram, all doses of PST-2744 resulted in significant decreases in the corrected QT interval. Toxic effects of PST-2744 were studied in guinea pigs; although no specific organ toxicity was noted, ventricular fibrillation was noted at high dosages (intravenous rate > 0.4 mg/kg/min).142 In the HORIZON-HF trial, the main adverse effects of istaroxime were vomiting and pain at the infusion site.144

**Gene Therapy and Stem Cell Therapy**

Besides the novel positive inotropic agents that are currently under investigation, interventions based on gene therapy are now proposed to increase myocardial contractility.145 Using an intracoronary approach to overexpress beta-adrenergic receptors in the myocardium results in a substantial increase in LV performance 1 week after delivery of the β-adrenergic receptor gene.146 Similarly, adenosivar gene transfer of the vasopressin 2 receptor into the myocardium increases contractility in vivo.147 Overexpression of SERCA2a in ventricular myocytes of patients with end-stage HF results in faster contraction velocity and enhanced relaxation velocity.148,149 Diastolic Ca²⁺ decreases in failing cardiomyocytes overexpressing SERCA2a. Overexpression of SERCA2a also normalizes the frequency response of failing myocytes with increasing contraction at increasing frequencies.144 Animal studies have demonstrated that transcoronary gene transfer of SERCA2a increases coronary blood flow and decreases cardio-myocyte size in a type 2 diabetic rat model.150-152 Human clinical trials using an associated adenosivar vector to deliver the SERCA2a gene via a transcoronary approach (CUPID Study) are currently underway.153,154

Stem cell therapies are also being evaluated in patients with HF to accelerate repair and replacement of damaged myocardial cells.155 Various cytokines are being evaluated to augment intrinsic stem cell activity (see Chapter 36, Cytokines and Myocardial Regeneration: A Novel Therapeutic Option for Acute Myocardial Infarction).

**Conclusion**

The need for safe and effective inotropes for the treatment of both acute decompensated HF and chronic HF remain a therapeutic goal. Inotropic agents still play a role in the management of patients with acutely decompensated CHF that is refractory to optimal standard therapy. Their hemodynamic effects are compared with other classes of drugs used to treat acute CHF in Table 13-4. Dobutamine and milrinone can be used in combination with vasodilator drugs and diuretics to maximize hemodynamic benefit. Digoxin, when used properly, is both safe and effective when added to diuretics and ACE inhibitors. Newer inotropes including calcium channel sensitizers, SERCA agonists, and sodium channel modulators work through novel pathways and appear to have a safer short- and long-term profile. Their place in the clinical armamentarium in the management of acute and CHF is still being...
sorted out through ongoing clinical trials. Gene-based therapies, which perhaps offer the greatest opportunity to specifically target and enhance cardiac cellular function, are early in their development.

Although the above-mentioned findings are promising, gene transfer therapy with the aim of enhancing myocardial contractility in patients with CHF will require long-term validation in animals before such an approach can be considered in humans.

*Note: References for this chapter can be found here: www.cvct3.com*

**Table 13-4. Relative Hemodynamic Effects of Agents in Heart Failure**

<table>
<thead>
<tr>
<th>Inotropic agents</th>
<th>Ventricular Filling Pressure</th>
<th>Peripheral Vascular Resistance</th>
<th>Cardiac Output</th>
<th>Blood Pressure</th>
<th>Ejection Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>—</td>
<td>↑</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>↓/NC</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>↑/NC</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>↓/NC</td>
<td>↑↑</td>
<td>↑/NC</td>
<td>↑↑</td>
<td>↑/NC</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↓/NC</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑/NC</td>
</tr>
</tbody>
</table>

**Inodilators**

| Milrinone        | ↓↓                           | ↓↓                             | ↑↑             | ↓             | ↑               |
| Diuretics        | ↓↓                           | ↑/NC                           | ↓/NC           | ↓/NC          | —               |

**Vasodilators**

| NTG—oral         | ↓↓                           | ↓↓                             | —              | ↓/NC          | —               |
| IV               | ↓↓↓                          | ↓↓↓                            | —              | ↓/NC          | —               |
| Nitroprusside    | ↓                            | ↓↓                            | ↑              | ↓             | —               |
| Hydralazine      | ↓/NC                        | ↓↓                            | ↑              | ↑/NC          | —               |
| ACE inhibitors   | ↓↓                           | ↓↓                            | ↑/NC           | ↓             | —               |
| β blockers       | ↓                            | ↓/NC                          | ↑/NC           | NC/↓          | ↑               |

↑ = increase; ↓ = decrease; ACE = angiotensin-converting enzyme; NC = no change; NTG = nitroglycerin.

The organic nitrates and sodium nitroprusside (NP) make up a class of drugs known as the nitrovasodilators. The common denominator of these agents is the production of nitric oxide (NO) within vascular smooth muscle cells and platelets.\textsuperscript{1,4} NO activates the enzyme guanylyl cyclase, which in turn results in an accumulation of intracellular cyclic guanosine 3' 5' monophosphate (cGMP). cGMP in turn activates a cGMP-dependent protein kinase, which has been shown to mediate vasorelaxation via phosphorylation of proteins that regulate intracellular Ca\textsuperscript{2+} levels. Smooth muscle-cell relaxation is induced by cGMP through fluxes in intracellular calcium. In the platelet, increases in cGMP exert an antiaggregatory action and thus decrease platelet activation, resulting in less thrombosis.\textsuperscript{5,6} The predominant actions of the nitrovasodilators are the hemodynamic perturbations resulting from vascular dilatation. In contrast to the majority of vasodilating agents available to the clinician, the nitrates and NP relax the venous capacitance bed as well as arteries and arterioles. The role of the antiplatelet and antithrombotic actions of these compounds remains somewhat controversial, although much recent evidence supports a true benefit for nitrate-induced decreases in platelet-thrombus activation.\textsuperscript{5-8}

Nitroglycerin (NTG) has been used in medicine for well over 100 years. This drug, initially employed for anginal chest pain, became a mainstay of the homeopathic tradition in the early part of the twentieth century.\textsuperscript{9,10} For the past four decades or more, NTG and the organic nitrates have been widely used for the acute and chronic therapy of ischemic chest pain. These compounds have also been employed in patients with acute and post-myocardial infarction (MI) and, importantly, as adjunctive therapy in congestive heart failure (CHF). NP, available only as an intravenous agent, is effective in the treatment of severe or acute hypertension, acute or chronic CHF, and pulmonary edema. As a general rule, NP is not used to alleviate myocardial ischemia, presumably due to excessive vasodilation.

Attenuation of nitrate effects, or nitrate tolerance, is the major obstacle to successful utilization of these drugs in clinical practice. There does not appear to be a significant degree of tolerance to the actions of NP, however. In recent years, a wide variety of nitrate formulations and compounds has become available (Table 14-1), whereas some older nitrate compounds (eg, pentaerythritol tetranitrate) are no longer in use.

The Organic Nitrates

Mechanisms of Action

Cellular

NTG, isosorbide dinitrate (ISDN), and 5-isosorbide mononitrate (ISMN) are metabolized by vascular tissue at or near the plasma membrane of smooth muscle cells of veins and arteries. It was previously believed that nitrates underwent a stepwise dinitration process that resulted in S-nitrosothiol (SNO) via the production of nitrite ion (NO\textsubscript{2}-). However, it now appears that these compounds may form NO directly through an enzymatic process that does not necessarily involve nitrite production as an intermediary.\textsuperscript{11} Furthermore, the obligatory role of SNOs remains controversial. Nitrates can be converted to SNO but are dominantly a direct precursor of SNO. Both NO and SNO can activate guanylate or guanylyl cyclase, leading to the production of cGMP, a second messenger that relaxes vascular smooth muscle cells.\textsuperscript{1,4}

The enzymatic conversion of the nitrovasodilators is not homogenous; NP and SNO appear to require different enzymes or “receptors,” which presumably accounts
for some of the differences in the hemodynamic spectrum among these agents and could also relate to the different susceptibility to tolerance among the organic nitrates, NP or SNO. Intracellular chemical processes also result in NO formation in a nonenzymatic manner; this is much less important for the organic nitrates than for NP. In the platelet, increases in cGMP have been correlated with the degree of vasodilation in the coronary arteries. Presumably, nitrate platelet activation is modulated via cGMP-induced processes.

Nitrate Tolerance
Whereas the precise mechanisms of tolerance remain the subject of intense investigation, it is now known that NO production and cGMP responses become attenuated in the setting of nitrate tolerance. Furthermore, the obligatory role of thiols during nitrate activation remains controversial as regards tolerance phenomena. Although it now seems clear that intracellular glutathione or cysteine stores remain adequate and thiol deficiency per se is not a factor in tolerance development, thiol or –SH groups are critical to SNO and thionitrate formation. Furthermore, a thiol moiety is a component of the enzyme that converts nitrates to NO. Thus, tolerance development may in part be related to thiols within the vascular smooth muscle cell in relationship to the production of SNO or the nitrate enzyme(s) responsible for NO formation. Fung hypothesized that nitrates may oxidize SH proteins, resulting in thionitrate production. This compound can act as a potent oxidant for intracellular proteins, perhaps initiating a cascade of events resulting in abnormalities of nitric oxide synthase (NOS), activation of vasoconstrictors, and interference with the conversion of 1-arginine to NO. Münzel et al. have documented endothelial cell production of free radicals and the subsequent activation of protein kinase leading to endothelin and angiotensin II production. It was also reported that nitrate tolerance was associated with increased activity of the cGMP phosphodiesterase, which decreases cGMP levels necessary for mediating vasorelaxation via phosphorylation of proteins that regulate intracellular Ca\(^{2+}\) levels. These phenomena contribute to a vasoconstrictor milieu, for which oxidant stress is the probable cause.

Nitrate Effects on the Regional Circulations
Administration of NTG or other nitrates in sufficient dosage results in dilatation of veins and large- to moderate-size arteries, with a fall in vascular impedance. At high concentrations, nitrates dilate the smaller arteries, and at very high doses, nitrates can relax arterioles and the microcirculation. Venodilatation is seen at low nitrate concentrations and is near maximal at moderate dosage. Interesting studies by Harrison’s group have suggested that the enzymes responsible for nitrate conversion to NO apparently are not present in the coronary microvessels.

### Table 14-1. Nitrate Formulations: Dosing Recommendations and Pharmacokinetics

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Usual Dose (mg)*</th>
<th>Onset of Action (min)</th>
<th>Effective Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual NTG</td>
<td>0.3–0.6</td>
<td>2–5</td>
<td>20–30 min</td>
</tr>
<tr>
<td>Sublingual ISDN</td>
<td>2.5–10.0</td>
<td>5–20</td>
<td>45–120 min</td>
</tr>
<tr>
<td>Buccal NTG</td>
<td>1–3 bid tid</td>
<td>2–5</td>
<td>30–300 min†</td>
</tr>
<tr>
<td>Oral ISDN</td>
<td>10–60 bid tid</td>
<td>15–45</td>
<td>2–6 h</td>
</tr>
<tr>
<td>Oral ISDN-SR</td>
<td>80–120 once daily</td>
<td>60–90</td>
<td>10–14 h</td>
</tr>
<tr>
<td>Oral ISMN</td>
<td>20 bid&quot;</td>
<td>30–60</td>
<td>3–6 h</td>
</tr>
<tr>
<td>Oral ISMN-SR</td>
<td>60–120 qd</td>
<td>60–90</td>
<td>10–14 h</td>
</tr>
<tr>
<td>NTG ointment</td>
<td>0.5–2.0 tid</td>
<td>15–60</td>
<td>3–8 h</td>
</tr>
<tr>
<td>NTG patch</td>
<td>0.4–0.8 mg/h&quot;</td>
<td>30–60</td>
<td>8–12 h</td>
</tr>
<tr>
<td>NTG IV</td>
<td>5–200 mg/min</td>
<td>immediate</td>
<td>3–5 min</td>
</tr>
</tbody>
</table>

ISDN = isosorbide dinitrate; ISMN = isosorbide mononitrate; SR = sustained release; NTG = glyceryl trinitrate (nitroglycerin).

Higher doses are often required in heart failure; † Effect persists only while tablet intact in buccal cavity; ‡ Two daily doses 7 h apart; § Patch should be removed daily for 10–12 h.

thus limiting the degree of increase in coronary blood flow and decrease in coronary vascular resistance that can be achieved with NTG through dilatation of these small coronary vessels.3,19 NP, on the other hand, directly forms NO in the microcirculation and readily relaxes the resistance vessels18; this can cause a fall in distal coronary bed pressure and may also allow for a coronary steal phenomenon in vessels beyond a coronary atherosclerotic obstruction.20

Nitrates dilate the epicardial coronary arteries and, to a lesser degree, the smaller or distal coronary vessels,3,18,21 Coronary blood flow transiently increases and then declines below baseline as myocardial energy needs decrease. Systemic venous relaxation in the extremities and splanchnic circulation results in sequestration of the circulating blood volume away from the heart and lungs, with a fall in cardiac output.21,22 Nitrates also relax the splanchnic and mesenteric arterial beds, possibly contributing to the decrease in blood flow return to the heart.23

Renal blood flow is marginally affected by NTG; it may decrease to a modest degree.24 The cerebrovascular bed dilates with nitrates, and blood volume in the brain may increase. Thus, these agents are contraindicated when intracranial pressure is elevated.

An important clinical action of nitrates relates to the pulmonary circulation. These drugs consistently lower pulmonary venous and pulmonary capillary pressure, which contributes significantly to their efficacy in heart failure as well as myocardial ischemia. Relaxation of the pulmonary arterial bed is beneficial to subjects with secondary pulmonary hypertension; nitrates do not generally have a useful role in primary pulmonary hypertension.

### Hemodynamic Correlates of Clinical Nitrate Efficacy

Table 14-2 indicates the presumed mechanisms of action for the various clinical conditions for which these

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Clinical Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased myocardial oxygen consumption</td>
<td>Acute attacks and prophylaxis of stable angina pectoris</td>
</tr>
<tr>
<td>Decreased LV dimension</td>
<td></td>
</tr>
<tr>
<td>Decreased LV filling pressure</td>
<td></td>
</tr>
<tr>
<td>Decreased LV systolic pressure</td>
<td></td>
</tr>
<tr>
<td>Decreased vascular impedance</td>
<td></td>
</tr>
<tr>
<td>Increased coronary blood supply</td>
<td></td>
</tr>
<tr>
<td>Epicardial coronary artery dilation</td>
<td></td>
</tr>
<tr>
<td>Coronary stenosis enlargement</td>
<td></td>
</tr>
<tr>
<td>Improved coronary endothelial function</td>
<td></td>
</tr>
<tr>
<td>Dilatation of coronary collaterals or small distal coronary vessels</td>
<td></td>
</tr>
<tr>
<td>Decreased LV and RV dimensions (little data in CHF)</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>Same as above, plus antiplatelet, antithrombotic action</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Same as above, plus antiplatelet, antithrombotic action</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Decreased LV and RV filling-pressure</td>
<td>Systolic dysfunction</td>
</tr>
<tr>
<td>Decreased systemic vascular resistance</td>
<td>Decreased systemic vascular resistance</td>
</tr>
<tr>
<td>Decreased arterial pressure</td>
<td>Decreased arterial pressure</td>
</tr>
<tr>
<td>Decreased PA and RA pressure</td>
<td>Improved endothelial function</td>
</tr>
<tr>
<td>CAD patients: increased coronary blood flow</td>
<td>Decreased mitral regurgitation</td>
</tr>
<tr>
<td>Decreased LV filling pressure</td>
<td>Diastolic dysfunction</td>
</tr>
<tr>
<td>Decreased systolic blood pressure</td>
<td>Decreased LV filling pressure</td>
</tr>
<tr>
<td>Decreased systemic vascular resistance</td>
<td>Decreased systemic vascular resistance</td>
</tr>
<tr>
<td>Decreased LV preload—uncertain importance</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CHF = congestive heart failure; LV = left ventricular; PA = pulmonary artery; RA = right atrial; RV = right ventricular.

agents are prescribed. The traditional view has been that nitrate-induced reversal and/or prevention of myocardial ischemia are due to reductions in myocardial oxygen consumption related to reduced cardiac chamber size and decreased systolic and diastolic pressures within the heart. These alterations are predominately related to the venous and arterial vasodilating actions discussed above. The presumed paradigm is a major nitrate-induced decrease in cardiac work to match available coronary blood supply. However, in recent years much evidence and controversy have contributed to the view that the organic nitrates have important actions in increasing regional or nutrient coronary blood flow, particularly to areas of myocardial ischemia. In addition to epicardial coronary artery dilatation, other mechanisms may interact in a favorable fashion to alleviate or prevent ischemia by directly enhancing coronary blood supply to myocardium downstream from a fixed or dynamic coronary obstruction including (1) prevention or reversal of coronary artery vasoconstriction or spasm, (2) increased coronary collateral size and flow, (3) enhanced distal vessel and collateral caliber when constrictor forces predominate, (4) coronary atherosclerotic stenosis enlargement, and (5) improved coronary endothelial function and arterial vasodilating actions discussed above. The alterations are predominantly related to the venous and arterial physiology found in association with endothelial dysfunction common to heart failure. Enhanced sensitivity to catecholamines is part of the abnormal vascular physiology found in association with endothelial dysfunction; this phenomenon should be viewed as deleterious in heart failure as well as in CAD.

Nitrates, as donors of NO, have been called exogenous endothelium-derived relaxing factor (EDRF) agents; these drugs improve responses to a variety of stimuli in the presence of endothelial dysfunction. Thus, in the patient with CAD, it has been postulated that administration of organic nitrates can partially or completely normalize impaired endothelial-related vasodilation and, presumably but as yet unproved, restore endothelium-modulated antiplatelet activity toward normal. In fact, in some studies vascular responses to administered NTG appear to be more robust in the setting of endothelial dysfunction than in the normal state. Nitrates may also improve endothelial function in heart failure. However, in spite of suggestive favorable data from studies where nitrates are administered acutely, recent reports have suggested that in the presence of unequivocal nitrate tolerance, endothelial dysfunction may actually be induced, perhaps due to impaired eNOS activity and other intracellular perturbations of the NO cascade.

Nitroglycerin: The Exogenous Endothelium-Derived Relaxing Factor (Donor of Nitric Oxide)

Normal endothelial function is vasodilator- and platelet-antiaggregatory. In the presence of even mild coronary atherosclerosis, the dilating actions of the endothelium are impaired in both the coronary and systemic circulations. Thus, diminished vasodilation to physiologic stimuli (eg, shear stress, platelet release products) as well as impaired platelet antiadhesión and aggregation responses are present in many-to-most individuals with clinically evident coronary artery disease (CAD). Vasoconstrictor responses to exercise, mental stress, cold pressor testing, as well as the administration of endothelium-dependent dilator stimuli (eg, acetylcholine, bradykinin) have been well documented in CAD subjects. Diminished availability of NO and prostacyclin, as well as increased endothelin and angiotensin II expression, are common in such individuals; increased superoxide anions plays a major role in inducing the endothelial dysfunction common to CAD. Stenotic constriction or vasomotor-induced narrowing resulting from advanced manifestation of impaired endothelial function may substantially contribute to the precipitation of myocardial ischemia in patients with angina pectoris or silent ischemia NTG prevents or reverses this phenomenon, which has been documented with acetylcholine administration as well as exercise.

In CHF, disordered endothelial vasodilator activity is also common, importantly contributing to the vasoconstrictor state common to heart failure. Enhanced sensitivity to catecholamines is part of the abnormal vascular physiology found in association with endothelial dysfunction; this phenomenon should be viewed as deleterious in heart failure as well as in CAD.

Clinical Indications for Nitrates

Ischemic Heart Disease

The major cardiovascular conditions for which nitrates are effective are listed in Table 14-2. The role of NTG and the other organic nitrates in CAD is well established. Treatment and prophylaxis of anginal attacks as well as prevention of chest pain in chronic angina are the most important uses of these drugs. More problematic is the usefulness of nitrates in uncomplicated acute MI. Although sublingual or intravenous NTG are excellent drugs for recurrent ischemic chest pain, hypertension, or HF in the setting of an acute MI, there is considerable uncertainty as to the benefits of routine 24- or 48-hour infusions of NTG or the use of any nitrate when obvious clinical indications are absent in the setting of acute
In spite of promising but limited animal and human data, the European megatrials GISSI-3 (Gruppo Italiano per lo Studio della Supravivenza nell’Infarto Miocardico) and ISIS-4 (Fourth International Study of Infarct Survival) have failed to show an important role for early administration of nitrates weeks after an acute MI and continued use for the next 5 to 6 weeks.

There is a suggestion that NTG pretreatment in patients undergoing angioplasty can protect the myocardium against ischemia. The mechanism proposed is a delayed preconditioning mimetic effect of NTG.

In a general population admitted for chest pain, routine NTG should not be used to diagnose active CAD, such as myocardial ischemia. Clinical outcomes may or may not reflect active anginal causes of chest discomfort, which may be similar in patients with and without chest pain relief, even with NTG.

**Hypertensive Emergencies**

Intravenous NTG is an effective formulation for lowering blood pressure in the setting of acute hypertension or for the control of mean arterial pressure during a variety of delicate surgical procedures. This agent has been successfully employed for post–coronary bypass patients with elevated blood pressure or hypertensive emergency. Oral nitrates, while used extensively in the early part of this century for hypertension, are not part of contemporary conventional therapy of systemic hypertension, in part because of the appearance of tolerance to the systolic pressure-lowering effects of these drugs. However, this premise is being challenged by new clinical data. A report from France indicates a potential benefit for oral ISDN treatment in systolic hypertension of the elderly.

**Cerebral Vasospasm**

There is also available experimental evidence to suggest that NTG may be useful in reversing cerebral vasospasm in patients with subarachnoid hemorrhage.

**Congestive Heart Failure**

Nitrates are underutilized in CHF. In intravenous, topical, or sublingual forms, they are useful as a treatment for acute pulmonary edema in conjunction with diuretics. With symptomatic CHF, nitrates are useful for improving exercise tolerance and have been combined with angiotensin-converting enzyme (ACE) inhibitors for the treatment of symptomatic HF. Large doses of nitrates are often required in these patients. Nitrate resistance has been described in advanced CHF.

Concurrent hydralazine therapy with nitrates appears to prevent the development of hemodynamic tolerance in CHF. It is now recognized that hydralazine may act as an antioxidant, reducing the oxidant effect of nitrates, thereby preventing tolerance. Clinical studies in patients with CHF have demonstrated that the combination of oral ISDN and hydralazine has clinical benefit without causing tolerance. In the first Veterans Administration Cooperative Chronic Heart Failure mortality trial (V-HeFT-I), the combination of ISDN 40 mg 4 times daily and hydralazine 75 mg 4 times daily reduced mortality compared to the placebo and the alpha blocker prazosin. However, the combination proved to be less effective on mortality in the subsequent V-HeFT II than monotherapy with enalapril.

In a retrospective analysis of both V-HeFT I and II, it was observed that the ISDN–hydralazine combination was more effective in black patients than white patients. It was suggested that blacks have decreased endothelial cell vasomotor responses and decreased NO responsiveness compared to whites and therefore would be more favorably affected by NO availability provided by an ISDN–hydralazine combination. The African-American Heart Failure Trial (A-HeFT) compared the combination of up to 40 mg of ISDN and 75 mg of hydralazine used 3 times daily to the placebo in black patients with moderate to severe HF receiving standard HF treatment. Mortality was reduced significantly by 43% compared to the placebo (Figure 14-1). In addition, active treatment was associated with a lower incidence of first hospitalizations for HF and an improved quality of life score. With active treatment, there was a higher incidence of dizziness, nausea, vomiting, and hypotension compared to the placebo.
Based on the results of A-HeFT, the FDA approved an ISDN-hydralazine combination pill (BiDil) for use as add-on therapy to standard treatment for self-identified black patients with moderate to severe HF.\textsuperscript{75-77} However, there is little experience with the combination in class IV HF patients. There is evidence that the combination may be useful for treating diastolic dysfunction in hypertension-induced diastolic HF.\textsuperscript{78}

### Nitrate Formulations and Nitrate Pharmacokinetics

Three organic nitrate compounds—NTG, ISDN, and ISMN—are currently used throughout the world and have been shown to provide benefits in angina and CHF. There does not appear to be any difference in clinical efficacy among these compounds. Choice of formulation, dosage, use of a tolerance-avoidance regimen, and physician experience and bias are major factors influencing which nitrate is prescribed for which patient. Tolerance is a problem for all nitrate formulations except for sublingual NTG and ISDN or transmucosal NTG, which are not designed to be administered continuously. Appropriately designed dosing regimens can prevent the appearance of significant nitrate tolerance, but limited available data suggest that attenuation of nitrate’s hemodynamic action may begin to appear within hours of nitrate administration (Tables 14-1 and 14-3).

### Nitroglycerin

The classic prototype nitrate is NTG, which is available in many formulations (Table 14-1). This molecule has a very short half-life of several minutes; cessation of an intravenous NTG infusion or removal of a transdermal patch results in a rapid fall in NTG plasma levels within 20 to 40 minutes. The metabolism of NTG occurs within the vascular wall. Veins take up NTG more avidly than arteries. It is not useful or practical to measure NTG plasma levels in clinical practice; this assay is technically difficult, and the relationship between plasma NTG level and effect changes as tolerance develops. Early studies with sublingual NTG suggest that the therapeutic NTG level is at least 1 ng/mL.\textsuperscript{70} Plasma concentrations with the NTG patch are substantially lower. The minimum recommended dose of the patch is 0.4 mg/h, with larger amounts often being more effective, particularly in HF.

Several studies confirm a true anti-ischemic action of these agents,\textsuperscript{79-81} which must be administered in an on-off fashion. The patch should be applied continuously for only 12 to 14 hours each day. Rebound angina and vasoconstriction are possible adverse effects of intermittent therapy.\textsuperscript{82,83} Several dosing systems for NTG have been available to physicians but are not widely used and may not be available in many pharmacies. These include the buccal or transmucosal formulation, NTG ointment, and oral sustained-release NTG capsules. Ointment and buccal NTG are effective but difficult for patients to use. NTG ointment is recommended for hospitalized or homebound patients with nocturnal angina or symptomatic CHF. Oral NTG has virtually no reliable data supporting its effectiveness.

### Isosorbide Dinitrate

ISDN is perhaps the most widely used long-acting nitrate in the world. It is available in short-acting and sustained-release formulations; the majority of clinical studies in the literature have employed short-acting oral ISDN. Table 14-4 outlines the relevant pharmacokinetic features of ISDN and ISMN. Sustained-release ISDN should be used only once daily. In Europe, intravenous ISDN is commercially available. Sublingual or chewable ISDN products have long been used for acute attacks of chest pain or angina prophylaxis, but these formulations are infrequently prescribed in the United States.

When ISDN is administered, the parent compound is converted to 2 active metabolites, 2- and 5-isosorbide mononitrate.\textsuperscript{86} The latter is a pharmacologically active molecule that is commercially synthesized and available in short-acting and sustained-release formulations. A dose of the parent compound ISDN results in plasma concentrations of all 3 molecules.\textsuperscript{86} ISDN has a short half-life of 50 to 60 minutes and rapidly disappears from the circulation. ISMN has a much longer half-life of 4 to 6 hours and accounts for the protracted nitrate effects following administration of ISDN. Approximately 50% to 60% of

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**Table 14-3. Factors That Influence Nitrate Tolerance**

<table>
<thead>
<tr>
<th>Induce Tolerance</th>
<th>Prevent Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous or prolonged nitrate</td>
<td>Intermittent dosing exposure (eg, transdermal patches, intravenous)</td>
</tr>
<tr>
<td>Large doses</td>
<td>Small doses</td>
</tr>
<tr>
<td>Frequent dosing</td>
<td>Infrequent dosing</td>
</tr>
<tr>
<td>Sustained-action formulations</td>
<td>Short-acting formulations</td>
</tr>
<tr>
<td>No or brief nitrate-free interval</td>
<td>Provision of adequate nitrate-free interval</td>
</tr>
</tbody>
</table>

ISDN is converted to 5-ISMN. Thus, although only 20% to 25% of ISDN itself is bioavailable when taken orally, a substantial component of the administered dose becomes pharmacologically active as 5-ISMN (Table 14-4).

Isosorbide 5-Mononitrate

The 5-mononitrate is the most recent nitrate formulation released in the United States. It was initially available only in the short-acting form; to avoid tolerance, short-acting 5-ISMN is recommended to be taken in a twice-daily regimen, with 7 to 8 hours between doses (Table 14-1).66,67 Earlier Scandinavian and European experience suggested that a q 12 hours regimen was satisfactory to avoid tolerance, but American trials with this compound indicated that a longer overnight interval was necessary to avoid attenuation of clinical effectiveness.66,67 Sustained-release 5-ISMN is effective on a once-daily basis.68 A minimum of 60 mg per day is recommended; a large American multicenter trial suggested that higher doses, such as 120 or 240 mg daily, may be necessary for sustained anti-anginal efficacy without tolerance.69 A 50-mg once-daily, immediate-release/sustained-release ISMN formulation is now available, which appears to maintain antianginal efficacy without tolerance.69,70

Suggestions for Nitrate Dosing

It is important to start nitrate therapy with small doses and to carefully increase to a predetermined endpoint or maximally tolerated amount over time. Headache and dizziness are the limiting symptoms with nitrate administration. Some individuals are extremely sensitive to organic nitrates; others experience few or no side effects. Syncope or severe dizziness, especially with new nitrate therapy, is well known.

Many, if not most, patients are underdosed with long-acting nitrates, at least with respect to clinical trial data. For instance, 10 mg of oral ISDN, 30 or 60 mg of ISMN-SR, or 0.2 to 0.4 mg/h of the NTG patch are less likely to be clinically effective doses. If the angina is well controlled with these relatively low doses, it is satisfactory to continue such a regimen. However, the physician should be sure that the more desirable clinical response has been achieved; if so, higher amounts of the nitrate should be tried. In chronic CHF, the dosage of nitrates used alone to achieve a significant hemodynamic effect is usually considerably higher than in patients with normal LV function. With the hydralazine-ISDN combination formulation, the recommended initial dose is 1 tab 3 times daily (37.5 mg hydralazine/20 mg ISDN), titrated up to 2 tabs 3 times daily; if the drug is not tolerated, ½ tablet 3 times a day can be used.

Table 14-4. Pharmacokinetics of Isosorbide Dinitrate and 5-Mononitrate

<table>
<thead>
<tr>
<th></th>
<th>ISDN</th>
<th>5-ISMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>20–25%*</td>
<td>100%</td>
</tr>
<tr>
<td>Half-life</td>
<td>30–60 min</td>
<td>4–5 h</td>
</tr>
<tr>
<td>Metabolites</td>
<td>2-ISMN, 5-ISMN</td>
<td>None</td>
</tr>
<tr>
<td>Plasma levels</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Formulations*</td>
<td>SL, oral, oral sustained release</td>
<td>Oral, oral extended release</td>
</tr>
</tbody>
</table>

*Extensive hepatic first-pass effect.

\% Only oral and sublingual compounds available in the United States.

Often patients who are troubled with nitrate headaches with initial nitrate dosing can be effectively treated with analgesics (aspirin, acetaminophen) to control the headache symptoms, which usually decrease or disappear over time. Nitrate hypotension is best handled by reducing the dose; concomitant therapy with calcium channel antagonists, hydralazine, phosphodiesterase inhibitors, ACE inhibitors, or hypovolemia increase the likelihood of dizziness and/or syncope owing to low blood pressure following nitrate administration.

Adverse Effects

In addition to headache and hypotension-related dizziness or even syncope, nitrates can occasionally cause nausea. As noted, patients with CHF tolerate large doses of nitrates surprisingly well. Patients with HF often require large doses of a nitrate. Rare cases of nitrate syncope have been reported, as have marked vasovagal responses and even atrioventricular block. Nitrates should be given with great care in the setting of right ventricular infarction complicating inferior MI, as these drugs lower right ventricular-filling pressure and can further depress cardiac output. Nitrates should also be used with greater care in patients receiving phosphodiesterase-5 inhibitors such as sildenafil because of the possibility of a major hypotensive effect with this combination.92 Intravenous NTG has been suggested to interfere with the actions of heparin,
resulting in increased heparin requirements to achieve the desired prolongation of the activated clotting time.\textsuperscript{95–97} This interaction remains controversial. One report suggests that NTG may impair tissue plasminogen activator activity during thrombolysis,\textsuperscript{96} and an experimental report suggested that NTG might have adverse effects on atherosclerotic plaque instability by activating matrix metalloproteinase activity.\textsuperscript{97}

These effects may explain the lack of a positive association between NTG therapy and beneficial effects on plaque progression or coronary event rates, despite nitroglycerin's vasodilator activity.\textsuperscript{97} In general, the organic nitrates are well-tolerated drugs with little serious adverse sequelae. Headache, the most problematic symptom related to nitrate therapy,\textsuperscript{98} can be controlled in many patients. However, a possible 20% to 30% of individuals cannot tolerate long-acting nitrate therapy. Doses for CHF often need to be quite large, but careful administration is necessary to avoid syncope.

The hydralazine-ISDN combination is associated with a higher rate of dizziness, nausea and vomiting, headache, hypotension, sinus congestion, and tachycardia when compared to the placebo in HF patients receiving other standard therapy.

### Nitrate Tolerance

Clearly, the most vexing issue regarding nitrate therapy is the attenuation of nitrate efficacy with repeated dosing. This subject has an enormous literature\textsuperscript{12–16,99–116} and continues to engender considerable controversy. However, almost all experts agree that tolerance will predictably appear when protolerant dosing regimens are utilized. Dozens of high-quality clinical and basic research studies underscore the magnitude of this problem. The rapid onset of tolerance can be substantiated after several repeated doses of oral or transdermal nitrate given with too short an interdose interval.\textsuperscript{104,105} Major attenuation of nitrate action in angina has been repeatedly demonstrated with continuous 24-hour application of transdermal NTG;\textsuperscript{97,107} in fact, an antianginal effect can no longer be detected by the second day of continuous patch therapy, even when very large doses are used.\textsuperscript{101} Similar findings have been demonstrated for intravenous NTG, as well as the oral agents ISDN and ISMN, when these drugs are not administered in a tolerance-avoidance regimen. Table 14-3 lists the cardinal principles for avoiding nitrate tolerance. Table 14-1 outlines the recommended dosing schedules for the available nitrates. Intravenous NTG administered for the acute ischemic syndromes of unstable angina or acute MI should not be abruptly terminated so as to avoid tolerance; rebound phenomena are well known, and sudden withdrawal of intravenous NTG may be dangerous in this setting, even if some degree of hemodynamic tolerance is present.

The conundrum of nitrate tolerance remains incompletely resolved. Data confirm that endothelial vasodilator function is markedly impaired during nitrate tolerance.\textsuperscript{38–42,109,110,115,116} The precise cause of this abnormality remains controversial. Abnormalities of L-arginine availability, NO synthase function, and particularly excessive oxidant stress have all been postulated as potential mechanisms, based on a variety of experimental observations.\textsuperscript{38–42,103–115,118} Table 14-5 lists a variety of hypotheses regarding nitrate tolerance. Older research suggested that nitrate tolerance is related to poor sulphydryl or thiol group availability, plasma volume expansion, and/or neurohumoral activation of the renin-angiotensin system. Several studies suggest that antioxidants, such as hydralazine and vitamin C, can prevent or reverse nitrate tolerance;\textsuperscript{112–114,119} however, this approach remains as yet an unproven hypothesis. There is some evidence that not all organic nitrates have a comparable ability or potential to induce nitrate tolerance.

Much of the available data suggest that during experimentally-induced nitrate tolerance, there is an enhanced

### Table 14-5. Some Proposed Mechanisms of Nitrate Tolerance

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphydryl depletion: inadequate generation of reduced –SH or cysteine groups required for organic nitrate biotransformation to NO.</td>
</tr>
<tr>
<td>Desensitization of soluble guanylate cyclase; impaired activity of the enzyme guanylate cyclase.</td>
</tr>
<tr>
<td>Counter-regulatory neurohormonal activation: nitrate-induced increases in catecholamines, arginine vasopressin, plasma renin, aldosterone, and angiotensin II activity, with resultant vasoconstriction and fluid retention.</td>
</tr>
<tr>
<td>Plasma volume shifts: increased intravascular blood volume related to decreased capillary pressure.</td>
</tr>
<tr>
<td>Oxygen free radical destruction of nitric oxide with production of peroxynitrates resulting in enhanced sensitivity to vasoconstrictors, especially angiotensin II).</td>
</tr>
<tr>
<td>Upregulation of PDE 1A1 expression resulting in decreased formation of cGMP.</td>
</tr>
<tr>
<td>Mitochondrial aldehyde hydrogenase inhibition.</td>
</tr>
</tbody>
</table>

Tolerance is clearly multifactorial, involving mainly an enhanced NO availability via the B_{2}–kinin receptor. Investigators have documented major perturbations of endothelial vasodilator function in the setting of induced nitrate tolerance, as well as easily demonstrated coronary vasoconstriction to acetylcholine after an NTG patch is removed in the setting of nitrate tolerance. These investigators have hypothesized abnormalities of NOS function as a contributor to the endothelial dysfunction in nitrate tolerance. Folic acid supplementation has been suggested to prevent nitrate tolerance presumed to be related to increased tetrahydrobiopterin availability, resulting in enhanced eNO synthase function. Tolerance is clearly multifactorial, and a clinical solution is not yet available. For the more interested reader, a variety of reviews and commentaries are available.

**Clinical Implications of Nitrate Tolerance**

In addition to the loss of the desired actions of nitrates for specific cardiovascular disorders, nitrate tolerance may be associated with other adverse disturbances in vascular function, including withdrawal chest pain and/or ischemia as well as reflex vasoconstriction of coronary arteries or atherosclerotic stenoses. Several reports suggest that long-term nitrate use may result in adverse clinical outcomes in patients with CAD. At the very least, the disappointing results of the large ISIS-4 and GISSI-3 postinfarction trials could in part be related to heretofore unsuspected abnormalities of vascular endothelial function induced by conventional nitrate dosing. Intermittent dosing strategies may reduce or attenuate the likelihood of nitrate tolerance, but it is possible or even likely that even shorter periods of nitrate exposure (eg, less than 12–14 hours) may initiate intracellular and endothelial mechanisms leading to unwanted alterations in eNO synthase function and endothelial function modulated by a reduced availability of NO. There may be decreased NO synthesis as well as enhanced NO degradation induced by a variety of mechanisms. Thus, as some have suggested, chronic nitrate therapy for angina or CHF may sow the seeds for unwanted outcomes with respect to long-term morbidity and even mortality. This would be a remarkable reversal of our concepts about these drugs and their utility in clinical cardiovascular disease. Randomized clinical trial data are required to truly validate these concepts but are unlikely to become available in the future.

**Nitroprusside**

NP is an inorganic nitrovasodilator that results in abundant NO availability in vascular smooth muscle cells. It is likely that NP has antiplatelet activity, but there are limited data in this regard. NP is a ferrocyanide compound with a nitroso-moiety. Cyanide molecules are released as the molecule undergoes metabolism to NO, but in general, plasma cyanide and thiocyanate concentrations at clinically utilized dosages are too low to cause toxicity in subjects with normal renal function. NP provides NO throughout the vasculature; metabolic conversion to NO does not depend on enzymatic conversion to NO to any significant degree. Thus, NO is abundantly available in the microcirculation following NP infusion; these distal small vessels have a decreased capacity to metabolize the NTG molecule. This is an important dissimilarity between the 2 compounds, as their spectrum of vasodilation differs significantly. Because NP has a potent effect on the small resistance vessels of the heart, there is a greater possibility for a coronary steal phenomenon than with NTG. NP induces relaxation of the microcirculation throughout the myocardium, potentially allowing for diversion of nutrient coronary blood flow away from regions of ischemia distal to a coronary obstruction. NP appears to dilate collateral vessels to a lesser degree than NTG, which could exacerbate a potentially deleterious diversion of blood from ischemic zones (see below). NP is a potent venodilator. On the arterial side, it is more hemodynamically active than NTG, particularly regarding the smaller arterioles and resistance vessels. In general, there is a more equivalent degree of venous and arterial vasodilatation with NP than NTG, which has more dominant venodilator than arterial action, particularly at lower doses.

**Indications for Nitroprusside**

NP is a drug used exclusively in critical care settings and operating rooms. It is a highly effective vasodilator of great potency. NP was investigated extensively in the early days of vasodilator therapy for acute MI and congestive heart failure. Its balanced venous and arterial actions make it an ideal drug for the immediate therapy of acute and/or severe HF associated with high ventricular filling pressure and low stroke volume. The drug is also a first-line choice for treatment of severe hypertension and is probably preferable to intravenous NTG in this capacity because of its greater arterial dilator potency. At very
high NTG concentrations, the hemodynamic activity of intravenous NTG is quite similar to NP.

Nitroprusside has also been shown to be useful in decompensated patients with mitral and/or aortic regurgitation. The drug has been shown to be beneficial as an effective bridge to urgent valve replacement in patients with LV dysfunction and aortic stenosis.\textsuperscript{125,128}

A series of animal and human investigations have suggested a potential hazard for the use of NP in nonhypertensive ischemic states, such as acute MI and unstable angina. Decreases in regional myocardial blood flow and collateral flow associated with increased ischemia, have been demonstrated in human and canine studies when NP was compared to intravenous NTG.\textsuperscript{20,129} One early animal investigation suggested a more potent vasodilating action of NP on the smaller coronary vessels than NTG, which was more active in the larger coronary arteries.\textsuperscript{130}

Another trial successfully treated patients with immediate post–coronary bypass grafting hypertension with NP or intravenous NTG.\textsuperscript{131} The results of 2 conflicting trials of NP in the setting of acute MI were published in 1982.\textsuperscript{132,133} In the VA cooperative study, NP offered no advantage to patients given a 48-hour infusion of NP versus the placebo when the infusion was instituted a mean of 17 hours after onset of chest pain.\textsuperscript{132} However, a retrospective analysis suggested that patients treated early (within 9 hours of onset of symptoms) fared less well with NP than with the placebo, whereas subjects treated later had a decreased mortality rate. It was speculated that the former group may have had lower LV-filling pressures during the first day or two and thus may have been exposed to a NP-induced risk of hypoperfusion of the coronary bed or a coronary steal phenomenon; the late-treated cohort presumably had more patients with LV dysfunction and elevated filling pressures, and in these subjects NP would have been of benefit when compared with the placebo. However, another study from the Netherlands demonstrated a decrease in mortality in acute MI patients randomized to NP.\textsuperscript{133} The reasons for the different results are unknown, although it has been speculated that the latter study included a number of hypertensive subjects who may have derived additional benefits from NP, which may have affected the final outcome.\textsuperscript{134} In any case, this dilemma has not been resolved, and there have not been subsequent confirming studies. Warnings about the use of NP in acute MI are not new,\textsuperscript{134} and current guidelines for the therapy of MI include intravenous NTG but not NP.\textsuperscript{135} Tables 14-6 and 14-7 list the indications and precautions that accompany the use of NP.

### Table 14-6. Indications for Nitroprusside

| Severe hypertension            |
| Acute pulmonary edema         |
| Severe congestive heart failure |
| Acute and/or severe mitral or aortic regurgitation, aortic stenosis |
| Acute myocardial infarction complications: Heart failure or uncontrolled hypertension |
| Use extreme caution:          |
| Hypotension or borderline systolic blood pressure |
| Acute myocardial ischemia in the absence of heart failure |
| Renal insufficiency           |


### Table 14-7. Precautions in the Use of Nitroprusside

| Exposure of NP solution to light |
| Prolonged infusion (> 48 h)       |
| Renal insufficiency                |
| Infusion rates > 10 μg/kg/min      |
| Measure thiocyanate levels in high-risk subjects (prolonged infusion, azotemia) |


### Dosage

The infusion of NP should begin at 0.5 to 1 μg/kg/min, increasing to no more than 10 μg/kg/min. Most experts recommend reducing the mean or systolic arterial pressure by 10%, thereby avoiding central aortic hypotension. Meticulous care must be given to the patient with actual or potential myocardial ischemia so as to prevent an excessive central aortic pressure decrease. NP must be given with appropriate precautions, including protection from ambient light to prevent an accelerated release of NO and cyanide. The infusion should be limited in duration to 48 hours, as NP toxicity can occur over time as the cumulative dose increases. Renal and hepatic insufficiencies are risk factors for adverse reactions to NP, with excessive concentrations of cyanide and thiocyanate, the metabolic by-product of NP metabolism. Thiocyanate toxicity should be suspected in patients receiving NP who develop abdominal pain, mental status changes, or con-
vulsions. Cyanide toxicity can be manifest by a reduction in cardiac output and metabolic or lactic acidosis. Methemoglobinemia can be observed as a relatively pure manifestation of NP toxicity.

**Conclusion**

The available nitrovasodilators remain important cardiovascular drugs for the management of patients with ischemic heart disease, emergent hypertension, and CHF. Their actions appear to simulate many of the normal vascular physiologic processes involved in vasodilation and have provided tremendous insights into the pathophysiology of vascular disease. Nevertheless, nitrate tolerance remains a fascinating and complex subject, and recent work implicating tolerance-induced endothelial dysfunction raises more questions than answers. Informed and judicious use of the nitrates and NP should provide benefit for many individuals with cardiovascular disease.136

Note: References for this chapter can be found here: www.cvpct3.com
Despite recent decreases in cardiovascular mortality, ischemic heart disease (IHD) remains the leading cause of death in the United States. A constituent of IHD is chronic stable angina (CSA), which has been estimated to occur in 6 to 16 million Americans. Angina is a result of the deficiency between myocardial oxygen supply and demand. In the past, the treatment of CSA was directed at either decreasing myocardial oxygen demand or increasing oxygen supply. Pharmacologic therapy for CSA has 2 main goals: the first is to decrease acute coronary events and mortality, and the second is to decrease symptoms of angina pectoris and thereby hopefully improve quality of life. Patient with symptomatic CSA should receive the following agents to reduce the risk of myocardial infarction (MI) or death: aspirin and/or clopidogrel; beta-adrenergic receptor blocking agents, statins, and angiotensin-converting enzyme (ACE) inhibitors. CSA patients who remain symptomatic despite treatment have been treated with long-acting calcium channel antagonists or long-acting nitrates.

Despite revascularization and/or treatment with standard anti-anginal therapy, many patients continue to experience symptoms of CSA. Combination therapy is often limited due to adverse hemodynamic effects (Table 15-1). In some situations, patients with retractable symptoms who are already receiving standard therapy may not be candidates for coronary revascularization. Therefore, a new anti-anginal agent that could be used in combination with standard therapy, or as monotherapy for patients unable to tolerate standard therapy, is sorely needed. Ranolazine was recently approved for use as a first-line agent for the treatment of patients with chronic angina.

Ranolazine, a piperazine derivative, is a unique anti-anginal drug that was recently approved for clinical use in an extended-release formulation. Unlike other anti-anginal drug classes, ranolazine has no effect on hemodynamics, and its exact mechanism of action is still being determined.

In this chapter, the pharmacological properties of ranolazine are discussed and recommendations regarding its clinical use and safety are provided.

**Pharmacodynamic Properties**

Since ranolazine’s introduction into clinical trials over 15 years ago, it was thought that the drug worked to enhance myocardial metabolism in the heart by inhibiting fatty acid oxidation, thereby favoring the more efficient use of glucose as a myocardial substrate for energy. However, more recent data would suggest that the drug is working primarily by a different mechanism, the inhibition of the late inward sodium ion current (late $I_{Na}$) in myocardial cells.

**Inhibition of $I_{Na}$**

The late $I_{Na}$ may be increased in myocardial ischemia and congestive heart failure (CHF). An increase in the late $I_{Na}$ will result in an increase in intracellular levels of sodium with increased activity of the sodium-calcium exchange mechanism with increased entry of calcium into cardiac myocytes and a prolongation in duration of the action potential. An increase in intracellular calcium loading in the myocardium could cause mechanical and electrical dysfunction. Also, myocardial energy needs are increased, and microvascular perfusion of ischemic myocardium is decreased by impaired relaxation of the cardiomyocytes and by a decrease in ventricular end-diastolic pressure.

It has been proposed that ranolazine’s ability to inhibit the late $I_{Na}$ and calcium overload in cells could improve left ventricular (LV) diastolic stiffness and reduce...
myocardial ischemia in CSA,\textsuperscript{10,13} but confirmatory data regarding this mechanism are still needed.\textsuperscript{14}

**Metabolic Effects**

For many years, ranolazine was thought to work in angina by stimulating glucose oxidation in the myocardium and by inhibiting fatty acid oxidation.\textsuperscript{6,7} The functioning myocardial cell requires energy in the form of adenosine triphosphate (ATP), which is produced by 3 mechanisms: glycolysis, glucose oxidation, and fatty acid oxidation.\textsuperscript{15} Glycolysis results in the anaerobic conversion of glucose and glycogen to pyruvate and lactate. This is a less efficient mechanism of ATP production and only contributes up to 5% of the cell’s energy requirements. Glucose and fatty acid oxidation produce the remainder of the myocardial cells’ energy requirements and compete with one another for substrate availability.\textsuperscript{15} Under nonischemic conditions, the majority of ATP production (60% to 90%) is a result of fatty acid oxidation.\textsuperscript{16} Conversely, glucose oxidation contributes 10% to 40% of ATP generation.\textsuperscript{16} Fatty acid oxidation produces more ATP for each mole of carbon dioxide that is produced compared with glucose oxidation, and is therefore more “energy efficient.”\textsuperscript{16} However, fatty acid oxidation requires more oxygen than glucose oxidation and is therefore less “oxygen efficient.”\textsuperscript{17,18} In other words, for a given amount of oxygen, the oxidation of glucose in preference of fatty acids results in greater ATP production.\textsuperscript{17,18} Despite this, fatty acids are the preferred mammalian source of myocardial energy production. In times of stress, such as after an MI, catecholamines stimulate lipolysis, resulting in increased free fatty acids.\textsuperscript{19} However, recent data suggest that the plasma levels of ranolazine required for inhibition of fatty acid oxidation need to be much higher than those achieved by the usual therapeutic doses of the drug.\textsuperscript{20} In addition, a recent study demonstrated that the ischemic protection observed by the drug in heart perfusion experiments was not mediated by the inhibition of fatty acid oxidation.\textsuperscript{21}

**Effects on Adrenergic Receptors**

Ranolazine has been shown to have a low affinity for both $\beta_1$ and $\beta_2$-adrenergic receptors with weak activity at these receptors.\textsuperscript{22}

**Hemodynamic Effects**

Ranolazine causes significant changes in heart rate and blood pressure (Table 15-1) in patients who received both intravenous or oral formulations.\textsuperscript{9} In addition, there is no significant difference seen on the rate-pressure product responses at rest and during exercise compared to the placebo.\textsuperscript{10,23} When comparing atenolol to ranolazine, only atenolol reduces the rate-pressure product.\textsuperscript{24} When ranolazine is added to other anti-anginal drugs that reduce the rate-pressure product, there is no additional effect with ranolazine.\textsuperscript{10}

Ranolazine appears to have no negative inotropic effects\textsuperscript{25} and may improve ventricular function in patients with both systolic and diastolic dysfunction.\textsuperscript{26} The drug is not approved for heart failure treatment.

**Electrophysiologic Effects**

Ranolazine has been demonstrated to cause a modest prolongation of the QT interval in recent clinical studies.\textsuperscript{27,28} However, treatment with ranolazine was not associated with an increase in QT dispersion nor with any cases of torsades de pointes (TdP). The mechanism for ranolazine-induced QT prolongation has been elucidated and indicates that ranolazine may also be considered an antiarrhythmic agent.\textsuperscript{29-31} An in vitro animal model using canine myocardial cells demonstrated that ranolazine 2-6 $\mu$mol/L inhibits rapid delayed rectifier potassium current ($I_{Kr}$), which is responsible for repolarization.\textsuperscript{29} This results in prolongation of the action potential and consequently the QT interval. However, ranolazine also inhibits the late inward sodium current (late $I_{Na}$) and the late L-type cal-

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**Table 15-1. Effects of anti-anginal drug therapy on hemodynamic parameters**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Heart Rate</th>
<th>Systolic Pressure</th>
<th>LV Volume</th>
<th>Myocardial Contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$-blockers</td>
<td>↓↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Nitrates</td>
<td>↑</td>
<td>↓</td>
<td>↓↓</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>↑</td>
<td>↓↓</td>
<td>↔ or ↓</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Diltiazem and Verapamil</td>
<td>↓↓</td>
<td>↓</td>
<td>↔ or ↓</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>↔</td>
<td>↔</td>
<td>↔ or ↑</td>
<td>↔ or ↑</td>
</tr>
</tbody>
</table>

$\downarrow =$ decrease; $\uparrow =$ increase; $\leftrightarrow =$ no change.

cium current (\(I_{Ca,L}\)), both of which are depolarizing currents. Inhibition of these currents would have the effect of shortening the action potential duration (APD) and similarly decreasing the QT interval. As a result, within the therapeutic range, the net effect of ranolazine’s inhibition of \(I_{Kr}\), late \(I_{Na}\), and \(I_{Ca,L}\) is a modest increase in the QT interval.

An independent task force released a consensus guideline that provides methods to evaluate the risk of TdP during drug development. It states that the best predictor of TdP is an increase in transmural dispersion of repolarization (TDR). Drugs that prolong APD, induce early after-depolarizations (EADs) and ectopic beats, and increase dispersion of ventricular repolarization are likely to cause TdP (eg, d-sotalol). Ranolazine has not been associated with induction of EADs, ectopic beats, increased TDR, or TdP. The increase in APD with ranolazine was not dependent on heart rate, nor was it changed with hypokalemia. Ranolazine has also been shown to reduce APD, EADs, and TDR when given with drugs that decrease \(I_{Kr}\) or that increase late \(I_{Na}\). Therefore, ranolazine may possess antiarrhythmic activity in addition to anti-anginal activity.

**Pharmacokinetics**

Ranolazine has an oral bioavailability of 30% to 55%, plasma half-life of 2 hours, and an estimated volume of distribution of 80 L. Absorption of ranolazine is not affected by food. Ranolazine is metabolized by cytochrome P450 3A4, and to a lesser extent by 2D6 (CV Therapeutics data on file). At least 11 metabolites have been identified. Co-administration with diltiazem resulted in elevated ranolazine plasma concentrations that increased with increasing doses of diltiazem. The 3A4 inhibitors (ketoconazole and verapamil) increased ranolazine concentrations 3.9 and 2.3 fold, respectively (CV Therapeutics data on file). Concomitant administration of ranolazine with digoxin increased serum digoxin levels by 40% to 70%, presumably through competition for intestinal and renal p-glycoprotein (CV Therapeutics data on file).

From early clinical studies with immediate-release ranolazine, an apparent plasma concentration threshold was observed for anti-anginal efficacy. Trough ranolazine levels (approximately 8 hours post dose) were associated with decreased anti-anginal activity as compared with peak levels (1 hour post dose). Therefore, it was suggested that a sustained-release formulation of ranolazine be developed for clinical use. Recent phase 3 clinical studies have used the sustained-release formulation, which is dosed every 12 hours.

The pharmacokinetics of ranolazine were not shown to be altered to a clinically significant extent by gender or the presence of diabetes mellitus. Ranolazine dose titration should be done with caution in the elderly, in patients with low body weight (≤ 60 kg) and in patients with moderate to severe heart failure (NYHA [New York Heart Association] class III-IV).

**Clinical Studies**

Results of preliminary studies with immediate-release ranolazine have been reviewed previously. Initially, ranolazine was dosed 3 times daily as either monotherapy or add-on therapy and generally demonstrated improvements in exercise treadmill time and time to onset of angina compared with the placebo. One study did not demonstrate significant benefits with ranolazine; however, the dosing was much lower than the other studies, and the patient selection criteria was not as stringent.

In addition to providing evidence of benefit, these studies identified a minimal ranolazine concentration necessary to maintain efficacy throughout the dosing interval. For this reason a twice-daily sustained-release formulation of ranolazine was developed by CV Therapeutics Inc. (Palo Alto, CA).

A randomized, double-blind, placebo-controlled, crossover study of 158 patients with angina compared the effects on exercise duration of either ranolazine 400 mg 3 times daily, atenolol 100 mg daily, or a placebo for a period of 1 week. Both ranolazine and atenolol significantly increased exercise time, time to angina, and time to 1 mm ST segment depression compared with the placebo (\(P < .001\)). In addition, ranolazine was associated with a significantly longer exercise duration than atenolol (mean difference 21.1 sec, 95% confidence interval 6.2-36.0, \(P = .006\)). Atenolol was associated with a decrease in the maximal rate-pressure product (a common index of cardiac work) compared with both the placebo and ranolazine (\(P < .001\)), whereas ranolazine was associated with an increase in the maximal rate-pressure product compared with both the placebo and atenolol (\(P < .05\) and \(P < .001\) respectively). By increasing cardiac work and prolonging exercise duration and time to angina, ranolazine is likely to improve myocardial energy efficiency. This study is significant because it demonstrated at least an equal benefit of ranolazine compared with conventional anti-anginal therapy (atenolol). The results of 4 recently reported clinical trials with sustained-release ranolazine will be discussed below in more detail.

The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) study, which assessed withdrawal of anti-anginal therapy, randomized 191 patients with angina-limited exercise to the placebo or sustained-release ranolazine 500 mg, 1000 mg, or 1500 mg administered...
twice daily in a double-blind, 4-period, crossover design of 1 week duration per treatment period. Patients were eligible for the study if they had a documented history of coronary artery disease and at least a 3-month history of CSA. The presence of angina-limited exercise was determined during a single-blind, placebo run-in phase that followed anti-anginal withdrawal during which the patients completed 2 modified Bruce exercise treadmill tests (ETTs) approximately 1 week apart. Patients were randomized if they developed exercise-limiting angina and ≥ 1 mm ST segment depression between 3 and 9 minutes and if the difference in the duration between the 2 tests was < 20% of the longer test or 1 minute. Patients were excluded if they had: (1) resting ECG abnormalities that would interfere with ETT interpretation, (2) acute coronary syndrome or revascularization procedure within the previous 2 months, (3) current NYHA functional class III or IV heart failure, (4) corrected QT interval > 500 millisecond, (5) any medication capable of prolonging the QT interval, and/or (6) any medication with the potential for interaction through the cytochrome P450 3A4. The primary endpoint of the study was total exercise duration following ETT performed at trough ranolazine serum concentrations. Secondary endpoints included time to onset of angina and time to 1 mm ST segment depression during ETT at both trough and peak ranolazine concentrations. ETTs were performed at the end of each treatment cycle at times of peak and trough ranolazine concentrations (4 and 12 hours post dose, respectively).

Results of the study revealed that the majority of study patients were white (91%) and male (73%) with a mean age of 64.3 years. Compared to the placebo, ranolazine taken twice daily at all 3 doses demonstrated statistically significant increases in exercise duration, time to onset of angina, and time to 1 mm ST segment depression at both peak and trough plasma concentrations (Figure 15-1). There appeared to be a dose-response relationship between the 3 ranolazine doses, and the benefit was maintained throughout the dosing interval. As in previous studies, this study demonstrated improvements in exercise performance with little to no effect on heart rate and blood pressure. The ranolazine 1500 mg dose caused significant but minor decreases in trough and peak resting heart rate (< 3 beats/min; P ≤ .001) and peak resting systolic blood pressure (< 3 mmHg; P < .05) and peak and trough exercise systolic blood pressure (< 7 mmHg; P < .001).

Two separate sub-analyses of the MARISA study compared patients with diabetes mellitus and patients with CHF to patients without the respective condition. At both peak and trough ranolazine concentrations, the benefits in exercise duration, time to onset of angina, and time to 1 mm ST segment depression were similar between diabetics and nondiabetics. In addition, ranolazine had no effect on blood glucose or triglyceride levels in the patients with diabetes mellitus. At trough ranolazine concentrations, the magnitude of benefit was similar between CHF patients and non-CHF patients. However, at peak ranolazine concentrations, both the exercise duration and the time to 1 mm ST segment depression were increased to a greater extent versus the placebo in CHF patients than in non-CHF patients (P < .01). Subgroup analyses of gender and age (≥ 65 and < 65 years) did not reveal any heterogeneity of results with P values of treatment by subgroup interaction equal to 0.65 and 0.054 respectively.

The CARISA (Combination Assessment of Ranolazine in Stable Angina) trial was the second Phase 3 study completed. CARISA was a double-blind study that randomized patients to either the placebo arm, sustained-release ranolazine 750 mg arm, or 1000 mg arm twice daily for a duration of 12 weeks. Randomization was stratified according to the patients’ current anti-anginal therapy. Acceptable anti-anginal therapy included atenolol 50 mg/day, diltiazem CD 180 mg/day, or amiodipine 5 mg/day. Doses were held constant for the duration of the study. The inclusion and exclusion criteria as well as the study endpoints were the same as those used for the MARISA trial. ETTs were conducted at the time of trough drug levels on weeks 2, 6, and 12, and at peak drug levels on weeks 2 and 12. A total of 823 patients were randomized to either the placebo (n = 269); ranolazine 750 twice daily (n = 279); or ranolazine 1000 mg twice daily (n = 279). Baseline demographics were similar between the 3 groups. At baseline, patient background therapy consisted of atenolol (43%), amiodipine (31%), and diltiazem (26%). The primary endpoint of exercise duration was significantly increased by both ranolazine doses compared to placebo at trough and at peak levels (Figure 15-2). The increase in exercise duration following 1 week of ranolazine monotherapy.  

duration was seen at weeks 2, 6, and 12. Time to onset of angina and time to ischemia were all increased at peak and trough with either ranolazine dose as compared to the placebo (Figure 15-2). The differences between the placebo and ranolazine for the ETT results were larger at peak, although it should be noted that the times at peak were generally shorter than the times at trough. As opposed to the MARISA study, a dose response between the different doses of ranolazine was not seen; however, this might be explained by the smaller difference in dose used in CARISA. Background anti-anginal therapy did not modify response to therapy. Patients reported experiencing 4.5 angina attacks per week at baseline. Ranolazine reduced the number of attacks per week from 3.3 seen in the placebo to 2.5 with 750 mg (P < .001) and to 2.1 for 1000 mg (P < .001). Nitroglycerin use was also reduced significantly for each ranolazine dose as compared to the placebo. Similar to MARISA, changes in blood pressure and heart rate were minimal. Ranolazine 1000 mg decreased peak and trough resting systolic blood pressure by 2.8 mmHg (P = .02) and decreased end-exercise SBP by 3.3 mmHg at trough (P = .04).

After completing the MARISA and CARISA trials, subjects could participate in an open-label trial (Ranolazine Open-Label Experience, ROLE) in which all subjects received ranolazine ER with an average follow up of 2.8 years. In ROLE, patients received maximal doses of 500, 750, and 1000 mg twice daily. Long-term therapy with ranolazine seemed to be well tolerated in high-risk patients.

Survival analyses suggested that symptomatic improvements attributed to ranolazine are not offset by increased mortality. Ranolazine has been evaluated in patients with CSA who remained symptomatic despite treatment with the maximum dose of an anti-anginal agent. In the ERICA (Efficacy of Ranolazine in Chronic Angina) trial, 565 patients were randomized to receive an initial dose of ranolazine 500 mg twice daily or the placebo for 1 week, followed by 6 weeks of treatment with ranolazine 1000 mg twice daily or the placebo in addition to concomitant treatment with amlodipine 10 mg once daily. In addition, 45% of the study population also received long-acting nitrates. Subgroup analyses of patients in MARISA with diabetes mellitus and heart failure revealed no disease-state interactions for treatment benefit with ranolazine. In an analysis of patients with diabetes mellitus, glycemic control as measured by glycosylated hemoglobin (HgbA1c) revealed dose-related improvements in control for ranolazine treated patients. Patients randomized to ranolazine 750 mg and 1000 mg twice daily had reductions of 0.48% and 0.7% in the HgbA1c respectively compared to the placebo (P < .01).

MERLIN-TIMI-36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes) was a large randomized, placebo-controlled, double-blind, parallel design trial in 6,560 patients with non-ST elevation acute coronary syndrome (ACS). In addition to receiving standard therapy for non-ST elevation MI, patients were randomized to receive intravenous ranolazine or the placebo. A 200 mg dose of ranolazine was given intravenously, followed by an intravenous infusion of ranolazine 80 mg for 12 to 96 hours. At the end of the infusion period, oral ranolazine extended release (ER) 1000 mg twice daily or a placebo was administered. Patients were followed for up to 2 years.

The primary endpoint was a composite of cardiovascular death, MI, or recurrent ischemia. There was no benefit seen with ranolazine in the outcome measures. However, patients receiving ranolazine ER were significantly less likely to experience recurrent ischemia than those receiving the placebo. In addition, the study was somewhat reassuring regarding the potential proarrhythmic risk of ranolazine in that there was no difference between ranolazine and the placebo in the risk of all-cause mortality, and ventricular arrhythmias were less common with ranolazine. TdP was reported in 1 ranolazine ER patient and 1 patient who received the placebo.

In subgroup analyses of MERLIN-TIMI 36 evaluating patients having angina, the drug was shown to have favor-
able effects on myocardial ischemia and angina frequency. The drug was also shown to be particularly effective in women, in those with elevated brain natriuretic peptide levels, and in the control of diabetes mellitus.

**Adverse Effects**

In both the MARISA and CARISA trials, adverse effects that occurred more often with ranolazine than the placebo included dizziness, nausea, asthenia, and constipation (MARISA 1500 mg dose). The adverse event rate for the 500 mg dose in MARISA was identical to the placebo, increased by 4.8% for the 750 mg dose in CARISA, and was 6% higher than the placebo for the 1000 mg dose in both CARISA and MARISA. At the 1500 mg dose, the adverse event rate was 18% higher than compared to the placebo. A total of 15 patients withdrew from the MARISA trial as a result of adverse effects. The majority occurred while taking the 1500 mg twice daily dose (11 patients), while 2 patients discontinued on the placebo and 1 patient each discontinued while on 500 mg and 1000 mg twice daily. The results of earlier clinical studies showed similar adverse effects between ranolazine and the placebo. However, gastrointestinal complaints, headache, dizziness, and fatigue were reported more frequently with ranolazine than with the placebo and their incidence was dose-related. In addition, there were no clinically significant abnormalities in lipids, glucose, and renal or liver function. Syncope occurred in 5 patients randomized to 1000 mg of ranolazine during the CARISA trial. None of the 5 patients were injured and there was no evidence of ventricular arrhythmias. Four of the 5 patients were receiving concomitant diltiazem, which led the authors to postulate that the interaction resulted in higher ranolazine concentrations. Apparently, preclinical studies in healthy volunteers demonstrated orthostatic hypotension and syncope as an infrequent event when taking doses of 2000 mg twice daily. It is presumed that the hypotension may be a result of β₁-receptor antagonism. As was noted previously, dose-related prolongation in the QTc was discovered in both the MARISA and CARISA trials. The prolongation ranged from 5 milliseconds at peak ranolazine 500 mg levels to 14 milliseconds at peak ranolazine 1500 mg levels. There was no evidence of increased QT dispersion nor any documented cases of TdP in either trial. Overall, ranolazine seems to be well tolerated at doses up to 1000 mg. However, adverse effects such as QTc prolongation were greater at the 1500 mg dose. As a result of these studies, approval was sought for a maximal dose of 1000 mg twice daily. Ranolazine ER was generally well tolerated, although in MERLIN-TIMI 36 an increased low rate of dizziness, nausea, constipation, and syncope was observed with ranolazine compared to the placebo.

The safety of ranolazine in patient subgroups with diabetes and heart failure has been demonstrated, however, patients with advanced heart failure were excluded and the populations of both groups have been too small to make generalizations. Preclinical data in animal models of heart failure have demonstrated an ability of ranolazine to increase LV ejection fraction and stroke volume. However, ranolazine needs further evaluation in patients with systolic dysfunction before it is deemed safe for use in this population.

**Clinical Use**

Ranolazine is marketed as Ranexa in 500 mg and 1000 mg extended release tablets for the treatment of CSA. The package insert has been updated to include additional drug safety data. Ranolazine may be combined with beta blockers, nitrates, calcium-channel blockers, ACE inhibitors, and angiotensin II receptor blockers, and used as a first-line agent to treat patients with chronic angina. Ranolazine ER treatment is initiated with 500 mg tablets twice daily, and the dose can be increased to 1000 mg twice daily to maximize anginal symptom relief. It is not approved for use in unstable angina.

Ranolazine is primarily metabolized by CYP 3A and is a substrate of P-glycoprotein. Therefore, the drug should not be used with strong inhibitors of CYP 3A. When combined with moderate 3A inhibitors, such as diltiazem or verapamil, ranolazine should not be used at a dose higher than 500 mg twice daily. In patients receiving digoxin, a lower dose of ranolazine should also be considered.

Ranolazine is associated with modest dose-related increases in the ECG QTc interval; however, the drug does not seem to cause arrhythmias. There are limited data available with ranolazine combined with other QT interval-prolonging drugs or in individuals having hereditary QT interval-prolongation syndromes. Caution is recommended when considering ranolazine in these situations.

**Conclusion**

Ranolazine, a piperazine derivative, is a new anti-anginal drug whose mechanism of action has not been clearly defined. It can relieve symptoms of CSA and nitroglycerin consumption when used alone and in combination with other anti-anginal drugs. It is effective in both men and women and in patients aged 70 years or older. It does not have any apparent hemodynamic effects. It can cause a modest dose-related increase in the ECG QTc interval but does not increase the risk of arrhythmias. It appears to be well tolerated. It is not indicated for the treatment of unstable coronary syndromes or arrhythmia.

*Note: References for this chapter can be found here: www.cvpct3.com*
Increased systemic vascular resistance has been considered a hemodynamic characteristic of arterial hypertension. In essential hypertension and various forms of identifiable hypertension, raised systemic vascular resistance is nearly always found particularly when diastolic pressure or mean arterial pressure is elevated. Reduced compliance of medium-sized and large arteries also contributes to increased systolic pressures and wide pulse pressures in middle-aged and elderly hypertensives. Both increased systemic vascular resistance and reduced arterial compliance (increased stiffness) may be partly due to activation of arterial vascular smooth muscle. Drugs that relax vascular smooth muscle can then be effective for lowering pressure.

Hydralazine was one of the first of such drugs to be successfully explored for treatment of hypertension. Its mechanism of action remains somewhat unclear, but may be, in part, due to enhanced action of or release of nitric oxide. Other arterial vasodilators (minoxidil and diazoxide) are highly potent antihypertensive drugs that have been classified as K-ATP channel hyperpolarizers. The dihydropyridine-L calcium channel blockers are also arterial vasodilators, but are recognized as a separate drug class (see Chapter 8, Calcium Channel Blockers).

Treatment of hypertension with the vasodilators activates the sympathetic nervous system via the baroreflexes with increased cardiac output, in compensation for the reduction in systemic vascular resistance. Reduced renal perfusion leads to fluid-volume retention and activation of the renin-angiotensin system. By the 1970s, use of the orally active nonselective vasodilators (hydralazine and minoxidil) invariably required concurrent beta receptor blockade (to minimize reflex tachycardia) and effective diuretics (thiazides or loop active agents) in "triple-drug" strategies for the treatment of severe hypertension. With the availability of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor antagonists, and calcium-entry blockers, hydralazine and the K-ATP hyperpolarizers are now used as last-resort drugs for hypertension. However, there are a few specific situations where these drugs may play more specific or important therapeutic roles, as described in this chapter.

Pharmacology and Classification of the Nonspecific Vasodilators

**Hydralazine**

Hydralazine (1-Hydrazinophthalazine) was one of the first available orally active vasodilators whose action as a direct arteriolar vasodilator is independent of receptor blockade. Its mechanism of action remains somewhat unclear but seems to be dependent on endothelial cells and may be related to the formation of nitric oxide and/or hyperpolarization of vascular smooth muscle cells and interruption of intracellular calcium action. The hydrazine (HN-NH2) in position one of the double-ringed phthalazine confers its activity as a vasodilator.

Hydralazine lowers systemic vascular resistance resulting in activation of sympathetic reflexes, increased heart rate, and cardiac output on a neurogenic basis. The reflex-mediated changes in cardiac function after hydralazine treatment can be prevented by beta-receptor antagonists. Chronic administration of hydralazine stimulates renin release, raising plasma renin activity. Salt and water retention with gain in weight are also observed.

While the half-life of hydralazine reflected by plasma concentrations is 1 to 2 hours, the antihypertensive effect may last for 6 to 12 hours. Dosing 2-3 times daily at 8- to 12-hour intervals is necessary. The usual schedule is 25 mg to 100 mg every 8 to 12 hours.
After absorption from the gastrointestinal tract, hydralazine is acetylated in the liver to a varying degree. Slow and fast acetylators are represented almost equally in the population of the United States. Hydralazine is relatively less bioavailable for slow acetylators, who require higher oral doses for equal antihypertensive effect. Extrahepatic metabolism also occurs and accounts for the drug’s elimination after reaching the circulation.

Adverse effects of hydralazine may be divided into 2 categories: (1) those related to the hemodynamic effect of the drug and (2) those specifically linked to its unique biochemical characteristics. Headaches, flushing, tachycardia, palpitations, angina-like chest discomfort or true angina of myocardial ischemia, dizziness, and orthostatic hypotension are the consequences of the vasodilating action of hydralazine and the significant sympathetic reflex activation as a physiologic response. In contrast, the hydralazine lupus syndrome, serum-sickness-like reaction, hemolytic anemia, and glomerulonephritis syndromes seem best related to hydralazine itself and are more likely to occur in slow acetylators, often white women. Many patients treated with hydralazine who develop positive antinuclear antibodies (ANA) do not proceed to symptomatic lupus. However, with so many alternative drugs, there is little basis for continuing ANA-positive patients on hydralazine in most situations. Vitamin B₆ (pyridoxal-pyridoxine, reducing supply of the cofactor for many enzymes. Both hydralazine lupus syndromes and polyneuropathy usually occur during treatment with total daily doses ≥ 150 mg daily.

For treatment of essential hypertension, hydralazine is a fourth- or fifth-line drug choice to be added when pressure cannot be controlled on an ACE inhibitor (or ARB), diuretic, and beta blocker, and the addition of an alpha blocker or calcium blocker is ineffective or inappropriate.⁶⁷ Frequent dosing within the day for hydralazine may hinder adherence. However, hydralazine is inexpensive and may be cost-effective in those health care systems that have limited financial resources.⁷ The once-a-day, long-acting calcium-channel blockers (nifedipine in controlled-release formulations, amlodipine, and felodipine) have largely replaced hydralazine in the multidrug combinations used to treat more severe or refractory hypertension.⁴

Intramuscular or intravenous hydralazine remains useful for the treatment of severe pregnancy-induced hypertension, including toxemia.³⁸ Its value in oral form for treating mild to moderate hypertension in pregnancy is not established.⁴⁰ In studies of congestive heart failure (CHF), before the availability of the ACE inhibitors, hydralazine therapy used alone and in combination with isosorbide dinitrate was beneficial, especially when compared to the alpha₁-receptor blocker prazosin.¹¹ The advent of the ACE inhibitors and beta blockers and other strategies for the treatment of heart failure has reduced the overall use of hydralazine.¹² However, the combined use of hydralazine with isosorbide dinitrate has been reported to be effective for the treatment of heart failure in black patients already receiving standard therapy.¹³ (See Chapter 14, The Organic Nitrates andNitroprusside.)

ATP-K₁ Channel Openers: Minoxidil and Diazoxide

The powerful arteriolar vasodilators minoxidil and diazoxide were developed in the 1970s for use in the treatment of severe and refractory hypertension and hypertensive emergencies. Minoxidil became a part of the triple drug regimen for treatment of severe hypertension, especially for patients who were unresponsive or had significant adverse reactions to hydralazine.³ Minoxidil may be effective in patients having renal insufficiency and hypertension, where the drug can stabilize or improve renal function.⁴

Minoxidil is a prodrug that becomes active with sulfation of an N–O site by a hepatic sulfotransferase. Minoxidil and diazoxide activate K(ATPase) channels, causing hyperpolarization of smooth muscle cell membranes with relaxation (vasodilation). Other K(ATPase) channel activators—nicorandil, cromakalim, aprikalim, bimakalim, and emakalim —have been assessed as coronary artery vasodilators.¹⁴ Some of the ATP-K₁ channel activators inhibit release of insulin from pancreatic islet beta cells (long recognized as an effect of diazoxide), antagonizing the effect of the sulfonylureas at the K₁ channel. Experimental studies suggest that diazoxide is the most potent agent for inhibition of hypoglycemia due to a sulfonylurea.¹⁵

ATP-K₁ channel openers, like hydralazine, cause a profound nonselective reduction in systemic vascular resistance with activation of sympathetic reflexes, tachycardia, increased cardiac output, and fluid retention. Beta-receptor blockade¹⁶ and diuretics are required.⁴¹⁷ Sustained use of minoxidil may lead to increased pulmonary hypertension—due to a prolonged hyperdynamic state resulting from reduced precapillary vascular resistance and an arteriovenous shunt–like state. Other cardiovascular side effects of minoxidil include adverse effects on myocardial repolarization, peripheral edema, and pericardial effusions.⁴¹⁸

Minoxidil is used only for severe hypertension when other agents are ineffective. At a dose of 2.5 to 20 mg once or twice daily, minoxidil in combination with a beta-receptor blocker and a potent diuretic (most often a loop-active agent such as furosemide) is almost always effective.
in reducing blood pressure; in those patients with renal insufficiency, a higher minoxidil dose may be necessary. Minoxidil use may increase proteinuria when used with an ACE inhibitor, despite additional blood pressure reduction. Weight gain, despite diuretic use, often occurs. Hypertrichosis (hair growth) is inevitable and is usually cosmetically disfiguring, especially in women.

Diazoxide is a very potent vasodilator that was developed for intravenous injection to lower pressure in hypertensive emergencies. The reduction in pressure was unpredictable so that hypotension associated with coronary ischemia or stroke was a risk of its use. Prolonged treatment with diazoxide often led to hyperglycemia due to inhibition of insulin release, an effect explained by activation of ATP-K1 channels. There are now several superior intravenous agents to treat emergencies that allow better control of pressure: nitroprusside, labetalol, fenoldopam, nicardipine, and clevidipine.

Summary: Effectiveness and Current Use of Vasodilators

Hydralazine remains an effective third- or fourth-line drug for treatment of some patients with refractory hypertension, for pregnancy-related severe hypertension, and in combination with isosorbide dinitrate in black patients with CHF. Minoxidil’s use as an antihypertensive is limited to those with the most refractory hypertension who are willing to accept its adverse effects.

Diazoxide may still be useful for hypertensive emergencies, however, with so many more effective and safer parenteral agents now available, diazoxide has become almost obsolete.

Note: References for this chapter can be found here: www.cvpct3.com
Cardiac arrhythmias form a spectrum from clinically insignificant rhythms to life-threatening and lethal arrhythmias. Effective pharmacologic treatment of arrhythmias requires an understanding of the underlying mechanism of arrhythmia as well as the pharmacokinetics, pharmacodynamics, and electropharmacology of available antiarrhythmic medications. Whereas mechanisms have been established with some certainty for a number of arrhythmias, for many the mechanisms remain to be elucidated. Interrelationships between cardiac anatomy, nature and extent of structural heart disease, severity of functional impairment, cellular electrophysiology, metabolic fluxes, and factors such as ischemia and autonomic state are only beginning to be understood. Moreover, a profound revolution in our understanding of electrophysiology and electropharmacology is just emerging, based on major advances in genomics and molecular cardiology.\(^1\,^2\) Finally, the interface of advances in diagnostic techniques, interventional procedures, and devices must be integrated into any consideration of antiarrhythmic drugs in clinical practice. With these diverse factors acting within each patient, it should come as no surprise that antiarrhythmic drug action is often unpredictable\(^3\) and must be applied empirically to individual patients.

**Classification**

Several different classifications of antiarrhythmic drugs have been proposed in the past. A useful classification scheme should relate drug class, cellular electrophysiologic effects, and utility of various antiarrhythmic agents in specific clinical situations. Today, the most widely used classification system is a modification of the one proposed by Vaughn Williams\(^4\) (Table 17-1). It classifies drugs according to their effects on action potentials in individual cells. In this scheme, class I drugs block sodium channels responsible for the fast response in atrial, ventricular, and Purkinje tissues, depressing conduction velocity. Class I drugs are further divided into 3 subclasses based on (1) the kinetics of association and dissociation of the drug with the sodium channel, (2) the strength of channel blockade, and (3) the effects on repolarization. Class II drugs are beta-adrenergic receptor antagonists. Class III agents prolong cardiac repolarization, predominantly by blocking potassium channels during phases 2 and 3 of the action potential, thereby increasing tissue refractoriness. Class IV drugs block calcium channels, depressing the slow response in sinus nodal, atrioventricular (AV) nodal, and perhaps in other cells.

Admittedly, such a classification is a considerable oversimplification and does not account for autonomic nervous system effects or the action of agents such as digoxin or adenosine, for example, all of which need to be considered in discussing antiarrhythmic drugs. In addition, it has become clear that a single antiarrhythmic drug may have multiple effects on cardiac cells. For example, sotalol has beta-blocking activity (class II) and also significantly prolongs the action potential duration (class III). Amiodarone has been shown to have class I, II, III, and IV effects and perhaps other effects as well. Similarly, individual stereoisomers of drugs may have diverse effects. For example, the dextro isomer of sotalol possesses class III activity with only minimal beta-blocking activity, while the levo isomer possesses both beta-blocking and class III activity. Finally, many drugs undergo metabolism to electrophysiologically active metabolites, which may have electrophysiologic effects that differ from those of the parent compound. Procainamide, a class Ia drug, is metabolized in the liver to N-acetylpseudoamidemide (NAPA), a drug with significant class III effects. A more
recent classification scheme, called the Sicilian gambit, attempts to relate the various clinical effects of antiarrhythmic drugs to specific anatomic or physiologic weak points of target arrhythmias, based on an understanding of ion channels and receptors and modulators of membrane activity. Although scientifically based and clinically oriented and therefore more appealing, it is not clear that this new classification will be more useful than the Vaughn Williams classification.

Successful clinical application of antiarrhythmic agents requires not only an understanding of the cellular electrophysiology of the drugs and a thorough understanding of their pharmacology but also a knowledge of drug–drug interactions, hemodynamic effects, and the ancillary properties of these agents. Failure to consider these factors often results in drug inefficacy or toxicity. This chapter presents most antiarrhythmic drugs currently available in the United States. The pharmacology, electrophysiology, pharmacokinetics, antiarrhythmic effects, drug interactions, hemodynamic properties, adverse effects, indications, and dosing are presented. A complete discussion of these agents is beyond the scope of this chapter, and data for recently released drugs are often incomplete and based in a large measure on animal data and preliminary data from clinical studies. Adverse effects reported for new agents represent those effects seen in highly selected patient populations and are subject to investigator interpretation; they may not be representative of those seen in clinical practice. It should also be noted that virtually all antiarrhythmic drugs have the potential to depress automaticity, conduction, and contractility; all have potential proarrhythmic effects. One characteristic form of proarrhythmia is the occurrence of polymorphic ventricular tachycardia (VT) in association with QT prolongation, known as torsades de pointes. In addition, in many cases, there is relatively little information available on the effects of various drugs on abnormal myocardium or in patients with more advanced cardiac pathologies.

Antiarrhythmic drugs must also be considered potential cardiac toxins. A physician treating a patient with an arrhythmia hopes the drug is more toxic to tissue involved with the arrhythmia than to the rest of the heart or patient. Often this is not the case, as the therapeutic index of these drugs can be quite low. In addition, noncardiac adverse effects are frequent. Achievement of therapeutic drug levels does not guarantee efficacy or eliminate the risk of toxicity. Furthermore, agents effective for the acute management of arrhythmias may not be effective for chronic prophylaxis. The failure to reduce or paradoxically increase mortality also exists with antiarrhythmic drugs, as demonstrated by the Cardiac Arrhythmia Suppression Trial (CAST). Therefore, antiarrhythmic therapy should be used cautiously and ideally should be reserved for those situations that significantly affect a patient’s duration or quality of life. At the very least, it is incumbent upon practitioners to have knowledge of the full prescribing information for drugs approved for use in the United States so as to maximize the chance of benefit while minimizing the risk of harm. For most drugs, only limited information is available in special populations, such as pediatric and pregnant patients, and additional caution is warranted.

### Overview of Optimal Antiarrhythmic Management

Although a complete discussion of the clinical use of antiarrhythmic drugs is beyond the scope of this chapter,
the following generalizations for commonly occurring arrhythmias may be made.

Atrial Fibrillation

Atrial fibrillation is the most common sustained tachyarrhythmia encountered in clinical practice. Management goals include (1) prevention of thromboembolism and stroke, (2) control of ventricular rate, and (3) restoration and maintenance of sinus rhythm. Consensus guidelines have been published that provide a framework for the evidence-based management of patients with atrial fibrillation (AF).7 The decision to recommend anticoagulation with warfarin in patients with AF is based on associated clinical characteristics (hypertension, age, congestive heart failure, diabetes mellitus, coronary artery disease, prior stroke, or transient ischemic attack) and not on the pattern or frequency/duration of AF. To date, no antiarrhythmic drug has been associated with a reduction in stroke risk in patients with AF and therefore antiarrhythmic drug therapy is not indicated as a method to eliminate the need for systemic anticoagulation. Control of ventricular rate by slowing impulse conduction through the AV node has been achieved for more than a century with digitalis preparations. Although effective at rest, digitalis is unable to control ventricular rate adequately during exercise or other clinical states with elevated levels of catecholamines. In many patients, better control may be achieved by utilizing beta-blocking agents or calcium channel blockers such as verapamil or diltiazem. In many cases, a combination of rate-controlling medications is required to achieve adequate rate control. Intravenous agents such as esmolol or diltiazem can be used to rapidly achieve rate control; longer-acting drugs can then be used for chronic therapy. Other antiarrhythmics, such as class Ic drugs, amiodarone, and dronedarone also slow the ventricular rate. Patients with excessive tachycardia due to inadequate rate control (average heart rate during the day above 100 beats per minute and the maximum heart rate more than 110% of the maximum predicted heart rate for that patient) may develop cardiomyopathy with progression to congestive heart failure. Patients whose heart rate is uncontrollable using combinations of agents (ie, digoxin and verapamil or propranolol) can be considered for catheter ablative techniques with concomitant permanent pacemaker implantation. Antiarrhythmic drugs are useful to restore sinus rhythm and lessen the duration between episodes of AF. Agents used for these purposes include class Ia drugs (quinidine, procainamide, and disopyramide); class Ic drugs (propafenone and flecainide); and class III agents (sotalol, amiodarone, dofetilide, and dronedarone). In general, antiarrhythmic drugs do not eliminate recurrent episodes of AF but can increase the duration of sinus rhythm between recurrences. Beta-blocking drugs, although not classically viewed as antiarrhythmic drugs for AF, are associated with a reduction in the incidence of AF immediately after cardiac surgery. Class III agents (amiodarone, dronedarone, sotalol, and dofetilide) are being used more frequently for control of AF. Ibutilide, a class III agent, is used in bolus fashion to chemically cardiovert patients to sinus rhythm. It has been effective in approximately 40% to 70% of patients. Nonpharmacologic techniques for control of AF are widely used and include radiofrequency catheter ablation/isolation of pulmonary veins, minimally invasive surgical MAZE and the open or full surgical MAZE procedure. A large multicenter study has been conducted by the National Institutes of Health (NIH) to determine whether optimized antiarrhythmic drug therapy administered to maintain sinus rhythm in patients having episodes of atrial fibrillation/atrial flutter (AF/AFL) has an impact on total mortality and disabling stroke when compared to optimized therapy that merely controls heart rate in patients with AF/AFL. (AF follow-up investigation of rhythm management [AFFIRM]).8 This study has shown that in these selected patients who tolerated AF sufficiently well that they were candidates for rate control, a strategy of rhythm control with the currently available antiarrhythmic drugs did not result in better outcomes. Effective anticoagulation was important for reduction of stroke risk with both approaches. Among available treatments, amiodarone was the most effective in maintaining sinus rhythm.

Atrial Flutter (AFL)

In many ways, management of atrial flutter (AFL) is similar to that of AF. Acute control of ventricular rate is usually achieved through intravenous (IV) therapy, using either a beta-blocking agent such as esmolol or propranolol or a calcium-channel blocking drug such as verapamil or diltiazem. Infusions of esmolol or diltiazem may be preferred due to their short half-life, which permits finer control of ventricular rate with a faster offset in the event that hypotension or excessive bradycardia develops. Chronic control of ventricular rate with AFL is difficult, but similar types of agents, given orally, are commonly used. Digoxin alone is rarely sufficient except in patients with intrinsic AV nodal dysfunction. Direct current (DC) cardioversion or atrial overdrive pacing are the most rapid methods used to restore sinus rhythm, although pharmacologic conversion may become more frequent in the future. Ibutilide appears uniquely able to rapidly terminate established AFL in a majority of patients.9 The risk of embolization and stroke after conversion from AFL appears to be less than with AF, although the majority of clinicians also anticoagulate patients with AFL. Oral antiarrhythmic drugs—such as quinidine, procainamide,
disopyramide, sotalol, amiodarone, dronedarone, dofetilide, flecainide, and propafenone—may be used to restore and maintain sinus rhythm. Particular care must be used when administering class Ia or Ic agents to patients with AFL. These drugs may slow the atrial rate, whereas the anticholinergic effects of some of these agents may facilitate AV nodal conduction, resulting in an acceleration of ventricular rate. Occasionally, 1:1 conduction of the flutter impulse may occur, resulting in a ventricular rate between 220 and 250 beats per minute, which may cause hemodynamic compromise. This complication may be averted by ensuring adequate AV nodal blockade prior to instituting therapy with these agents. Amiodarone slows AV conduction in addition to other antiarrhythmic properties and may be used as a single agent. Administration of adenosine to patients with AFL will increase AV block, allowing visualization of flutter waves. AV conduction may paradoxically improve after adenosine administration and has also caused 1:1 AV conduction. Radiofrequency catheter ablation of the isthmus of atrial tissue between the tricuspid valve and inferior vena cava annulus is effective at preventing recurrences of AFL and is increasingly being used as first-line therapy for typical AFL.10

**AV-Nodal Reentrant Tachycardia**

After AF and AFL, AV-nodal re-entrant tachycardia is the most common form of supraventricular tachycardia. This arrhythmia is caused by a re-entrant circuit within the AV node and perinodal tissues. Therefore, pharmacologic therapies are directed toward the AV node. Acute management includes vagal maneuvers such as carotid sinus massage or the Valsalva maneuver. Administration of adenosine or verapamil intravenously will universally terminate this arrhythmia. Similarly, IV beta blockers, diltiazem, or verapamil can be effective. Agents useful for long-term pharmacologic management include digoxin, beta-adrenergic receptor antagonists, and calcium channel antagonists such as verapamil or diltiazem. In unusual cases, propafenone, flecainide, or amiodarone may be useful. Patients with this arrhythmia are also very effectively treated with radiofrequency catheter modification of the AV-nodal slow pathway, which is curative.

**AV-Re-entrant Tachycardia (Wolff-Parkinson-White Syndrome)**

Patients with Wolff-Parkinson-White (WPW) syndrome have an anatomic fiber of myocardium that directly connects the atria and ventricles. This fiber may conduct cardiac impulses unidirectionally from atria to ventricles or from the ventricles to atria, but bidirectional impulse conduction is also common. Because of the presence of dual pathways (the normal AV conduction system being the antegrade or retrograde limb) for impulse conduction from atria to ventricles, re-entrant arrhythmias are possible. The most common tachycardia (orthodromic reciprocating tachycardia) uses the bypass tract in a retrograde (ventriculoatrial) direction and generally results in a narrow QRS tachycardia. Atrial fibrillation or flutter commonly occurs in conjunction with WPW syndrome; if the accessory pathway is capable of antegrade (AV) conduction, an irregular rhythm with both wide and narrow QRS complexes will occur, often at rapid rates (if the antegrade effective refractory period of the accessory pathway is short). Rarely, such patients will develop ventricular fibrillation (VF) from exceedingly rapid ventricular rates. The least common arrhythmia, antidromic reciprocating tachycardia, uses the bypass tract in an antegrade direction and results in a regular wide-complex arrhythmia resembling VT. Any of the above arrhythmias should be terminated using synchronized DC cardioversion if hemodynamic collapse is present. Patients with a narrow QRS tachycardia are best treated with vagal maneuvers, followed, if necessary, by IV adenosine, esmolol, diltiazem, or verapamil. Caution should be used with adenosine in patients with known WPW syndrome, since adenosine may produce AF. If rapid antegrade conduction over the bypass tract is possible, hemodynamic collapse may occur. A DC defibrillator should always be immediately available whenever adenosine is used. Patients with wide complex tachycardias and WPW syndrome should be treated as if they had VT. Intravenous procainamide or ibutilide is the therapy of choice if DC cardioversion is not required. Digoxin should not be used to treat patients with a bypass tract capable of antegrade conduction as it may accelerate impulse conduction over the tract.

The need for chronic pharmacologic therapy for patients with WPW syndrome has almost been completely eliminated by the success of radiofrequency catheter ablation. When necessary, patients without antegrade bypass-tract conduction may often be treated with either a beta blocker or a calcium channel blocking drug. Patients with antegrade bypass tract conduction or those with arrhythmia recurrences during therapy with beta blockers or calcium-channel blocking drugs should be treated with a class Ia, Ic, or III drug. Flecainide, propafenone, quinidine, procainamide, or disopyramide may be used, often in conjunction with a beta-blocking agent. Sotalol, dronedarone, or amiodarone may also be used.

**Atrial Tachycardia**

Atrial tachycardia is an uncommon supraventricular tachycardia caused by abnormal automaticity, triggered activity, or re-entry within the atria. Patients with structural heart disease, especially after surgical correction
of congenital heart disease, have re-entrant atrial tachycardias due to atrial suture lines. Automatic atrial tachycardias are often self-limited and may disappear after several months to years. Patients with atrial tachycardias are often symptomatic, and pharmacologic treatment is justified. Long-standing tachycardias, with heart rates in excess of 130 beats per minute, may produce a dilated cardiomyopathy and congestive heart failure.

Inappropriate sinus tachycardia is an uncommon disorder, still poorly understood. Abnormal autonomic influence on the sinus node, either excessive sympathetic tone or reduced vagal tone, is one possible explanation. The first-line therapy should be pharmacologic, including beta blockers, calcium-channel blockers, and class Ia or Ic agents.

Automatic tachycardias are sometimes amenable to treatment with beta blocking or calcium-channel blocking drugs such as propranolol or verapamil. In more resistant cases, class Ic drugs such as flecainide or propafenone may be helpful. Some cases of atrial tachycardia are refractory to pharmacologic therapy and require catheter ablation for control. Re-entrant atrial tachycardias often require therapy with class Ia, Ic, or III antiarrhythmic drugs. Sotalol, flecainide, and amiodarone are often used. Unlike automatic arrhythmias, re-entrant arrhythmias rarely are self-limited, requiring therapy for life. Patients with these arrhythmias often undergo catheter ablation to avoid lifelong antiarrhythmic drug therapy. Multifocal atrial tachycardia appears to result from a diffuse increase in atrial automaticity. It is commonly seen in patients with severe lung disease and may be facilitated by theophylline, inhaled or oral beta-adrenergic stimulants, and possibly digoxin. Therapy with either verapamil or metoprolol has been shown to be helpful, although any long-term therapy should include improving underlying lung function.

**Ventricular Tachycardia (VT)**

VT is a heterogeneous collection of ventricular tachyarrhythmias caused by several different arrhythmia mechanisms that occur in patients with varying degrees of structural heart disease. Most commonly, VT is a re-entrant arrhythmia occurring in a patient with coronary artery disease, prior myocardial infarction (MI), and frequently left ventricular (LV) dysfunction. Hemodynamic collapse is a common result of VT that is not self-terminating; sudden cardiac death is often the final result. Occasionally, VT may be hemodynamically tolerated. In these individuals, IV infusion of lidocaine, procainamide, or amiodarone may result in the slowing and often termination of arrhythmia. Ventricular overdrive pacing is also effective, but synchronized DC cardioversion (with appropriate sedation and anesthesia) is the quickest method to restore a normal rhythm. However, most episodes of VT terminate spontaneously and produce no symptoms. Optimal management of these patients is currently unknown.

Intravenous lidocaine, procainamide, and amiodarone are useful acutely for termination and prevention of VT recurrences. Class III agents sotalol, dofetilide, and amiodarone are increasingly being used as chronic therapy for symptomatic VT. Other useful agents include mexiletine, quinidine, procainamide, disopyramide, propafenone, and flecainide. Flecainide and propafenone should only be used in patients with VT in the absence of structural heart disease. All these agents have appreciable cardiac and noncardiac adverse effects, and each may be effective in only 10% to 30% of patients. In most instances, these drugs are used as adjunctive therapy to prevent VT recurrences in patients with an implanted cardioverter defibrillator.

VT with a continuously changing QRS morphology occurring in the setting of a prolonged QT interval (torsades de pointes) is a unique form of VT. This arrhythmia is often due to effects of antiarrhythmic drugs that prolong the action potential (classes Ia and III). Although this form of VT often terminates spontaneously, VF and sudden death may occur. Acute therapy consists of normalization of potassium and magnesium levels, along with acceleration of the heart rate to 110 to 120 beats per minute by pacing or infusion of isoproterenol. Chronic therapy consists of elimination of all agents that prolong the duration of action potentials. If it is necessary to treat other arrhythmias, amiodarone appears safe for use in patients with torsades de pointes despite its ability to markedly prolong the QT interval. Torsades de pointes can also occur as a familial form of arrhythmia as a result of mutations to DNA encoding either the cardiac sodium- or potassium-channel proteins.

Unusual forms of VT may occur in apparently structurally normal hearts. VT with left bundle branch morphology and an inferior frontal plane axis often originates from the right ventricular outflow tract. This arrhythmia is often catecholamine-sensitive; it is frequently induced by exercise. Beta-blocker drugs, calcium-channel blockers, or catheter ablation is usually effective. Another unique type of VT, idiopathic LV VT, has a right-bundle-branch QRS morphology with a superior frontal-plane axis. This VT is often responsive to verapamil; catheter ablation is also effective. However, most patients with right-bundle superior axis VT will not have the verapamil-sensitive type. It is also worth noting that verapamil should not be administered to patients during VT except when the VT is known by prior electrophysiologic testing to be verapamil-sensitive. Administration of verapamil to patients with VT and coronary artery disease has resulted in hypotension and several deaths.
Implantable cardioverter-defibrillators (ICDs) are currently being increasingly used for patients with recurrent hemodynamically destabilizing VT as well as for primary prophylaxis in patients with history of coronary artery disease (CAD) and LV systolic dysfunction.\textsuperscript{15}

**Ventricular Fibrillation (VF)**

Immediate DC countershock is the appropriate response to VF. After a hemodynamically stable rhythm has been restored, antiarrhythmic therapy may be useful to prevent recurrences of this lethal arrhythmia.\textsuperscript{15} Acceptable IV medications include lidocaine, procainamide, and amiodarone. Adjunctive therapies, such as relief of myocardial ischemia and correction of electrolyte imbalance, are often helpful. Small doses of an IV beta-blocking agent—such as propranolol, metoprolol, or esmolol—can have a surprisingly beneficial effect as well. Patients with frequent recurrences of VF whose intrinsic rhythm is relatively bradycardic may be helped by temporary atrial or ventricular pacing at heart rates of approximately 100 to 120 beats per minute. Chronic antiarrhythmic drug therapy for the prevention of recurrences of VF includes sotalol or amiodarone and should be done in conjunction with an ICD. Empiric therapy with amiodarone has been evaluated as one therapy arm in the multicenter Antiarrhythmic Drug Versus Implantable Defibrillator (AVID) study. In this study of 1016 patients with CAD, EF % = ejection fractions < 40%, and VF or VT with syncope/hemodynamic compromise were randomized to empiric therapy with amiodarone plus Holter/EP (electrophysiologic)-guided sotalol versus ICD. ICD therapy has proven to be currently being increasingly used for many atrial and ventricular tachyarrhythmias.

**Quinidine**

**Pharmacologic Description**

Quinidine, an optical isomer of quinine, is an alkaloid derived from cinchona bark. First described by van Helmont in 1648, quinidine was given its present name by Louis Pasteur in 1853. Use of cinchona in patients with AF was described by Jean Baptiste de Senac of Paris in 1749.

**Electrophysiologic Action**

Quinidine is a prototypic class Ia antiarrhythmic agent. It decreases the slope of phase 0 of the action potential, decreases the amplitude of the action potential, and slows conduction velocity in atrial, ventricular, and Purkinje tissue.\textsuperscript{15} In addition, quinidine delays repolarization, thereby increasing the duration of action potentials. Electrocardiographic effects include prolongation of the QT as well as corrected QT (QTc) and QRS intervals. QRS prolongation greater than 35% to 50% of baseline is usually associated with toxicity.

**Pharmacokinetics and Metabolism**

Quinidine is currently available as quinidine sulfate, quinidine gluconate, and quinidine polygalacturonate. The bioavailability of quinidine ranges from 47% to 96%, averaging 75%.\textsuperscript{15} The milligrams of quinidine base in different preparations vary and thus should be considered in dosing, particularly when switching formulations. The bioavailability of the gluconate preparation is 10% less than that of the quinidine sulfate. After oral ingestion of quinidine sulfate, peak plasma concentrations occur within 60 to 90 minutes. The gluconate preparation is more slowly absorbed, with peak levels occurring 4 hours after dosing. The elimination half-life ranges between 6 and 8 hours. The clearance of quinidine is decreased in patients with significant hepatic insufficiency and with advancing age.\textsuperscript{20,21} Smaller maintenance doses are required in these patients. Advanced renal disease has only minimal effects on quinidine clearance.\textsuperscript{21} Approximately 90% of quinidine is bound to plasma proteins. Several cardioactive metabolites have been identified including (3S)-3-hydroxyquinidine, (3OH) quinidine, and quinidine-N-oxide (QNO).\textsuperscript{23} Although these metabolites are less active than the parent compound (approximately 25% and 4% for 3OH-Q and QNO, respectively), in approximately one-fourth of patients their concentrations may approach or even exceed that of quinidine and con-
Antiarrhythmic Drugs

Quinidine is an alpha-adrenergic receptor antagonist that lowers peripheral vascular resistance. Whereas large oral doses can produce hypotension through this mechanism, the problem is most common with IV dosing. Although quinidine directly depresses myocardial contractility, clinically significant myocardial depression usually does not occur except with large IV doses.

Antiarhythmic Effects
Quinidine can suppress a wide variety of supraventricular and ventricular arrhythmias. In life-threatening ventricular tachyarrhythmias, quinidine has shown long-term efficacy in 15% to 30% of patients with VT or cardiac arrest when guided by electrophysiologic testing.\textsuperscript{24,25} Quinidine can also terminate AFL or fibrillation in many patients, especially when these conditions are of recent onset and if the atria are not enlarged. Quinidine also has vagolytic effects, which can enhance AV-nodal conduction. In some patients, this can result in an increased ventricular rate with some atrial tachyarrhythmias, such as AFL, unless an AV-nodal blocking agent is also given. Typically, therapeutic levels range from 3 to 6 \( \mu \text{g/mL} \).

Adverse Effects
Gastrointestinal adverse effects are common, with diarrhea and nausea the most bothersome. Quinidine may cause tinnitus, blurred vision, dizziness, light-headedness, and tremor, a syndrome known as cinchonism. Rarely, severe antibody-mediated thrombocytopenia, pancytopenia, or hemolytic anemia may occur. Adverse effects may require cessation of therapy in as many as 30% of patients.\textsuperscript{26} Up to 3% to 4% of patients receiving quinidine may develop quinidine syncope, a form of proarrhythmia usually caused by rapid polymorphic VT associated with prolongation of the QT interval (torsades de pointes). Other cases have been attributed to sinus pauses or first-dose hypotension related in part to alpha-adrenergic receptor blockade. The risk of serious proarrhythmia is greatest during the first few days of dosing, during bradycardia or hypokalemia. Many advocate the initiation of quinidine therapy in the hospital with electrocardiographic (ECG) monitoring, particularly in patients with cardiac dysfunction.

Interactions
Drugs that alter the kinetics of hepatic enzyme systems—such as phenobarbital, phenytoin, and rifampin—can increase hepatic metabolism of quinidine and reduce its concentration. Cimetidine, on the other hand, decreases hepatic metabolism of quinidine, increasing the plasma concentration.\textsuperscript{27} In addition, the concomitant administration of amiodarone increases the concentration of many antiarrhythmic drugs, including quinidine. Quinidine decreases serum levels of digoxin by decreasing digoxin clearance, volume of distribution, and affinity of tissue receptors for digoxin, and thus may contribute to digoxin toxicity.\textsuperscript{28,29} Digitoxin levels are also increased. Recently quinidine has been shown to be a potent inhibitor of cytochrome P450db1, a genetically determined polymorphic enzyme responsible for the oxidative metabolism of many drugs by the liver. Because of inhibition of this enzyme system, quinidine substantially decreases the metabolism of some drugs, such as encainide and propafenone, decreasing the concentration of their metabolites while increasing the concentrations of the parent compounds.\textsuperscript{30,31}

Indications and Dosage
Quinidine is indicated for the treatment of incapacitating atrial, AV-nodal, and ventricular tachyarrhythmias. The usual adult dose of quinidine sulfate is 200 to 400 mg four times daily, or less frequently with longer-acting preparations. Intravenous quinidine gluconate is occasionally used in special situations such as the electrophysiology laboratory and may be given using a dose of 6 to 10 mg/kg at a rate of 0.3 to 0.5 mg/kg/minute with frequent checks of blood pressure and ECG parameters. In some patients, efficacy can be enhanced by the concomitant use of class Ib or class II antiarrhythmic drugs, such as mexiletine, propafenone, and propranolol.\textsuperscript{32}

Procainamide
Pharmacologic Description
Procainamide hydrochloride is an amide analogue of procaine hydrochloride, a local anesthetic agent. It was introduced in 1951 for the treatment of both supraventricular and ventricular arrhythmias.\textsuperscript{33,34}

Electrophysiologic Action
Procainamide is a class Ia antiarrhythmic agent. It decreases phase 0 of the action potential, decreases the amplitude of the action potential, and slows conduction velocity in atrial, ventricular, and Purkinje tissue. In addition, procainamide increases the effective refractory periods of atrial and ventricular cells.\textsuperscript{35} Its major electrophysiologic effects on myocardial tissues are similar to those of quinidine. Normal sinus node automaticity is not affected. Procainamide is less vagolytic than quinidine and does not induce an adrenergic blockade. The major metabolite of procainamide, N-acetylprocainamide (NAPA), has different electrophysiologic effects, predominantly prolonging the duration of the action potential, a class III effect. ECG effects of procainamide include prolongation of the QT, QTc, and QRS intervals.
other individual antiarrhythmic agents as well. Failure to respond to procainamide during electrophysiologic testing in these cases often predicts failure with threatening ventricular arrhythmias and cardiac arrest. Procainamide is bound to plasma proteins. In adults, the elimination half-life varies between 2.5 and 4 hours. Elimination is more rapid in children, averaging 1.7 hours. Approximately 50% of procainamide is excreted unchanged by the kidney. Of the remainder, a variable portion undergoes hepatic acetylation to NAPA, a cardioactive metabolite. Depending on a patient's genetically determined acetylator phenotype, 16% to 22% (slow acetylators) or 24% to 33% (fast acetylators) of procainamide is metabolized to NAPA. Elimination of NAPA is approximately 85% dependent on the kidney, with an elimination half-life of 7 to 8 hours. Small amounts of NAPA may be deacetylated to procainamide.

Hemodynamic Effects
Procainamide can depress myocardial contractility but is usually well tolerated hemodynamically even by patients with moderately severe cardiac dysfunction. When given intravenously, hypotension may result from vasodilatation due to a mild ganglionic blocking action.

Antiarrhythmic Effects
Procainamide can effectively suppress a variety of atrial, AV-nodal, and ventricular tachyarrhythmias, including 20% to 30% of patients with sustained ventricular tachyarrhythmias. It is the drug of choice in the acute medical treatment of wide-complex tachycardias including AF with ventricular pre-excitation (WPW syndrome). A mild vagolytic effect may result in an increased ventricular rate due to enhanced AV-nodal conduction when given for supraventricular tachyarrhythmias such as AFL. Suppression of ventricular arrhythmias has been shown to occur at plasma levels between 4 and 10 mg/mL of procainamide, but higher levels may be required for suppression of sustained ventricular tachyarrhythmias. In addition, the contribution of NAPA to efficacy cannot always be ascertained. Procainamide has been used extensively with electrophysiologic testing for life-threatening ventricular arrhythmias and cardiac arrest. Failure to respond to procainamide during electrophysiologic testing in these cases often predicts failure with other individual antiarrhythmic agents as well.

Adverse Effects
Major adverse effects of procainamide are gastrointestinal, with nausea, vomiting, anorexia, or diarrhea occurring in up to 30% of patients. A bitter taste, dizziness, mental depression, and psychosis have also been reported. Drug-induced fever, rash, and hepatitis may occur. Agranulocytosis, sometimes fatal, has been described. Most patients will develop a positive antinuclear antibody titer if exposed to the drug for prolonged intervals. Of these, up to 30% can develop a drug-induced systemic lupus like syndrome. Slow acetylators may be at increased risk of procainamide-induced lupus due to increased production of a hydroxylamine metabolite, which appears to be important in the pathogenesis of this syndrome. Recently, procainamide-induced lupus anticoagulants have been described, which may increase the risk of thrombosis in some patients. As in the case of quinidine, new-onset polymorphic VT in the setting of QT prolongation has been reported. Procainamide usually causes only minimal depression of cardiac function with chronic dosing, but hypotension is not uncommon with rapid IV infusions.

Interactions
Unlike quinidine, procainamide does not significantly alter the pharmacokinetics of digoxin. Trimethoprim and cimetidine decrease renal clearance of procainamide and NAPA, resulting in increased plasma levels of both. Concomitant administration of amiodarone also increases procainamide levels.

Indications and Dosage
Procainamide is indicated for the treatment of incapacitating atrial, AV-nodal, and ventricular tachyarrhythmias. An average oral daily dose for patients under 50 years of age is 30 to 60 mg/kg, divided into equal doses given every 3, 4, or 6 hours. Various sustained-release formulations facilitate dosing on a 2-, 3-, or 4-times-per-day basis with lower peak and higher trough levels. In addition, efficacy may be enhanced in some patients with concomitant use of other agents, including beta blockers. Older patients or patients with renal insufficiency require smaller doses. Intravenous therapy can be initiated with loading infusion of up to 20 mg/kg given at a rate not to exceed 50 mg/minute. Frequent blood pressure and ECG checks are required. A maintenance IV dose is approximately 30 to 60 mg/kg/minute in a patient with normal renal function.

Disopyramide
Pharmacologic Description
Disopyramide phosphate was first noted to have antiarhythmic properties in 1962. It was subsequently released for clinical use in the United States in 1978. As currently available, disopyramide exists as a racemic combination of d and l enantiomers.

Electrophysiologic Action
The electrophysiologic effects of disopyramide are similar
to those of other class Ia agents, such as quinidine and procainamide. It produces a rate-dependent decrease in the rate of rise of phase 0 of the action potential, slows conduction velocity, and prolongs the effective refractory period more than it prolongs the action potential duration. Disopyramide may prolong the action potential duration to a greater extent in normal cells than in cells from infarcted regions of the heart. The different enantiomers of disopyramide have differing electrophysiologic effects: The d enantiomer prolongs action potential duration while the l enantiomer shortens it. The d enantiomer has approximately one-third the vagolytic properties of the l enantiomer. Disopyramide exerts strong anticholinergic effects that tend to counteract some of its direct electrophysiologic effects, particularly in the sinus and AV nodes. In humans, AV-nodal conduction is minimally affected by disopyramide. However, in the denervated heart, AV-nodal conduction is markedly depressed. Disopyramide can either increase or decrease the sinus rate, depending on prevailing cholinergic tone.

ECG effects of disopyramide include prolongation of the QRS, QT, and QTc intervals.

Pharmacokinetics and Metabolism
Disopyramide is available in regular and sustained-release capsule formulations. An IV preparation is undergoing clinical investigation. After an oral dose, disopyramide is almost completely absorbed with peak plasma concentrations occurring within 2 hours. Peak levels occur from 4 to 6 hours after ingestion of sustained-release disopyramide capsules. The elimination half-life is 6 to 9 hours, with 40% to 60% excreted unchanged by the kidney. Approximately 50% of disopyramide is excreted unchanged in the urine; an additional 20% is excreted as the monon-dealkylated metabolite, with another 10% excreted as other metabolites. Protein binding is highly variable, ranging from 40% to 90% depending on plasma concentration. At higher doses, a greater concentration of drug is unbound, resulting in a greater pharmacologic effect than would be predicted based on the total plasma level. The clinical significance of this effect is unknown. Alpha-1-acid glycoprotein accounts for the majority of protein binding with albumin accounting for only 5% to 10% of the total.

Hemodynamic Effects
Disopyramide causes significant depression of myocardial contractility with reductions in systemic blood pressure, stroke index, and cardiac index. Systemic vascular resistance and right atrial pressure increase. Patients with LV dysfunction tolerate disopyramide poorly. In a retrospective study among patients with pre-existing congestive heart failure, 55% of patients given disopyramide had clinically significant worsening of their heart failure. In contrast, only 3% of patients without a history of congestive heart failure developed this complication during disopyramide therapy. The drug has been used as a treatment for hypertrophic cardiomyopathy, both as a monotherapy and in combination with beta blockers.

Antiarrhythmic Effects
Like other class Ia antiarrhythmic drugs, disopyramide is effective in a variety of supraventricular and ventricular tachyarrhythmias. Disopyramide can suppress premature ventricular contractions with plasma concentrations in the range of 3 to 8 mg/mL but is less effective with sustained VT as assessed by electrophysiologic testing. Disopyramide has been combined with other antiarrhythmic agents, such as mexiletine, for increased efficacy in treating ventricular arrhythmias with fewer adverse effects. Disopyramide has been used successfully for the treatment of AFL and AF, including patients with WPW syndrome. Disopyramide may also be effective for preventing inducible and spontaneous neurally mediated syncope due to its negative inotropic and anticholinergic properties.

Adverse Effects
Disopyramide significantly depresses myocardial contractility and must be used with caution if at all in patients with LV dysfunction. Anticholinergic adverse effects are frequent and in up to 10% of patients may necessitate discontinuation of the drug. These symptoms include dry mouth, blurred vision, and particularly in older men, urine retention. Disopyramide can also precipitate acute angle-closure glaucoma. Gastrointestinal symptoms are uncommon. As with other drugs that prolong ventricular repolarization and the QT interval, disopyramide can induce polymorphic VT (torsades de pointes). Rare adverse effects include rash, cholestatic jaundice, psychosis, and agranulocytosis. Hypoglycemia occurs infrequently, apparently owing to increased pancreatic secretion of insulin.

Interactions
Drugs that induce hepatic enzymes, such as phenytoin and phenobarbital, increase hepatic metabolism of disopyramide and result in lower serum levels. Disopyramide does not induce hepatic enzymes, however. Disopyramide does not alter serum digoxin levels. Erythromycin has been reported to increase disopyramide levels, with development of potentially fatal ventricular arrhythmias. The potent negative inotropic effects of disopyramide warrant additional caution in patients with possible cardiac dysfunction requiring therapy with beta blockers or calcium-channel blockers for indications such as ischemic heart disease.

Indications and Dosage
Disopyramide is indicated for the prevention or suppres-
sion of premature ventricular contractions and VT. It has also been used to treat atrial arrhythmias. The usual adult oral dose is 300 to 1600 mg daily, divided into 3 or 4 equal doses. Dosage must be reduced in elderly patients and in patients with renal insufficiency. The controlled-release capsules may be given every 12 hours.

**Class Ib Agents**

Class Ib drugs also block sodium channels but to a lesser degree than class Ia drugs. The association and disassociation kinetics are more rapid than in class Ia drugs, typically less than one second. In addition, repolarization tends to be mildly shortened. Class Ib drugs often suppress premature ventricular contractions but are only occasionally effective as monotherapy for life-threatening ventricular tachyarrhythmias. Class Ib drugs, as a class, are generally ineffective for atrial arrhythmias.

**Lidocaine**

**Pharmacologic Description**
Initially synthesized in 1943, lidocaine is widely used as a local anesthetic agent. Its antiarrhythmic properties were noted in the 1950s, but its use did not become common until the advent of coronary care units in the 1960s.

**Electrophysiologic Action**

Lidocaine is classified as a class Ib antiarrhythmic drug. The action potential duration and effective refractory period of Purkinje and ventricular tissues are shortened. At high concentrations, it depresses the rate of rise of phase 4 of the action potential and decreases conduction velocity in Purkinje fibers. Lidocaine has minimal effects on AV and intraventricular conduction except at high velocity in Purkinje fibers. Lidocaine has minimal effects on AV and intraventricular conduction except at high velocity in Purkinje fibers. In patients with severe His-Purkinje system disease, lidocaine may precipitate complete AV block. Lidocaine decreases phase 4 diastolic depolarizations in Purkinje tissue and decreases automaticity. Consequently, lidocaine may depress both the sinus node and potential subsidiary escape pacemakers, rarely causing asystolic pauses. Lidocaine increases the VF threshold. In abnormal myocardium, the effects of lidocaine in depressing conduction may be more pronounced.

**Pharmacokinetics and Metabolism**

Lidocaine is almost completely absorbed after oral administration, but approximately 70% is rapidly metabolized by hepatic first-pass biotransformation. Less than 10% of an administered dose is recovered unchanged in the urine. For this reason, the drug is almost always given parenterally; however, rectal administration is feasible, as is intramuscular administration, particularly in the prehospital phase of the management of acute MI. Lidocaine is approximately 60% to 80% protein-bound, depending on the concentration of alpha₁-acid glycoprotein in the serum. During acute MI, serum levels of alpha₁-acid glycoprotein are increased, resulting in more drug bound to alpha₁-acid glycoprotein and less free (active) drug. Thus, higher total lidocaine levels may be required during acute MI. Lidocaine is almost completely cleared by the liver, with clearance proportional to hepatic blood flow. The mean elimination half-life of lidocaine in humans is 1.5 to 2 hours, which is increased in the elderly, patients with reduced cardiac output, and patients with hepatic disease. Elimination is also delayed during prolonged infusions in patients with acute MI, the mechanism of which is not understood. The two principal metabolites are glycinexylidide and monoethyglycinexylidide (MEGX), both of which have weaker antiarrhythmic effects in humans than does lidocaine but can contribute measurably to the central nervous system toxicity of lidocaine. Both metabolites are renally excreted, and glycinexylidide may accumulate in patients with renal failure.

**Hemodynamic Effects**
At usual doses, lidocaine causes minimal hemodynamic effects. Minimal decreases in cardiac output, arterial blood pressure, heart rate, and ventricular contractility have been reported.

**Antiarrhythmic Effects**

Lidocaine can be effective for the suppression of ventricular tachyarrhythmias, particularly in patients with myocardial ischemia. Prophylactic use of lidocaine after MI, once a common practice, has been abandoned as prophylactic use of any class Ia agents after MI has been associated with increased mortality. It also appears to reduce the incidence of VF. Therapeutic plasma concentrations range from 2 to 5 μg/mL.

**Adverse Effects**
Adverse effects of lidocaine almost always involve the central nervous system. Early, transient effects include paresthesias, dizziness, and drowsiness, which can be managed by interrupting the drug temporarily. Later, more persistent effects include hallucinations, confusion, somnolence, and muscle tremor, which presage impending seizures, respiratory, or cardiac arrest. Rarer, lidocaine can depress sinus node function or precipitate heart block in patients with severe His-Purkinje system disease; it can also inhibit escape rhythms from His-Purkinje tissue. Adverse effects of lidocaine are common when the plasma concentration exceeds 6 μg/mL.

**Interactions**
Lidocaine is highly dependent on hepatic metabolism for
elimination. Drugs that alter hepatic metabolism cause marked changes in lidocaine pharmacokinetics. Propranolol, metoprolol, cimetidine, and halothane decrease lidocaine clearance.102

Indications and Dosage
Lidocaine is indicated for the acute management of ventricular arrhythmias, such as those associated with acute MI or cardiac surgery. It may be administered intravenously as a bolus of 0.7 to 1.4 mg/kg at a rate of 25 to 50 mg per minute. If necessary, this dose may be repeated in 5 minutes followed by a continuous infusion of 0.014 to 0.057 mg/kg (1–4 mg/minute). Alternative loading and maintenance infusion regimens have also been advocated, typically entailing a total of 2 to 4 mg/kg in divided doses over 30 minutes. Lidocaine may be given by intramuscular injection of 300 to 400 mg (4.3 mg/kg) for use during acute MI.99 The deltoid muscle is the preferred injection site. Lidocaine has also been used in combination with other agents including procainamide, bretylium, and beta blockers.

**Mexiletine**

Pharmacologic Description
Mexiletine hydrochloride is a drug closely related in structure to lidocaine. Initially developed as an anticonvulsant, mexiletine has been recognized to have antiarrhythmic properties since 1972.99,100 Used in Europe to treat ventricular arrhythmias since 1976, it became available in the United States in 1986.

Electrophysiologic Action
Mexiletine decreases the rate of rise of phase 0 of the action potential and shortens the action potential’s duration.99,101 The effective refractory period is decreased in Purkinje tissue but not in ventricular muscle.102 The slope of phase 4 diastolic depolarization is decreased. The electrophysiologic effects of mexiletine are similar to those of other class Ib agents. Usually, no significant changes occur in the PR, QRS, QT, or QTc intervals with either IV or oral mexiletine.103 In patients with normal His-Purkinje function, no significant changes are observed after mexiletine. Patients with His-Purkinje system disease may develop prolongation of conduction and rarely block, however. In addition, prolongation of QRS duration has been reported with mexiletine toxicity.104

Pharmacokinetics and Metabolism
Mexiletine is highly bioavailable, with approximately 90% absorption.105 Absorption occurs in the alkaline environment of the proximal small bowel. Peak plasma levels occur in 2 to 3 hours but may be delayed in clinical situations, such as acute MI or diabetes mellitus, in which gastric emptying is delayed. Some 50% to 60% of mexiletine is protein-bound. Mexiletine is extensively metabolized in the liver; only 10% is excreted unchanged by the kidney.106 Several metabolites have minor electrophysiologic activity, the most potent (N-methylmexiletine) having less than 20% of the effect of the parent compound. In healthy subjects, the average elimination half-life is 10 hours, ranging from 8 to 12 hours.106 Renal insufficiency has minimal effect on elimination half-life, whereas hepatic insufficiency or reduced hepatic blood flow reduces mexiletine clearance.105,107

Hemodynamic Effects
Mexiletine generally has minimal negative inotropic effects at therapeutic levels. Small decreases in blood pressure and LV contractility with increased LV end diastolic pressure have been observed in some studies. Administered orally, mexiletine produced no changes in LV EF, blood pressure, heart rate, or exercise capacity.106

Antiarrhythmic Effects
Mexiletine may be used to suppress frequent and high-grade ventricular arrhythmias, including those that have failed to respond to class Ia antiarrhythmic drugs. Used alone, mexiletine is only infrequently effective in suppressing life-threatening ventricular arrhythmias.109 Combination therapy with class Ia antiarrhythmic agents can be more effective than either agent alone, with potentially less toxicity.109-112 Mexiletine is effective in suppressing warning ventricular arrhythmias in a number of patients with acute MI.113,114 The antiarrhythmic response to lidocaine may be used as a sensitive but nonspecific predictor of mexiletine efficacy.115,116 Thus, failure to respond to IV lidocaine is a strong predictor of mexiletine inefficacy, while lidocaine efficacy only weakly predicts mexiletine efficacy. Similarly, the response to either tocainide or mexiletine is not necessarily predictive of the response to the other. Plasma concentrations of 0.5 to 2.0 mg/mL are associated with efficacy in many patients.

Adverse Effects
Adverse effects are common with mexiletine, occurring in up to 40% to 60% of patients in some series.103 The most frequent adverse effects are related to the central nervous system or the gastrointestinal tract and include nausea, vomiting, dizziness, tremor, ataxia, slurred speech, blurred vision, memory impairment, and personality changes. Skin rash and hepatitis occur infrequently. Rarely, seizures have been reported. Gastrointestinal adverse effects may be reduced by administering the drug with food or by reducing the dosage. Adverse cardiac effects are rare, but worsening of congestive heart failure and proarrhythmic effects have been reported.

Interactions
No specific adverse effects have been reported to date.
from combining mexiletine with other cardiotoxic agents, such as beta blocking drugs or other antiarrhythmics. Significant alkalinization of the urine by drugs may decrease renal clearance and result in elevated blood levels. Drugs such as phenobarbital or phenytoin, which induce hepatic enzymes, enhance mexiletine metabolism; cimetidine reduces metabolism and results in increased mexiletine levels.

**Indications and Dosage**

Mexiletine is indicated for the suppression of incapacitating ventricular arrhythmias, including VT. Effective oral regimens usually require 200 to 400 mg every 8 hours. Doses should be given with food to minimize adverse effects. Dosages may be increased or decreased by 50 to 100 mg at intervals of at least 2 to 3 days. An IV preparation is not available in the United States and is associated with a relatively high incidence of adverse effects. Intravenous therapy has been given as a loading dose of 400 mg over 40 minutes with 600 to 900 mg per day for maintenance therapy.

**Class Ic Agents**

Class Ic drugs are potent sodium-channel blocking agents. They have little effect on repolarization and have long half-time kinetics of channel association and dissociation, usually greater than 20 to 30 seconds. Thus, drug effects are potentiated at moderate to rapid heart rates. They are effective for a variety of atrial and ventricular tachyarrhythmias. As a class, the Ic drugs are highly effective in suppressing chronic ventricular ectopy. Unfortunately, the marked slowing of conduction induced by these agents is an efficient mechanism to induce ventricular proarrhythmia. This effect is most marked in patients with significant structural heart disease but may occur in normal individuals, especially in the setting of rapid heart rates, such as those produced by exercise.

**Flecainide**

**Pharmacologic Description**

Flecainide acetate, a fluorobenzamide, is a derivative of procainamide first synthesized in 1972. Its antiarrhythmic effects were first reported in 1975, and it was released for the treatment of ventricular arrhythmias in the United States in 1985. Subsequently it has been approved for the treatment of supraventricular arrhythmias in the United States in 1985. Subsequently it has been approved for the treatment of ventricular arrhythmias in the United States in 1985,117 Subsequently it has been approved for the treatment of supraventricular arrhythmias including AFL and AF in patients with structurally normal hearts.

**Electrophysiologic Action**

Flecainide exhibits potent sodium channel blocking action, depressing phase 0 of the action potential and slowing conduction in a frequency- and dose-dependent manner throughout the heart. His-Purkinje tissue and ventricular muscle are affected the most, followed by atrial muscle, accessory AV pathways, and AV-nodal tissue. In most studies, the action potential duration is not significantly affected. Sinus rate, sinoatrial conduction, and sinus node recovery times are usually not affected by flecainide. However, patients with sinus node dysfunction may have significant increases in the corrected sinus node recovery time.119 Flecainide produces a concentration-dependent increase in PR, QRS, and intra-atrial conduction intervals as well as prolongation of the ventricular effective refractory period.120,121 An IV dose of 2 mg/kg (mean level 335 mg/L) produced a mean QRS increase of 23%.121 The QT interval increases, reflecting QRS prolongation, with minimal to no change in the JT interval.

**Pharmacokinetics and Metabolism**

Flecainide is well absorbed (95%), with peak plasma concentrations occurring 2 to 4 hours after dosing. Flecainide is 30% to 40% bound to plasma proteins, independent of drug level, over a range of 0.015 to 3.4 μg/mL.122 Clinically important drug interactions based on protein-binding effects would therefore not be expected. In healthy subjects, 30% (range 10% to 50%) of flecainide is excreted unchanged in the urine. Approximately 70% of flecainide is metabolized in the liver. The major metabolite (meta-O-dealkylated flecainide) is approximately 20% as potent as the parent compound, while the minor metabolite (meta-O-dealkylated lactam of flecainide) is electrophysiologically inactive. The average elimination half-life is 20 hours after repeated doses, but is highly variable and ranges between 12 and 27 hours.123,124 Steady-state levels are not obtained for 3 to 5 days. Since flecainide is extensively metabolized, the relationship between flecainide elimination and creatinine clearance is complex. Reduced doses must be used in patients with renal or hepatic insufficiency.125,126

**Hemodynamic Effects**

Flecainide produces dose-dependent depression of cardiac contractility and cardiac output. Oral treatment is generally well tolerated, but patients with LV dysfunction may develop new or worsening congestive heart failure. Flecainide should not be used in patients with LV dysfunction.127,128

**Antiarrhythmic Effects**

Flecainide is effective in suppressing both supraventricular and ventricular tachyarrhythmias and premature contractions. Flecainide is able to suppress chronic premature ventricular contractions by more than 75% and repetitive forms by more than 90% in most patients, including patients resistant to other antiarrhythmic
Propafenone

Pharmacologic Description

Propafenone hydrochloride, an antiarrhythmic agent structurally similar to beta-blocking drugs, was first synthesized in 1970. Commercially available since 1977 in Europe, propafenone is approved in the United States for the treatment of life-threatening ventricular arrhythmias and supraventricular arrhythmias in patients with structurally normal hearts. Propafenone exists as a racemic mixture of d-propafenone and l-propafenone.

Electrophysiologic Action

Propafenone blocks the fast inward sodium current in atrial, ventricular, and His-Purkinje tissue, decreasing the rate of rise of phase 0 of the action potential. The blocking effect is concentration-dependent, with ischemic tissue being more susceptible. In patients with ventricular pre-excitation or bypass tracts, propafenone decreases conduction velocity and increases refractoriness of the accessory pathway. Sinus node automaticity may be depressed, especially in the presence of preexisting sinus node dysfunction. Propafenone possesses weak beta-adrenergic and calcium-channel antagonist activities. Both stereoisomers appear to have equal sodium channel blocking ability while d-propafenone is responsible for the clinically observed beta blockade. Propafenone suppresses delayed afterdepolarizations in ischemic Purkinje fibers. Endocardial pacing thresholds are increased. Electrocardiographic effects include prolongation of the PR and QRS intervals without significant change of the QT interval.

Pharmacokinetics and Metabolism

Absorption of propafenone is almost complete after oral dosing, with peak plasma levels obtained in 2 to 3 hours, but extensive first-pass metabolism reduces systemic bioavailability to approximately 12%. The availability appears to vary with the dose, so that higher doses have increased bioavailability, probably due to saturation of hepatic microsomal enzymes with larger doses. About 77% to 79% of propafenone is protein-bound, with alpha,-acid glycoprotein being the major binding protein. The metabolism of propafenone is polymorphic and segregates with the debrisoquin metabolic phenotype. Extensive metabolizers form 2 major metabolites (5-hydroxypropafenone and N-depropyl-propafenone). Poor metabolizers have high levels of propafenone and therefore more beta-blocking effect and minimal levels of active metabolites. Overall, however, electrophysiologic effects appear similar in both groups given comparable doses. Elimination of propafenone is mostly hepatic; less than 1% is recovered intact in the urine. The average elimination half-life ranges from 3.6 to 7.2 hours.

Indications and Dosage

Flecainide is indicated for the treatment of life-threatening ventricular arrhythmias such as sustained VT, as well as resistant supraventricular arrhythmias in patients with normal ventricular function. In patients with normal renal and hepatic function, treatment may be begun with 100 mg every 12 hours. Dose adjustments should be no larger than 50 mg per dose every 4 days to minimize toxicity. Total daily doses of 200 to 300 mg are associated with efficacy in most patients. Patients with LV dysfunction or a history of VT should have therapy initiated using smaller dosages with continuous electrocardiographic monitoring in a hospital environment.
patients with hepatic disease, the elimination half-life is prolonged, averaging 14 hours. Doses must be decreased in these patients.

Hemodynamic Effects
Propafenone has negative inotropic effects. In several studies, occasional patients with depressed cardiac function have had hemodynamic deterioration. Most patients experience no change in resting LV EF, although EF may decrease with exercise. One study using IV propafenone (2 mg/kg) showed a slight depression of cardiac index with increased pulmonary vascular resistance but no change in systemic arterial pressure. Thus, caution is necessary if propafenone is used in patients with LV dysfunction.

Antiarrhythmic Effects
Propafenone appears effective in treating both supraventricular and ventricular arrhythmias. As other class Ic antiarrhythmic agents, propafenone is effective in suppressing frequent premature ventricular contractions, including complex forms. It is less effective in treating life-threatening ventricular arrhythmias, but even in this difficult population, up to 25% of patients may respond. Propafenone has also been shown to be effective in treating supraventricular tachyarrhythmias, such as AF/AFL, including patients with WPW syndrome. Propafenone should be used cautiously in patients with recent MI in view of the recent CAST findings showing increased mortality in this population when treated with other class Ic drugs (flecainide or encainide).

Adverse Effects
Approximately 21% to 32% of patients experience adverse reactions to propafenone; 3% to 7% require discontinuation of the medication. Worsening of ventricular arrhythmias was reported to occur in 6.1% of 1,579 patients in early clinical trials of propafenone. Patients at highest risk include those with LV dysfunction and those with preexisting sustained VT. Noncardiac adverse effects are predominantly gastrointestinal or related to the central nervous system. Dizziness, light-headedness, nausea, vomiting, or a metallic taste occurs most frequently. Central nervous system effects and effects related to beta-adrenergic blockade may be more frequent in individuals with a poor metabolizer phenotype.

Interactions
Propafenone in a dose of 300 mg every 8 hours orally increases digoxin levels an average of 83%; the magnitude of increase seems related to the dose of propafenone. Significant increases in plasma warfarin concentrations and prothrombin times have been reported. Propafenone concentrations may increase with concomitant cimetidine therapy. Propafenone also decreases metoprolol elimination, resulting in increased beta-adrenergic blockade. Quinidine in low doses effectively stops hepatic metabolism of propafenone, converting rapid metabolizers to poor metabolizers. The clinical significance of this interaction is unknown.

Indications and Dosage
Propafenone is approved for the treatment of ventricular arrhythmias. Therapy for both supraventricular and ventricular arrhythmias may be initiated using a dosage of 150 mg three times a day; doses up to 900 mg (occasionally 1,200 mg) daily have been used. High-dose oral propafenone (600 mg) has also been shown to be very safe and effective in restoring sinus rhythm in patients with recent onset AF with conversion rates of up to 76% at 8 hours after treatment. Intravenous propafenone has been evaluated for supraventricular and ventricular arrhythmias at doses such as 2 mg/kg followed by a maintenance infusion, but this formulation remains investigational in the United States. A new sustained-release formulation has been proven safe and effective and will be available soon for clinical use.

Class II Agents
Class II drugs are beta-adrenergic blocking agents. Different beta blockers will vary with respect to lipid solubility, membrane-stabilizing effect, relative specificity for the beta, receptor, cardioselectivity, and partial agonist activity (intrinsic sympathomimetic activity). As a class, beta blockers are useful for the treatment of many atrial and AV-nodal arrhythmias (see Chapter 5, Alpha- and Beta-Adrenergic Blocking Drugs). In addition, some beta blockers may reduce ventricular ectopy. Several beta-blocking agents have been shown to reduce mortality when administered after acute MI and may be useful as primary or adjunctive agents in some patients with or at risk for life-threatening ventricular tachyarrhythmias.

Propranolol
Pharmacologic Description
Propranolol hydrochloride is a nonselective beta-adrenergic-receptor blocking agent. It is indicated in the United States for the treatment of supraventricular and ventricular arrhythmias. It is also indicated for the treatment of hypertrophic cardiomyopathy, acute MI, angina pectoris, hypertension, and numerous noncardiac conditions such as migraine headache and essential tremor.

Electrophysiologic Action
The electrophysiologic effects of propranolol relate primarily to its beta-blocking activity, an effect almost en-
Propranolol is a competitive nonselective beta blocker. Beta receptors predominate in cardiac tissue, blockade of which produces an increase in the sinus node cycle length and slowing of AV nodal conduction. At high concentrations, propranolol depresses the inward sodium current in Purkinje fibers, the so-called membrane-stabilizing or quinidine-like effect. This effect generally occurs only at concentrations several times that required for beta blockade and is thus probably insignificant clinically. Propranolol can shorten the duration of action potentials acutely in Purkinje fibers and to a lesser extent in atrial and ventricular muscle. With chronic administration, the action potential may lengthen. ECG effects include a slowing of sinus rate and an increase in the PR interval with minimal or no change in QRS and QTc intervals. The effective refractory period is minimally increased.

**Pharmacokinetics and Metabolism**

Propranolol is almost completely absorbed after oral administration but undergoes extensive first-pass metabolism in the liver, resulting in a bioavailability of approximately 30%. Peak clinical effects occur between 60 and 90 minutes after oral dosing. The average biologic half-life is 4 hours. A long-acting formulation is also available for once-daily use. Elimination is hepatic and is proportional to hepatic blood flow. With oral dosing, a total of 160 to 240 mg daily is considered necessary for achieving effective beta blockade, although smaller doses are often used in antiarrhythmic regimens. With IV dosing, a total dose of 0.2 mg/kg achieves effective beta blockade, with activity evident almost immediately.

**Hemodynamic Effects**

Propranolol is a negative inotropic agent by virtue of its beta-blocking action. It may precipitate or worsen congestive heart failure. By blocking beta receptors in the peripheral circulation, propranolol may increase vascular resistance.

**Antiarrhythmic Effects**

Propranolol is an effective agent for the treatment of supraventricular arrhythmias such as atrial tachycardia. It will slow the ventricular response to AF/AFL and may terminate arrhythmias requiring participation of the AV node, such as AV-nodal reciprocating tachycardias and those associated with WPW syndrome and accessory pathways. Propranolol has a variable effect on the rapid ventricular response to AF due to accessory pathway conduction. Propranolol can be effective in treating arrhythmias due to digitalis toxicity, thyrotoxicosis, and anesthesia and as adjunctive therapy for pheochromocytoma. Ventricular premature contractions may be suppressed by propranolol, but it is infrequently effective as a single agent in the treatment of life-threatening ventricular tachyarrhythmias. Propranolol may be more effective in preventing rapid polymorphic VTs or VF than monomorphic VT when assessed by electrophysiologic testing. Propranolol can be an effective adjunctive agent in combination with other agents, with caution to avoid additive depressant effects on conduction and contractility. Beta blockers have also been used successfully in some patients with congenital QT prolongation and associated ventricular tachyarrhythmias, including torsades de pointes. Therapeutic plasma levels for propranolol are highly variable but often range from 50 to 100 ng/mL.

**Adverse Effects**

Common adverse effects include bradycardia, hypotension, claudication, Raynaud’s phenomenon, and AV block. Worsening of heart failure or asthma may occur. Propranolol is lipophilic and easily penetrates the blood-brain barrier, contributing to central nervous system adverse effects such as vivid dreams, insomnia, mental depression, and possibly fatigue and impotence. Insulin-dependent diabetics may be at increased risk for hypoglycemia. Sudden discontinuation of beta blockade may worsen angina and may even precipitate acute MI.

**Interactions**

Negative inotropic drugs such as verapamil or disopyramide should be used cautiously with propranolol in patients with LV dysfunction. Propranolol and verapamil in combination may occasionally precipitate AV block. Antacids containing aluminum hydroxide significantly reduce absorption of propranolol. Phenytoin, phenobarbital, and rifampin accelerate hepatic metabolism of propranolol, resulting in reduced serum concentrations; cimetidine increases serum concentrations of propranolol. Propranolol, by decreasing cardiac output, can reduce the systemic clearance of lidocaine, theophylline, and antipyrine.

**Indications and Dosage**

Arrhythmic indications for propranolol include supraventricular arrhythmias and arrhythmias associated with thyrotoxicosis or digitalis toxicity as well as arrhythmias associated with increased catecholamine states. Propranolol may be effective for ventricular ectopy and some ventricular tachyarrhythmias. Propranolol, along with other beta-blocking agents, has been shown to reduce cardiovascular mortality for at least 2 to 3 years after acute MI. As a class, these drugs are the only antiarrhythmic agents shown to reduce mortality in patients following acute MI. Intravenous doses should be given under ECG monitoring beginning with 0.25 to 1.0 mg using up to 0.2 mg/kg total dose. Oral dosages are highly variable, ranging from 20 to 240 mg daily or more, divided into 3 or 4 intervals for antiarrhythmic therapy. Longer-acting preparations
may allow once- or twice-daily dosing. Doses of 180 to 240 mg daily in 2 or 3 divided doses are recommended to reduce mortality after MI.\textsuperscript{170}

**Acebutolol**

**Pharmacologic Description**

Acebutolol hydrochloride is a relatively cardioselective beta\textsubscript{1}-adrenergic receptor antagonist with mild intrinsic sympathomimetic activity. It is available in the United States for the treatment of hypertension and ventricular arrhythmias.

**Electrophysiologic Action**

The electrophysiologic effects of acebutolol are predominantly related to its beta\textsubscript{1}-receptor blocking activity. At rest, the sinus cycle length increases minimally owing to intrinsic sympathomimetic activity. The sinus response to exercise is markedly blunted, however. Although acebutolol possesses membrane-stabilizing activity (sodium-channel blocking ability) in high concentrations, this effect does not appear to be important clinically.\textsuperscript{172} ECG effects consist of prolongation of the PR interval (AH interval) with minimal if any change in the QTc interval. The QRS duration is unchanged.

**Pharmacokinetics and Metabolism**

Following oral administration, acebutolol is well absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism, resulting in an absolute bioavailability of 40% (range 20% to 60%). The major metabolite, an N-acetyl derivative (diacetolol), is approximately equally active but is more cardioselective than the parent compound. Acebutolol is 26% bound to plasma proteins.\textsuperscript{173} Peak plasma concentrations of acebutolol are reached 2.5 hours after oral ingestion, whereas peak levels of diacetolol occur at 3.5 hours. The elimination half-life of acebutolol is 3 to 4 hours, whereas the half-life for diacetolol is 8 to 13 hours. Forty percent of acebutolol is eliminated by the kidneys; diacetolol is almost entirely renally excreted. In the presence of renal impairment, plasma concentrations of acebutolol are not significantly changed, but concentrations of diacetolol increase two to threefold. Therefore, dose reduction is necessary with renal insufficiency.

Because acebutolol and diacetolol are hydrophilic, only minimal concentrations of these compounds are found within the central nervous system.

**Hemodynamic Effects**

Like propranolol, acebutolol decreases heart rate and cardiac contractility. The potential for heart rate slowing is somewhat less with acebutolol owing to its partial agonist activity. Blood pressure reduction typically is proportional to baseline pressure, but hypotension may occur in previously normotensive individuals.

**Antiarrhythmic Effects**

The beta-blocking activity of acebutolol is approximately 25% that of propranolol on a milligram-to-milligram basis. Acebutolol can suppress premature ventricular contractions, including complex forms, in many patients. Patients with exercise-induced arrhythmias may respond favorably to acebutolol. Acebutolol is also effective for various supraventricular arrhythmias, especially those related to excessive catecholamine states or those which require participation of the AV node, such as AV-nodal and AV reciprocating tachycardias. A randomized, double blind, placebo-controlled trial including 600 post-MI patients (APSI trial), demonstrated that a rather low dose of acebutolol, 200 mg twice daily, decreased cardiovascular mortality by 58%.\textsuperscript{174}

**Adverse Effects**

Adverse effects related to acebutolol are similar to those of other beta-blocking agents. Patients with congestive heart failure, hypotension, severe peripheral vascular disease, brittle diabetes mellitus, or bronchospastic lung disease should not be treated with acebutolol, despite its partial agonist activity. Similarly, acebutolol may depress sinus node and AV-nodal function. Fatigue, headache, reversible mental depression, skin rash, agranulocytosis, development of antinuclear antibodies, alopecia, and Peyronie's disease have been reported.

**Interactions**

Although specific interactions have not been reported with acebutolol, caution should be used if it is given with other drugs known to depress automaticity, conduction, or cardiac contractility or other drugs known to interact with beta blockers.

**Indications and Dosage**

Acebutolol is indicated for treatment of ventricular premature contractions. It is also effective for some supraventricular arrhythmias. The initial antiarrhythmic dosage usually is 200 mg twice daily, with total daily doses up to 600 to 1200 mg necessary in some patients.\textsuperscript{175}

**Esmolol**

**Pharmacologic Description**

Esmolol hydrochloride, a phenoxypropanolamine, is a beta\textsubscript{1}-selective adrenergic-receptor blocking agent. Esmolol is similar in chemical structure to the beta blocker metoprolol but contains an ester linkage on the para position of the phenyl ring. Because of this ester linkage, esmolol has an ultrashort plasma half-life of 9 minutes. It has no
appreciable intrinsic sympathomimetic or membrane-stabilizing activity. On a milligram-to-milligram basis, esmolol is approximately 1/50th as potent as propranolol.

Electrophysiologic Action
Electrophysiologic effects of esmolol are those typical of beta blockade. Esmolol increases the sinus node’s cycle length and slows AV-nodal conduction. AV-nodal refractoriness is increased as a result of decreased sympathetic tone. Thus, esmolol may be effective when used to slow the ventricular response to AF or AFL in treating arrhythmias requiring participation of the AV node, such as reciprocating tachycardias. Electrocardiographic effects consist of prolongation of the PR interval with no significant changes in QRS or QTc duration.

Pharmacokinetics and Metabolism
Esmolol is rapidly metabolized by hydrolysis of the ester linkage, chiefly by esterases in the cytosol of red blood cells. The distribution half-life of esmolol is 2 minutes; the elimination half-life is 9 minutes, necessitating continuous infusion or repeated boluses for sustained effects. Metabolism of esmolol results in a negligible amount of methanol and an acid metabolite. Less than 2% of esmolol is recovered in the urine. The metabolite has about 1/1500th the beta-blocking activity of esmolol and is eliminated with a half-life of 3.7 hours in individuals with normal renal function. Unlike the metabolism of many other agents with ester groups, the metabolism of esmolol is unaffected by plasma cholinesterase. With continuous high-dose infusion of esmolol, levels of methanol approximate endogenous methanol levels with concentrations reaching only 2% of those associated with methanol toxicity. Esmolol is about 55% bound to plasma proteins, while the acid metabolite is only 10% bound.

Hemodynamic Effects
Esmolol produces a dose-dependent decrease in heart rate, cardiac contractility, cardiac output, and blood pressure. Recovery of these effects is nearly complete within 15 to 30 minutes after discontinuation of the infusion. In clinical trials, approximately 10% to 30% of patients (particularly those with borderline-low or low-normal pretreatment blood pressures) treated with esmolol developed transient hypotension, defined as a systolic pressure less than 90 mm Hg or a diastolic pressure less than 50 mm Hg. Twelve percent of patients were symptomatic.

Antiarrhythmic Effects
Esmolol has been used mainly in acute settings to control the ventricular response to supraventricular arrhythmias. In a multicenter double-blind, randomized study, esmolol was as effective as propranolol, resulting in at least a 20% reduction in ventricular rate in 72% of patients. Conversion to sinus rhythm occurred in 14%. In other studies, esmolol compared favorably with verapamil, with a significantly greater percentage of conversion to sinus rhythm.

Adverse Effects
The principal adverse effect of esmolol is hypotension. Other adverse effects are typical of beta blockers and include increased heart failure, dyspnea, Bradycardia, decreased peripheral perfusion, nausea, vomiting, irritation at the infusion site, and headache. To avoid phlebitis, esmolol should not be infused using concentrations in excess of 10 mg/mL. For a typical patient requiring 50 to 150 mg/minute, 20 to 60 mL/h of fluid administration is required, necessitating attention to volume status.

Interactions
Esmolol can be very effective when used in combination with digoxin, and the effects on the AV node are additive. Concomitant administration of esmolol and morphine results in a 46% increase in steady-state levels of esmolol. Esmolol prolongs the metabolism of succinylcholine-induced neuromuscular blockade by 5 to 8 minutes. Esmolol should be administered with caution in patients prone to bradycardia, AV block, or hypotension or patients on other medications likely to potentiate these effects.

Indications and Dosage
Esmolol is indicated for the acute management and rapid control of ventricular rate in patients with AF or AFL and in some patients with noncompensatory sinus tachycardia. Therapy is usually initiated with a loading dose of 500 μg/kg over one minute, followed by a maintenance infusion of 25 to 50 μg/kg/minute. Dose titration can be performed after 5 minutes and consists of additional boluses of 500 μg/kg over one minute, followed by an increase in the maintenance infusion by 25 to 50 μg/kg/minute. Most patients are controlled with a maintenance infusion of 50 to 200 μg/kg/minute. Esmolol may also be useful in the management of acute myocardial ischemia or infarction, although this has not been studied extensively. The effects of prolonged infusions of esmolol (longer than 48 hours) also have not been fully evaluated.

Class III Agents
Class III drugs prolong the duration of action potential and increase refractoriness. The effect is often mediated by blockade of potassium channels during phase 2 or 3 of the action potential. Some newer agents prolong the duration of the action potential by activating sodium channels during the plateau phase.
Amiodarone

Pharmacologic Description

Amiodarone hydrochloride, an iodinated benzofuran derivative, was initially developed as a vasodilating agent for the treatment of angina. Thirty-seven percent of its molecular weight is iodine. In 1970, it was subsequently found to have potent antiarrhythmic properties. It has been used extensively for the treatment of supraventricular and ventricular arrhythmias, especially in Argentina, Israel, and Europe. Both oral and IV preparations are available in the United States for the treatment of life-threatening ventricular arrhythmias.

Electrophysiologic Action

Amiodarone has been shown to have class I, II, III, and IV effects. It is a weak, noncompetitive inhibitor of alpha- and beta-adrenergic receptors. Its predominant action on cardiac tissue consists of prolongation of the duration of the action potential and increases in refactoriness. It is a weak, noncompetitive inhibitor of alpha- and beta-adrenergic receptors. Its predominant action on cardiac tissue consists of prolongation of the duration of the action potential and increases in refactoriness. Amiodarone has only slight effects on the rate of rise of phase 0 of the action potential. Conduction velocity is decreased, however, apparently owing to effects on resistance to passive current flow rather than effects on the inward sodium current.

Amiodarone has differential effects on the 2 components of cardiac rectifier K⁺ current, depending on the length of treatment. ECG effects consist of a slowing of the sinus rate and prolongation of the PR, QRS, and QT intervals. Amiodarone also prolongs the refractory period of accessory AV pathways in patients with bypass tracts or WPW syndrome. The time course of onset of antiarrhythmic action varies, with effects on the sinus and AV nodes occurring within 2 weeks of therapy, while prolongation of the ventricular functional refractory period, QT prolongation, and ventricular antiarrhythmic effects are not maximal for up to 10 weeks.

Pharmacokinetics and Metabolism

When the drug is administered orally, absorption of amiodarone is slow and erratic. Bioavailability ranges from 22% to 65% in most patients. Peak plasma concentrations occur between 3 and 7 hours after a single oral dose. Even with loading doses, maximal antiarrhythmic effects may not appear for several days to months. Amiodarone is 95% protein-bound and has a large but variable volume of distribution of approximately 60 L/kg. Amiodarone and its major metabolite, desethylamiodarone, are highly lipophilic and accumulate throughout the body, including liver, adipose tissue, lung, myocardium, kidney, thyroid, skin, eye, and skeletal muscle. Elimination is principally hepatic via biliary excretion.

Enterohepatic recirculation may occur. The elimination of amiodarone is biphasic, with an initial half-life of 2.5 to 10 days; the terminal elimination half-life is 26 to 107 days, with most patients in the 40- to 55-day range. Desethylamiodarone has an elimination half-life averaging 61 days.

Hemodynamic Effects

With IV administration, amiodarone decreases heart rate, myocardial contractility, and systemic vascular resistance. Coronary vasodilatation may also occur. Rapid IV administration may produce profound hypotension, partly related to systemic vasodilation caused by the vehicle Tween-80. A cyclodextrin-based formulation of IV amiodarone to reduce hypotension is currently in development. Oral amiodarone usually does not worsen congestive heart failure, even in patients with severe LV dysfunction, although caution is warranted, especially with high doses used during drug loading, since some patients may show hemodynamic deterioration.

Antiarrhythmic Effects

A large number of studies have documented the efficacy of amiodarone in suppressing supraventricular and ventricular arrhythmias even when other agents were ineffective. Amiodarone is very effective in chronic maintenance of sinus rhythm in patients with AF, although it is not approved for this indication in the United States. Daily doses of 200 to 400 mg have shown the efficacy of 53% to 79% for sinus rhythm maintenance. It was more effective than sotalol or propafenone in the maintenance of sinus rhythm in patients with chronic paroxysmal or persistent AF. The drug is often used in patients with life-threatening ventricular tachyarrhythmias who are unresponsive to other antiarrhythmic agents. A composite of 10 reports from the literature showed that amiodarone prevented recurrent sustained VT or VF in 66% of 567 patients during a mean follow-up of 13 months.

The prognostic utility of electrophysiologic testing with amiodarone remains controversial. The ability to induce VT using programmed ventricular stimulation during therapy with amiodarone does not preclude a good outcome. Patients rendered not inducible by amiodarone have a good outcome. Induction of a hemodynamically well-tolerated ventricular tachyarrhythmia apparently suggests a relatively favorable prognosis. Suppression of ventricular ectopy on ambulatory monitoring by amiodarone is an unreliable indicator of success, whereas failure to suppress ventricular ectopy appears to indicate a worse prognosis. Therapeutic plasma concentrations are usually between 1.0 and 2.0 μg/mL with chronic dosing. Several trials have shown that amiodarone may improve mortality, or at least not worsen mor-
Amiodarone is a nonselective beta-adrenergic antagonist introduced in 1965 for the treatment of hypertension. It is without significant intrinsic sympathomimetic activity or membrane-stabilizing activity. Sotalol prolongs the action potential duration, however, accounting for its class III designation. The antiarrhythmic effects in humans were reported in 1970. Sotalol is a nonselective beta-adrenergic antagonist introduced in 1965 for the treatment of hypertension. It is without significant intrinsic sympathomimetic activity or membrane-stabilizing activity. Sotalol prolongs the action potential duration, however, accounting for its class III designation. The antiarrhythmic effects in humans were reported in 1970.

The electrophysiologic effects of sotalol are those of beta blockade and class III activity. Sotalol exists as a racemic mixture of d-sotalol and l-sotalol. The d-sotalol form has about 1/50th the beta-blocking activity of l-sotalol, but both are equally responsible for class III effects. Sotalol causes an increase in the duration of the action potential and the refractory period of human
atria, ventricles, AV node, Purkinje fibers, and accessory pathways. Conduction velocity is reportedly not decreased by sotalol except for the beta-blocking effects on nodal tissues. ECG effects consist of increases in the PR, QT, and QTc intervals. QRS duration and the HV interval are unchanged.

Pharmacokinetics and Metabolism
Sotalol is rapidly absorbed following oral administration, with bioavailability varying from 60% to nearly 100%. Sotalol is not bound to plasma proteins, and more than 75% of an administered dose is recovered unchanged in the urine. No metabolites have been detected. The elimination half-life averages 10 to 15 hours, permitting twice daily dosing. Sotalol will accumulate in patients with renal but not hepatic insufficiency.

Hemodynamic Effects
Prolongation of the duration of the action potential allows more time for calcium ions to enter a cell, potentially increasing the inotropic state of the cell. Sotalol appears unique among beta-blocking agents in this regard. Studies in isolated muscle preparations, animals, and humans suggest that sotalol may cause less depression of contractility than other beta-blocking drugs. Nevertheless, sotalol can reduce blood pressure and precipitate or worsen congestive heart failure in some patients.

Antiarrhythmic Effects
Sotalol has been used effectively for the treatment of supraventricular and ventricular tachyarrhythmias, including WPW syndrome. Sotalol has been effective in terminating many supraventricular arrhythmias or slowing the ventricular response to AF or flutter. In 1 study, oral sotalol produced a beneficial response in 31 of 33 patients with atrial arrhythmias. Other studies have found sotalol effective in the treatment of life-threatening ventricular arrhythmias when assessed by electrophysiologic testing, including those refractory to class I antiarrhythmic agents. Polymorphic VT (torsades de pointes) in the setting of a prolonged QT interval has occurred with sotalol, often in association with either hypokalemia or renal insufficiency (high sotalol levels). Sotalol has also been shown to reduce defibrillation thresholds as well as the frequency of ICD shocks for VT/VF.

Adverse Effects
Rates of bronchospasm, fatigue, impotence, depression, and headache are similar to those of other beta-blocking drugs. Sinus node slowing, AV block, hypotension, and worsening of congestive heart failure may occur. Rare cases of retroperitoneal fibrosis have been reported. Polymorphic VT is a potentially life-threatening adverse reaction to sotalol. Its incidence may be minimized by careful attention to electrolyte status as well as avoiding high serum concentrations or excessive bradycardia. Chronic oral therapy with sotalol can increase the serum level of cholesterol as in the case of other beta blockers without partial agonist activity. The clinical significance of this effect is unknown.

Interactions
Significant drug interactions have not been reported. However, sotalol should be administered with caution with agents that produce hypokalemia or prolong the QT interval. In addition, sotalol should be used cautiously with drugs that depress cardiac contractility, especially in patients with LV dysfunction and those with contraindications to beta blockers.

Indications and Dosage
Sotalol is effective for the treatment of supraventricular and ventricular tachyarrhythmias. Oral therapy is usually begun with 80 mg administered twice daily. Total daily doses greater than 480 mg should rarely be used. Dosage reduction is necessary in patients with mild to moderate renal insufficiency, and sotalol should probably not be used in patients with severe renal insufficiency. IV doses of 0.2 to 1.0 mg/kg, now available, have been used in the acute treatment of arrhythmias. The d stereoisomer of sotalol (d-sotalol) was withdrawn from further clinical testing after it was shown to be associated with increased cardiac and all-cause mortality as compared with a placebo in patients with history of MI and reduced LV function.

Ibutilide
Pharmacologic Description
Ibutilide fumarate, a class III antiarrhythmic agent that prolongs repolarization, was approved by the US Food and Drug Administration (FDA) for IV use in the United States. Ibutilide is structurally similar to sotalol but is devoid of any clinically significant beta-adrenergic blocking activity.

Electrophysiologic Action
Ibutilide affects the duration of action potentials of atrial, ventricular, and His-Purkinje cells in a unique dose-dependent manner. At low concentrations, ibutilide prolongs the duration of action potentials, whereas at higher concentrations, the duration decreases. Unlike other class III agents, such as sotalol or N-acetylpromacainamide, ibutilide prolongs the duration of action potentials by activating an inward sodium current during the plateau phase of the action potential in addition to blocking an outward potassium current.

Pharmacokinetics and Metabolism
Ibutilide is well absorbed after oral administration but,
like lidocaine, is rapidly metabolized in the liver to a degree that oral bioavailability is small. Thus, oral administration does not appear practical. Ibutilide has a large volume of distribution (10 to 15 L/kg), with a terminal elimination half-life of between 6 and 9 hours. Rapid distribution after IV administration accounts for the disappearance of QT prolongation several minutes after dosing.

**Hemodynamic Effects**

No significant effects on cardiac contractility have been seen in animal models. In addition, a study of hemodynamic function in patients with EFs both above and below 35% showed no clinically significant effects on cardiac output, mean pulmonary artery pressure, or pulmonary capillary wedge pressure at doses of up to 0.03 mg/kg.

**Antiarrhythmic Effects**

In animal studies and in phase 2 clinical trials, ibutilide has shown efficacy in prevention of induction of VT during programmed electrical stimulation. Ibutilide appears to decrease the defibrillation threshold in dogs. In human studies, ibutilide has been investigated most extensively for its ability to terminate established AFL or AF. Up to 60% of patients with AFL and approximately 40% of those with AF will revert to sinus rhythm with 0.025 mg/kg of ibutilide given intravenously. Patients with a more recent onset of arrhythmia had a higher rate of conversion. Ibutilide pretreatment can also facilitate electrocardioversion of AF.

**Adverse Effects**

To date, the most significant adverse effect observed in clinical trials of ibutilide is the development of polymorphic VT (torsades de pointes), which has occasionally become sustained and requires cardioversion. It occurs in about 1.7% of patients treated and is dose-related. The risk of polymorphic VT is higher in patients with systolic dysfunction. Rare episodes of advanced-degree AV block and infra-His conduction block have been reported.

**Interactions**

Class Ia as well as class III antiarrhythmic drugs should not be given concomitantly with ibutilide infusion or within 4 hours postinfusion because of their potential to prolong refractoriness. The potential for proarrhythmia may increase with the administration of ibutilide to patients who are being treated with drugs that prolong the QT interval, such as phenothiazines, tricyclic antidepressants, and certain antihistamine drugs.

**Indications and Dosage**

Ibutilide is indicated for the acute treatment (cardioversion) of recent onset AFL or AF. Patients whose atrial arrhythmias were sustained longer than 90 days were not evaluated in clinical trials. A dose of 1 mg is administered over 10 minutes intravenously. After an additional 10 minutes, the dose may be repeated if needed. Patients weighing under 60 kg should have the dose reduced.

**Dofetilide**

**Pharmacologic Description**

Dofetilide has Vaughn Williams class III antiarrhythmic activity. The mechanism of action is the blockade of the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current I\textsubscript{Kr}. At all studied concentrations, dofetilide blocks only I\textsubscript{Kr} with no relevant block of the other repolarizing potassium currents. It has no effect on sodium channels, alpha receptors, or beta receptors.

**Electrophysiologic Action**

Dofetilide increases the duration of action potentials in a predictable, concentration-dependent manner, primarily due to delayed repolarization. It increases the effective refractory period of both atria and ventricles. It does not have an effect on PR interval or QRS width. Dofetilide does not increase the electrical energy required to convert electrically induced VF, and it significantly reduces the defibrillation threshold in patients with VT and VF undergoing implantation of a cardioverter-defibrillator device.

**Pharmacokinetics and Metabolism**

The oral bioavailability of dofetilide is > 90%, with maximum plasma concentration occurring at about 2 to 3 hours. Oral bioavailability is not affected by food intake or antacid use. Steady-state concentration is reached within 2 to 3 days, and half-life is about 10 hours. Plasma protein binding is 60% to 70%, and the volume of distribution is 3 L/kg. Eighty percent of the drug is excreted in urine unchanged and the remaining 20% comprises five minimally active metabolites. In patients with renal impairment, the half-life is longer and the clearance of dofetilide is decreased.

**Hemodynamic Effects**

In hemodynamic studies, dofetilide had no effect on cardiac output, cardiac index, stroke volume index, systemic vascular resistance in patients with VT, mild to moderate congestive heart failure or angina, and either normal or low LV EF. There was no evidence of a negative inotropic effect related to dofetilide therapy in patients with AF. There was no increase in heart failure in patients with significant LV dysfunction or any significant change in blood pressure. Heart rate was decreased by 4 to 6 beats per minute in studies.

Dofetilide use is usually safe in patients with structural heart disease, including patients with impaired LV function.
function (EF ≤ 35%) (Diamond CHF)\textsuperscript{233-235} or recent MI (Diamond MI).\textsuperscript{236}

**Antiarrhythmic Effects**

Dofetilide, like most other class III antiarrhythmic agents, has antifibrillatory activity in the atria; this property is of importance for the conversion and maintenance of sinus rhythm in patients with AF/AFL.\textsuperscript{237-239} In a placebo-controlled blinded study, the conversion rate was 31% in AF patients, 54% in AFL patients, and 0% in those on the placebo.\textsuperscript{240}

**Adverse Effects**

Dofetilide can cause ventricular arrhythmia, primarily torsades de pointes associated with QT prolongation. Prolongation of the QT interval is directly related to the plasma concentration of dofetilide. Factors such as reduced creatinine clearance or dofetilide drug interactions will increase the plasma concentration of dofetilide. The risk of torsades de pointes can be reduced by controlling the plasma concentration through adjustment of the initial dofetilide dose according to creatinine clearance and by monitoring the ECG for excessive increases in the QT interval.

In patients with supraventricular arrhythmias, the overall incidence of torsades was 0.8% to 3.3% in patients with congestive heart failure (CHF) and 0.9% in patients on dofetilide with recent MI. The majority of the episodes of torsades de pointes occurred within the first 3 days of treatment. The rate of torsades de pointes was reduced when patients were dosed according to their renal function. Other adverse reactions reported were headache, chest pain, dizziness, and respiratory tract infection.

**Interactions**

The use of dofetilide in conjunction with other drugs that prolong the QT interval is not recommended. Such drugs include phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides. Class I or III antiarrhythmic should be withheld for at least 3 half-lives prior to dosing with dofetilide. In clinical trials, dofetilide was administered to patients previously treated with oral amiodarone only if serum amiodarone levels were below 0.3 mg/L or amiodarone had been withdrawn for at least 3 months.

Dofetilide is metabolized to a small degree by the CYP3A4 isoenzyme of the cytochrome P450 system, and an inhibitor of this system could increase systemic dofetilide exposure. Concomitant use of the following drugs is contraindicated: cimetidine, verapamil, ketoconazole, and trimethoprim alone or in combination with sulfamethoxazole.

**Indication and Dosage**

The use of dofetilide is indicated for the maintenance of normal sinus rhythm (delay in time to recurrence of AF/AFL in patients with AF/AFL of greater than one week’s duration who have been converted to normal sinus rhythm. Because dofetilide can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom AF/AFL is highly symptomatic. Dofetilide is also indicated for the conversion of AF/AFL to normal sinus rhythm. Dofetilide has not been shown to be effective in patients with paroxysmal AF.

Therapy with dofetilide must be initiated (and if necessary reinitiated) in a setting that provides continuous ECG monitoring. Patients should continue to be monitored in this way for a minimum of 3 days. Additionally, patients should not be discharged within 12 hours of electrical or pharmacologic conversion to normal sinus rhythm.

Because prolongation of QT interval and the risk of torsades de pointes are directly related to plasma concentrations of dofetilide, dose adjustment must be individualized according to calculated creatinine clearance and QTc. The QT interval should be used if the heart rate is < 60 beats per minute. If the QTc > 440 milliseconds (500 milliseconds in bundle branch block) or creatinine clearance < 20 mL/minute, dofetilide is contraindicated. The dose adjustment according to the creatinine clearance is shown in Table 17-2. During loading, a 12-lead ECG should be done 2 to 3 hours after the dose and the QT checked.

If patients do not convert to normal sinus rhythm within 72 hours of initiation of dofetilide therapy, electrical conversion should be considered, with subsequent monitoring for 12 hours postcardioversion.

**Table 17-2. Dofetilide Dose Adjustment According to Calculated Creatinine Clearance**

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dofetilide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 mL/min</td>
<td>Dofetilide is contraindicated</td>
</tr>
<tr>
<td>20 to 40 mL/min</td>
<td>125 μg bid</td>
</tr>
<tr>
<td>40 to 60 mL/min</td>
<td>250 μg bid</td>
</tr>
<tr>
<td>&gt; 60 mL/min</td>
<td>500 μg bid</td>
</tr>
</tbody>
</table>


**Dronedarone**

**Pharmacologic Description**

Dronedarone is a deiodinated benzofuran derivative. It has a structure similar to amiodarone without the iodine moieties and with the addition of a methylsulfonamide
group.241-242a The elimination of iodine moieties was intended to reduce the likelihood of thyroid and possibly other organ toxicity. The addition of the methylsulfonamide group was intended to reduce the lipophilicity of dronedarone and thus reduce the neurotoxicity associated with amiodarone.

Electrophysiologic Action
Dronedarone, like amiodarone, is an inhibitor of multiple transmembrane potassium currents including the delayed rectifier (I_{Kt} and I_{Kp}); ultrarapid-delayed rectifier (I_{Ksr}); inward rectifier (I_{Kr}) and transient outward current (I_{to}); as well as sodium and L-type calcium currents. The short-term effects of dronedarone are similar to those of amiodarone.242b In animal studies, dronedarone inhibited ischemia-induced arrhythmias, reduced sinus rate, and had a sympatholytic effect characteristic of amiodarone.243 Animal data have shown that despite the deletion of iodine from the molecule, the major electrophysiologic properties of dronedarone are very similar to those of amiodarone. It reduced sinus frequency in vivo and in vitro, with a significant prolongation of the duration of action potentials in the rabbit ventricular myocardium and a corresponding prolongation of ventricular refractory period; it exhibited even less reverse-use dependency of repolarization than that found with amiodarone.244 There also appears to be an AV nodal slowing effect as demonstrated by a reduction in the ventricular rate during AF seen in clinical trials.245

Pharmacokinetics and Metabolism
Dronedarone has a half-life of 30 hours with increased bioavailability in the presence of food intake. It is largely metabolized by the cytochrome P-450 3A4 isof orm (CYP3A4) with minimal renal clearance. Dronedarone inhibits the renal tubular secretion of creatinine, which can lead to an increase in plasma creatinine levels without a clear reduction in renal function.

Hemodynamic Effects
Resting values of LV EF, fractional shortening, LV dP/dT, and mean blood pressure remained unchanged after dronedarone administration, whereas resting heart rate was significantly and dose-dependently reduced in dogs with healed MI.246

Antiarrhythmic Effects
A series of large clinical trials have been conducted with Dronedarone. Two trials (ADONIS and EURIDIS) evaluating the effectiveness of dronedarone as an antiarrhythmic drug to maintain sinus rhythm in patients with AF—demonstrated rates of sinus rhythm of approximately 35% compared to 25% with the placebo after 1 year of therapy.246 The DIONYSOS study compared dronedarone with amiodarone in a 6-month study of efficacy for the suppression of AF and found that dronedarone was not as effective as amiodarone in maintaining sinus rhythm but was better tolerated in regard to adverse effects.247 The ANDROMEDA study (Antiarrhythmic trial with Dronedarone in Moderate to Severe Heart Failure Evaluating Morbidity Decrease) tested the effectiveness of dronedarone to reduce mortality in patients with symptomatic chronic heart failure and depressed LV function. The study was terminated early due to excessive mortality in patients treated with dronedarone.248 The reason for this excessive mortality remains unclear but resulted in the need for the ATHENA trial, a large safety trial,249 evaluating the safety of dronedarone in approximately 4500 patients with AF, among whom 25% had depressed LV function, but none had severe heart failure. In this trial dronedarone was associated with a reduction in arrhythmic deaths but not total mortality and a 25% reduction in cardiovascular hospitalizations largely due to a decrease in AF-related admissions. In addition, post hoc analysis revealed a reduction in stroke incidence with dronedarone.250 The ERATO study formally evaluated the utility of dronedarone as a rate-controlling drug (Efficacy and Safety of Dronedarone for the Control of Ventricular Rate),251 and it was found to be a safe and effective agent for ventricular rate control in patients with AF.

Adverse Effects
The major adverse effects associated with dronedarone are gastrointestinal including abdominal pain, nausea and diarrhea in up to 6% of patients. There appears to be no increased incidence of thyroid, liver, lung, skin or neurological adverse effects.

Interactions
Dronedarone is a CYP3A4 substrate with a significant increase in drug concentration associated with concomitant use of potent CYP3A4 inhibitors such as ketoconazole. Grapefruit juice is a moderate inhibitor of CYP3A and can result in a three-fold increase in dronedarone effect. Statin therapy has also been associated with an increase in dronedarone exposure. Dronedarone should not be taken in patients with class IV heart failure, nor in those receiving drugs or herbs that prolong the ECG QT interval. Dronedarone also blocks the P-glycoprotein transporter and may result in a two-fold increase in digoxin levels. There appears to be no significant increase in INR in association with concomitant warfarin use, and there is an interaction with some HMG CoA reductase inhibitors. There is also a mild food-fast effect, so it is recommended to be taken with meals.

Indications and Dosage
Dronedarone is indicated for the suppression of AF/AFL
and to reduce the risk of cardiovascular hospitalizations in patients with paroxysmal or persistent AF or atrial flutter. The dose is 400 mg PO twice daily without a loading protocol.

New Class III Agents in Development

See Chapter 37, Cardiovascular Drugs in Development.

Celivarone (SSR149744C)

Celivarone is another noniondinated amiodarone derivative that is a multichannel blocker with antiadrenergic properties.\(^{252}\) In a safety and efficacy study in patients with AF, Celivarone was found to be generally safe and moderately effective.\(^{253}\)

Budiodarone

Budiodarone (ATI-2042) is another amiodarone-like drug in clinical development.\(^{254}\) It is structurally similar to amiodarone, including the iodine moieties that may be an important component of its antiarrhythmic effect. It differs from amiodarone in that it is more rapidly metabolized through the esterase pathway and may have a lower likelihood of accumulation in end organs such as the liver, lung, and thyroid.

Vernakalant

Vernakalant is a novel chemical agent that is the first in a new class of “atrially selective” drugs.\(^{255}\) These agents target ion channels that are limited to the atrium (\(I_{\text{ur}}\) and \(I_{\text{ach}}\)) and therefore minimize the chance for significant toxicity in the form of ventricular proarrhythmia. Vernakalant is a multichannel blocker that predominantly blocks the \(I_{\text{ur}}\) channel with some inhibition of \(I_{\text{to}}\) and \(I_{\text{Na}}\) as well. The \(I_{\text{Na}}\) blockade is frequency dependent and results in minimal slowing of conduction due to the very rapid offset kinetics of this drug. Human studies have also demonstrated a modest AV nodal rate-slowing effect during AF.\(^{256}\) Vernakalant use is associated with mild QT prolongation but no reported cases of torsades de pointes.

Vernakalant is available in the IV and oral formulations. The half-life of vernakalant is 2 to 3 hours. It is administered at a dose of 3 mg/kg over 10 minutes followed by a 15-minute observation period. A second dose of 2 mg/kg can be administered if AF persists. The IV form of vernakalant has been demonstrated to restore sinus rhythm in 50% of patients with short duration AF (< 72 hours) with a lower efficacy for longer duration AF.\(^{257}\) A similar study demonstrated efficacy for conversion of AF in the post cardiac surgery population.\(^{258}\) Vernakalant has been demonstrated to convert AF to atrial flutter in approximately 8% of cases but has not been associated with atrial flutter and 1:1 conduction. Vernakalant is not effective at terminating AFL.

The most common adverse effects of IV vernakalant include nausea, sneezing, and alterations in taste, all of which resolve within 15 minutes of therapy.

Class IV Agents

Class IV antiarrhythmic drugs are the nondihydropyridine calcium-channel blocking agents (see Chapter 8, Calcium Channel Blockers).

Verapamil

Pharmacologic Description

Verapamil hydrochloride, a synthetic papaverine derivative, was the first calcium-channel blocking agent to be used clinically. It is indicated for the treatment of supraventricular arrhythmias and for control of ventricular rate at rest and during exercise in patients with AF/AFL, as well as in certain forms of ventricular tachyarrhythmias that occur in patients with structurally normal hearts.

Electrophysiologic Action

The principal electrophysiologic effect of verapamil is inhibition of the slow inward calcium current. Verapamil prolongs the time-dependent recovery of excitability and the effective refractory period of AV-nodal fibers.\(^{259}\) It has little effect on fibers in the lower AV node (NH region) and no effect on atrial or Purkinje action potentials, which are activated by a rapid sodium current. However, verapamil may be effective in suppressing triggered arrhythmias arising from ventricular or Purkinje tissue.\(^{260}\) Expected ECG changes consist of prolongation of the PR interval with no significant change in QRS or QT duration. Verapamil may also depress sinus node function (automaticity and conduction), particularly when it is abnormal.

Pharmacokinetics and Metabolism

Verapamil is almost completely (more than 90%) absorbed after oral administration but undergoes extensive first-pass metabolism. Absolute bioavailability ranges from 20% to 35%, with peak plasma levels occurring 1 to 2 hours after dosing.\(^{261}\) Verapamil is 90% bound to plasma proteins. The l isomer of verapamil undergoes more rapid metabolism than the d isomer; the l-verapamil isomer is also more active electrophysiologically.\(^{261}\) Twelve metabolites of verapamil have been identified; the major one, norverapamil, can reach concentrations equal to those of the parent compound with chronic dosing.
The cardiovascular activity of norverapamil is approximately 20% that of verapamil. After single oral doses, the elimination half-life of verapamil varies from 3 to 7 hours; with multiple doses, the half-life ranges from 3 to 12 hours. Elimination half-life is usually prolonged with increasing age. In 1 study, the elimination half-life in patients over the age of 61 years was 7.4 hours, compared with 3.8 hours in individuals under 36 years of age. The elimination of verapamil may also be prolonged in patients with AF or with hepatic dysfunction.

Hemodynamic Effects
Verapamil produces negative inotropic, dromotropic (AV and SA nodes), and chronotropic (SA node) effects. However, it is well tolerated in most individuals, even in those with LV dysfunction. Hypotension, bradycardia, AV block, and asystole have occurred on occasion. Simultaneous use of verapamil with a beta blocker may result in significant hypotension and depression of cardiac function. This risk is more pronounced with IV administration of verapamil.

Antiarrhythmic Effects
Verapamil will slow the ventricular response to AF/AFL even in patients with normal AV conduction. Patients with AF and accessory AV pathways may experience increases in ventricular rate after verapamil administration, related to either a reflex increase in sympathetic tone following vasodilation or decreased AV-nodal conduction with less retrograde penetration of the bypass tract. Verapamil can slow and terminate most arrhythmias utilizing the AV node as part of the re-entrant circuit, such as AV-nodal re-entry or AV reciprocating tachycardia using an accessory pathway. Oral verapamil is consistently less effective than IV verapamil in terminating these arrhythmias, a difference that may be explained in part by the differences in bioavailability and metabolism of the more active l isomer when the racemic mixture of d- and l-verapamil is given by these 2 routes. Verapamil can be effective monotherapy for long-term control of ventricular rate in patients with AF or as adjunctive therapy in combination with digoxin. Verapamil is generally ineffective in treating re-entrant VT but may be effective in certain ventricular tachyarrhythmias, usually seen in younger patients, presumably due to triggered activity. Verapamil may also be used to suppress or reduce the ventricular rate in patients with multifocal atrial tachycardia.

Adverse Effects
IV verapamil may produce hypotension, bradycardia, AV block, and occasionally asystole. The risk of hypotension may be lessened by the prior administration of 1000 mg IV calcium chloride without interfering with the acute depressant effects of IV verapamil on AV-nodal conduc-

Interactions
Verapamil reduces the clearance of digoxin by 35%, with an increase in serum digoxin concentrations of 50% to 75% within the first week of verapamil therapy. Concomitant administration of verapamil and quinidine may result in significant hypotension, since both drugs antagonize the effects of catecholamines on alpha-adrenergic receptors. Other drugs with negative inotropic properties, such as disopyramide or flecainide, should be used cautiously with verapamil. Simultaneous administration of beta blockers and verapamil may result in hypotension, bradycardia, or AV block. Verapamil appears to variably increase the bioavailability of metoprolol from 0% to 28%.

Indications and Dosage
Verapamil is indicated for the termination of supraventricular tachycardias involving the AV node. It is also indicated to control the ventricular rate in patients with AF or flutter and normal AV conduction. IV doses of 5 to 10 mg given over no fewer than two minutes are often effective. The dose may be repeated if necessary in 30 minutes. Alternatively, smaller doses (eg, 2.5 mg) repeated as indicated at more frequent intervals also may be effective. In contrast to certain class I and III antiarrhythmic agents, verapamil is rarely effective in converting AF/AFL to sinus rhythm. Oral therapy using doses of 160 mg to 480 mg per day, in 3 or 4 divided doses, can be effective for chronic control of ventricular response with AF or prophylaxis of paroxysmal supraventricular tachycardia. Sustained-release preparations may allow once- or twice-daily dosing in many patients.

Diltiazem
Pharmacologic Description
Diltiazem hydrochloride is a benzothiazepine derivative that blocks influx of calcium ions during cell depolarization in cardiac and vascular smooth muscle. It is indicated for therapy of supraventricular arrhythmias and for control of ventricular rate to AF/AFL.

Electrophysiologic Action
The principal electrophysiologic effect of diltiazem is inhibition of the slow inward calcium current. It prolongs the time-dependent recovery of excitability and the effec-
tive refractory period of AV-nodal fibers. Expected ECG changes consist of prolongation of the PR (AH) interval with no significant change in QRS or QT duration. Diltiazem also may depress sinus node function (automaticity and conduction), particularly when it is abnormal.

Pharmacokinetics and Metabolism
Diltiazem binds to both alpha,-acid glycoprotein (40%) and serum albumin (30%). Diltiazem is extensively metabolized in the liver by the cytochrome P450 system. Little diltiazem is renally eliminated. As such, diltiazem doses do not need to be adjusted in the presence of renal insufficiency or failure. The elimination half-life of IV diltiazem is approximately 3.4 hours.

Hemodynamic Effects
IV diltiazem produces negative inotropic, dromotropic, and chronotropic effects. Administered acutely, diltiazem lowers both systolic and diastolic blood pressure and systemic vascular resistance. Coronary artery vascular resistance also decreases, increasing coronary blood flow.

Antiarrhythmic Effects
Diltiazem increases AV-nodal conduction time and increases AV-nodal refractoriness. The effects of diltiazem on the AV node demonstrate use dependence, being more pronounced at faster heart rates. In addition, diltiazem slows the rate of depolarization of the sinus node. AV-nodal reentry and reciprocating tachycardia may be terminated by direct effects on the AV node. Increased AV nodal refractoriness also slows the ventricular response to AF/AFL.

Adverse Effects
Hypotension is the most common adverse effect of diltiazem, occurring in approximately 4.3% of patients in clinical trials. Although the sinus rate decreases with IV diltiazem, sinus bradycardia or high-grade AV block rarely occurs. Likewise, elevations of serum aminotransferase enzyme levels rarely occur.

Interactions
Drugs that produce hypotension or interfere with sinus and AV-nodal function would be expected to produce synergistic effects with diltiazem. Agents that interfere or induce the hepatic microsomal enzyme system would be expected to alter diltiazem levels. Diltiazem increases propranolol levels by 50%.

Indications and Dosage
IV diltiazem is indicated for temporary control of the rapid ventricular rate associated with supraventricular tachyarrhythmias such as AF/AFL, AV-nodal re-entrant tachycardia, or reciprocating tachycardia using an AV bypass tract. Diltiazem should not be used to treat patients with AF/AFL and AV bypass tracts. Initial therapy with IV diltiazem is usually administered as a bolus dose of 15 mg to 25 mg (0.25 mg/kg), followed by an infusion of between 5 mg to 15 mg/hour. If ventricular rate control is not achieved after the first bolus, the bolus dose may be repeated in 15 minutes. An 11 mg/h infusion approximates the steady-state levels achieved with a 360 mg sustained-release preparation of diltiazem. Oral preparations are available in immediate-release tablets of between 30 mg to 120 mg used every 6 to 8 hours and a sustained-release form of between 180 mg to 300 mg requiring only once-daily dosing. Although effective, oral forms of diltiazem are not approved for treatment of arrhythmias.

Unclassified Antiarrhythmic Agents

Adenosine and ATP
Pharmacologic Description
Adenosine is an endogenous compound found within every cell of the human body. It is approved by the FDA for use in the United States. Adenosine 5’ triphosphate (ATP), a nucleotide, has been used in Europe since 1929. Adenosine and ATP have short half-lives, enabling multiple doses without danger of cumulative or long-lasting effects.

Electrophysiologic Action
Adenosine and ATP both exert negative chronotropic and dromotropic effects on the sinus and AV nodes. Both decrease the duration of action potentials and hyperpolarize atrial myocardial cells. No direct effect on ventricular tissue has been demonstrated; however, catecholamine-enhanced ventricular automaticity may be suppressed by adenosine. The electrophysiologic effects of ATP, and to a lesser extent adenosine, may be mediated in part by a vagal reflex. ECG effects consist of slowing of the sinus rate and prolongation of the PR interval.

Pharmacokinetics and Metabolism
Both adenosine and ATP have half-lives of less than 10 seconds. ATP is metabolized to adenosine by extracellular enzymes. Adenosine is degraded by extracellular deaminases as well as by intracellular deaminases after it is rapidly transported into cells, forming inosine.

Hemodynamic Effects
Adenosine and ATP are potent vasodilators that tend to reduce systolic blood pressure. Hemodynamic effects are transient following single bolus doses of either agent,
which are usually well tolerated. Adenosine is also a potent coronary artery vasodilator.

Antiarhythmic Effects
Both adenosine and ATP are effective in terminating supraventricular tachyarrhythmias requiring participation of the AV-node, such as AV-nodal reentry or AV reciprocating tachycardia in patients with accessory pathways. In 1 study of 21 patients, ATP (100%) was more effective than verapamil (80%) in terminating paroxysmal AV nodal tachycardia. Compared with verapamil, adenosine may be more likely to unmask latent ventricular pre-excitation after termination of AV re-entrant tachycardia in patients with WPW syndrome. It may also cause fewer hemodynamically significant arrhythmias after termination of AV re-entrant tachycardia. Overall, adenosine has been effective in 60% to more than 90% of patients in different small series, in part reflecting dosing regimens, patient selection, and arrhythmia mechanism. Occasionally, transient AF has been reported following administration of adenosine or ATP; therefore, caution is warranted in administering these agents to patients with pre-excitation. In patients with various atrial tachyarrhythmias, including AF, adenosine will depress AV-nodal conduction, which can be useful diagnostically. ATP and adenosine can also be effective for certain types of VT in both animal models and humans, including catecholamine-sensitive tachyarrhythmias in young adults. Further studies are required, however, to determine the efficacy and utility of adenosine and ATP in the treatment of ventricular tachyarrhythmias.

Adverse Effects
Both adenosine and ATP produce transient flushing and dyspnea following IV administration. Additional adverse effects, more prominent with ATP, include bronchospasm, dyspnea, vomiting, retching, cramps, headache, and, rarely, cardiac arrest. The reported difference in adverse effects may be related in part to the fact that ATP has been in clinical usage for over 50 years, whereas adenosine has been studied for only a short time. But, in addition, ATP triggers a more marked vagal reflex. Side effects with either compound are transient, and the potential for long-lasting adverse effects is minimal. Nevertheless, the possibility of profound bradycardia, AV block, or AF (especially in WPW patients with accelerated accessory AV conduction) justifies appropriate caution. Selective adenosine agonists are currently being developed to avoid these problems.

Interactions
Numerous drugs affect adenosine transport or degradation, often potentiating the effect of adenosine, in experimental models. Examples include dipyridamole, digitalis, verapamil, and benzodiazepines. Aminophylline and other methylxanthines antagonize the effects of both adenosine and ATP in humans. In 1 documented case, a patient receiving sustained-release theophylline failed to respond to high-dose adenosine.

Indications and Dosage
Adenosine and ATP are effective agents in the acute management of paroxysmal supraventricular and AV reciprocating tachycardias involving the AV node. Adenosine is usually administered in doses of 3 mg to 12 mg (3 mg/mL) by rapid IV bolus. ATP has been given in doses of 2 mg to 20 mg. To be maximally effective, these agents must be given as rapid IV bolus injections, administered directly in a free-flowing IV line; effects are more marked with injection into a central line. Injection into a circumferential line of peripheral tubing may be ineffective.

Ranolazine
See Chapter 15, Ranolazine: A Piperazine Derivative.

Digitalis

Pharmacologic Description
Digitalis glycosides are among the oldest antiarrhythmic agents still used today (see Chapter 13, Inotropic Agents). Medicinal use of foxglove (digitalis) was mentioned by Welsh physicians as early as 1250. It was used to treat heart failure and arrhythmias in patients in 1775, and William Withering described his experiences with digitalis 10 years later in the classic monograph “An Account of the Foxglove and Some of Its Medical Uses.” Digitalis preparations are steroid glycosides mostly derived from the leaves of the common flowering plants Digitalis purpurea (digitoxin) and Digitalis lanata (digoxin, lanatoside C, and deslanoside). Ouabain, a rapidly acting digitalis preparation, is derived from seeds of Strophanthus gratus. Digoxin and, to a much lesser extent, digitoxin are the most commonly used digitalis preparations.

Electrophysiologic Action
Digitalis glycosides produce electrophysiologic effects by a direct effect on myocardial cells as well as by indirect effects mediated by the autonomic nervous system. Digitalis preparations are specific inhibitors of a magnesium- and ATP-dependent sodium-potassium ATPase enzyme. Inhibition of this enzyme indirectly promotes an increased concentration of intracellular calcium ions. Increased intracellular calcium results in an increased force of myocardial contraction and also appears to be responsible for many of the arrhythmic effects seen with digitalis toxicity.

Indirect effects result from a vagomimetic action and include negative chronotropic and dromotropic (AV
node) effects. At toxic levels, digitalis results in increased sympathetic activity. Effective refractory periods of atrial and ventricular muscle generally decrease, while those of the AV node and Purkinje fibers increase. Refractory periods of accessory AV pathways may decrease in some patients, which can increase the rate of AV conduction in these patients with AF.\textsuperscript{278} In most individuals, digitalis does not appreciably alter the sinus rate. Sinus rate may slow markedly in patients with heart failure treated with digitalis, however, owing in part to vagal effects and to withdrawal of sympathetic tone. ECG effects include prolongation of the PR (AH) interval with various changes in the ST segment and T wave, characteristically with concave coving of downward-sloping ST segments.

**Pharmacokinetics and Metabolism**

Digoxin is 60% to 80% bioavailable when administered orally in tablets. A capsule preparation of digoxin in solution is 90% to 100% bioavailable. In as many as 10% of patients, intestinal bacteria may degrade up to 40% of digoxin to cardioinactive products such as dihydrodigoxin, resulting in reduced digoxin serum levels. Digoxin is 20% to 25% protein-bound. Elimination is mostly renal, with a half-life averaging 36 to 48 hours in normal individuals. Severe renal insufficiency can prolong the elimination half-life up to 4.4 days.

Digitoxin is a less polar glycoside that constitutes the principal active ingredient of the digitalis leaf. Digitoxin is nearly completely bioavailable after oral administration and is approximately 95% bound to serum proteins. Elimination is predominantly hepatic with an elimination half-life averaging 7 to 9 days.

**Hemodynamic Effects**

Digitalis produces positive inotropic effects in both normal and failing hearts.\textsuperscript{279} Cardiac output does not increase in normal individuals, however, owing to counteracting changes in preload and afterload.\textsuperscript{280} Digitalis increases arterial and venous tone, increasing systemic vascular resistance.\textsuperscript{281} Vascular resistance may increase prior to positive inotropic effects. Thus caution is required when digitalis is administered acutely in patients in whom an increase in vascular resistance would be deleterious. Rapid administration increases coronary vascular resistance, an effect that may be avoided by slow administration.\textsuperscript{282} In addition, increased mesenteric vascular tone may possibly, on occasion, result in ischemic bowel necrosis.\textsuperscript{283}

**Antiarrhythmic Effects**

Antiarrhythmic effects result predominantly from conduction slowing within the AV node. Thus, digitalis is most useful in controlling the ventricular rate in patients with AF. It is somewhat less effective in adequately slowing AV conduction in patients with atrial flutter or atrial tachycardia or in cases where sympathetic tone is high. Addition of a beta blocker or calcium-channel antagonist such as verapamil or diltiazem typically results in additive electrophysiologic effects. Whether digitalis can reduce the frequency of these arrhythmias or facilitate their conversion to sinus rhythm has not been clearly established.\textsuperscript{284} Digitalis may also be effective in the chronic prophylactic or acute management of patients with AV-nodal re-entrant tachycardia. Therapeutic plasma levels range from 0.8 to 2.0 ng/mL for digoxin and from 14 to 26 ng/mL for digitoxin.

**Adverse Effects**

Adverse reactions most commonly involve the heart, central nervous system, and gastrointestinal tract. Hypersensitivity reactions are rare, and gynecomastia occurs infrequently. Patients with abnormal AV-nodal function may experience heart block in the absence of toxicity. Digitalis toxicity results in many cardiac and noncardiac manifestations. Noncardiac effects include nausea, vomiting, abdominal pain, headache, and visual disturbances, especially a yellow-green color distortion. Ventricular premature contractions are perhaps the most common manifestation of cardiac toxicity; however, VT or fibrillation may occur. In addition, advanced-degree AV block, atrial tachycardia, and accelerated junctional rhythms are commonly seen. Combinations of enhanced automaticity (or triggered activity) with AV block (eg, paroxysmal atrial tachycardia with AV block) are suggestive of digitalis toxicity.

Toxicity may be treated with potassium if serum concentrations of potassium are low or normal, with monitoring to avoid high-grade AV block. Magnesium, lidocaine, propranolol, and temporary cardiac pacing may be helpful in selected cases when withdrawal of digoxin is not sufficient to resolve toxicity. In some patients with WPW syndrome and accelerated AV conduction, digoxin may shorten the refractory period of the bypass tract, making rapid anomalous conduction more likely if AF occurs.\textsuperscript{278} In cases of severe digoxin or digitoxin toxicity associated with life-threatening ventricular arrhythmias, hyperkalemia, and/or heart block, rapid reversal of toxicity is possible with the administration of bovine digoxin immune antigen-binding fragments (Fab).\textsuperscript{285} Free levels of digoxin drop to undetectable levels within one minute of administration, with favorable cardiac effects usually occurring within 30 minutes. Each vial of antigen fragments (40 mg) will bind approximately 0.6 mg of digoxin or digitoxin. The average dose of Fab used during clinical trials was 10 vials; however, up to 20 vials or more may be necessary in suicidal overdose situations. Antigen-binding fragments are excreted mainly by the kidneys with an elimination half-life averaging 15 to 20 hours in patients with normal renal function. Patients with significant re-
nal insufficiency must be observed closely for the reemergence of digitalis toxicity. The Fab fragments may not be excreted from the body in these patients but rather are degraded by other processes with subsequent liberation of previously bound digitalis.

Interactions
Concomitant administration of quinidine, verapamil, amiodarone, flecainide, or propafenone increases digoxin levels and may precipitate digitalis toxicity. Potassium-depleting diuretics and corticosteroids may also precipitate digitalis toxicity. Antibiotics may increase digoxin absorption by reducing metabolism of digoxin by intestinal bacteria. Antacids and resins such as cholestyramine may reduce digoxin absorption. Concomitant administration of calcium channel antagonists or beta blockers may produce heart block when administered with digitalis preparations. Digitoxin metabolism may be enhanced by agents such as phenobarbital and phenytoin, which enhance hepatic microsomal enzyme activity.

Indications and Dosage
Digitalis preparations are indicated as antiarrhythmic agents to control the ventricular rate in patients with paroxysmal or chronic AF and in those with AV-nodal re-entrant or AV reciprocating tachycardias. Complete digitalization of an adult typically requires 0.6 to 1.2 mg of digoxin administered in divided doses intravenously or orally; however, differences in bioavailability between preparations must be considered. Maintenance doses of digoxin usually range from 0.125 to 0.25 mg daily but must be substantially reduced in patients with renal insufficiency. When rapid digitalization is not required, therapy may be begun with maintenance therapy, with steady-state levels achieved in approximately 7 days in patients with normal renal function. Digitoxin may be useful in patients with renal insufficiency since its metabolism is not dependent on renal excretion. Digitalization may be accomplished by giving 0.2 mg digitoxin orally twice daily for 4 days. Maintenance therapy ranges from 0.1 to 0.3 mg daily.

Electrolytes
Although not traditionally considered antiarrhythmic agents, serum electrolytes can have a profound effect on many cardiac arrhythmias. Alterations in the concentration of sodium, potassium, magnesium, or calcium may exacerbate many cardiac arrhythmias. In some cases, arrhythmias may be entirely due to electrolyte imbalance, and correction of electrolyte imbalance may be all that is required to treat these patients. Electrolyte abnormalities may be particularly arrhythmogenic in the setting of hypoxemia, ischemia, high-catecholamine states, cardiac hypertrophy or dilatation, and altered pH and in the presence of digitalis. During MI, hypokalemia increases the risk of VT and fibrillation. In addition, hypokalemia diminishes the effectiveness of class I antiarrhythmic agents; it may also increase the risk of toxicity or proarrhythmia, especially with class Ia antiarrhythmic agents (torsades de pointes). Arrhythmias due to digitalis toxicity may often be treated successfully with potassium supplementation provided that the serum potassium concentration is not elevated, and with monitoring to avoid high-degree AV block. Hypokalemia, hypoxia, and high-catecholamine states also may cause or exacerbate abnormal atrial tachyarrhythmias, especially multifocal atrial tachycardia. In some patients, hypokalemia may be refractory to oral repletion unless concomitant magnesium replacement is undertaken.

Magnesium
Pharmacologic Description
Magnesium is the second most abundant intracellular cation (after potassium). It is involved as a cofactor in many diverse intracellular biochemical processes (see Chapter 12, Magnesium, Potassium, and Calcium as Cardiovascular Disease Therapies), including cellular energy production, protein synthesis, DNA synthesis, and maintenance of cellular electrolyte composition (potassium and calcium). All enzymatic reactions involving ATP have an absolute requirement for magnesium. Use of magnesium to treat cardiac arrhythmias was first documented by Zwilling in 1935. Until recently, its use in the treatment of arrhythmias has been largely ignored, with only occasional case reports being published. Magnesium deficiency has become more common with the widespread use of thiazide and loop diuretics.

Electrophysiologic Action
Magnesium's effects on the heart may be direct or indirect via effects on potassium and calcium homeostasis. Magnesium increases the length of the sinus cycle, slows AV-nodal conduction, and slows intra-atrial and intraventricular conduction. It also increases the effective refractory periods of the atria, AV node, and ventricles. Hypomagnesemia often produces opposite effects, such as sinus tachycardia and shortening of effective refractory intervals. Magnesium is essential for the proper functioning of sodium-potassium ATPase; thus, magnesium deficiency reduces the ability of a cell to maintain a normal intracellular potassium concentration, producing intracellular hypokalemia. These alterations increase automaticity and excitability while reducing conduction velocity, predisposing to arrhythmogenesis.

In addition, magnesium is a physiologic calcium-channel antagonist. ECG effects of magnesium administration include prolongation of the PR and QRS
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intervals and a shortening of the QT interval. Magnesium deficiency may produce ST-segment and T-wave abnormalities; occasionally, a prolonged QT interval and U wave are seen. In general, however, hypomagnesemia cannot be recognized with certainty on the ECG, and many of these changes may reflect hypokalemia, which is a commonly associated abnormality.

Pharmacokinetics and Metabolism
Magnesium is mostly contained within bones and soft tissues. Only 1% of total body magnesium is found in the serum. Thus, serum concentrations may not accurately reflect total body magnesium content. Absorption of magnesium occurs in the small bowel, typically beginning within 1 hour of ingestion and continuing at a steady rate for 2 to 8 hours. The kidney is the principal organ responsible for the maintenance of magnesium homeostasis. In the presence of hypomagnesemia, urinary excretion decreases to less than 1 mEq per day. Parathyroid hormone and vitamin D may also be important in magnesium regulation. In the presence of normal renal function, hypermagnesemia is difficult to maintain.

Hemodynamic Effects
Administration of magnesium may cause an increase in stroke volume and coronary blood flow related to arterial dilatation, which may also result in mild blood pressure reduction. Cardiac output may decrease, however, owing in part to a decrease in heart rate.

Antiarrhythmic Effects
Antiarrhythmic effects of magnesium have been demonstrated for the treatment of both digitalis toxicity and polymorphic VT associated with a prolonged QT interval (torsades de pointes). Accumulating evidence also suggests that magnesium may be beneficial in the treatment of VF and VT. Correction of magnesium deficiency has been shown to reduce the frequency of ventricular ectopy. Administration of magnesium sulfate in doses sufficient to double the serum magnesium concentration (65 mmol per day) significantly reduced the number of deaths and serious ventricular arrhythmias in patients with acute MI in 1 study.

Adverse Effects
Progressive increases in magnesium concentration produces hypotension, PR and QRS interval prolongation, and peaked T waves. At concentrations greater than 5.0 mmol/L, areflexia, respiratory paralysis, and cardiac arrest may occur. Hypermagnesemia most commonly occurs in patients with renal insufficiency.

Indications and Dosing
Magnesium may be beneficial in the treatment of many arrhythmias; however, arrhythmias secondary to magnesium deficiency, digitalis toxicity, and torsades de pointes appear especially responsive. Acute treatment of arrhythmias may be accomplished by the administration of 2 g of magnesium sulfate intravenously. If necessary, an additional 2 g may be administered in 5 to 15 minutes. Doses should be administered over 1 to 2 minutes. Maintenance infusions may be used, with doses ranging from 3 to 20 mg/minute. Continuous electrocardiographic monitoring is required, and serum magnesium levels should be checked frequently, especially in patients with renal insufficiency. Oral therapy with magnesium chloride (eg, two to six 500-mg tablets daily) or magnesium oxide (eg, 400 to 800 mg daily) may be used to prevent or treat diuretic-induced magnesium depletion. Substitution or addition of potassium- and magnesium-sparing diuretics (eg, spironolactone, amiloride, or triamterene) may also be beneficial.

Drugs with the Potential for Prevention of Atrial Fibrillation
The development and perpetuation of AF are believed to be related to structural and electrical remodeling of the atria. The renin-angiotensin-aldosterone system is felt to be integral to this process of atrial remodeling, and interruption of angiotensin 2 has been postulated to be a method to prevent the development of AF. The exact mechanism by which these drugs may prevent AF is uncertain, but at present the best evidence in support of this therapy is in patients with heart failure and/or LV dysfunction. The GISSI AF trial tested the benefit of valsartan as an agent to prevent the recurrence of AF in patients with a history of cardiovascular disease, diabetes mellitus, or left atrial enlargement. In this randomized, prospective, placebo-controlled study, there was no benefit to therapy with valsartan over the placebo.

In addition, hypolipidemic drugs such as statins and gemfibrozil have been used to prevent AF. Gemfibrozil was shown to be effective.

Conclusion
Cardiac arrhythmias range from benign rhythms to those that are life threatening. Effective pharmacotherapy of arrhythmias requires an individualized patient approach and an understanding of drug mechanisms and their adverse effects. The use of antiarrhythmic drugs with and without device therapy has revolutionized the management approach to patients. The drugs have also served as biologic probes to bring greater understanding of the etiology of arrhythmias.

Note: References for this chapter can be found here: www.cvpct3.com
Remarkable advances have occurred in the management of ischemic heart disease (IHD) with innovative antiplatelet, antithrombotic, and thrombolytic therapies leading the list of breakthrough drugs. In this chapter, antiplatelet drugs and antithrombotic drugs are reviewed, focusing on the management of cardiovascular diseases. Newer antiplatelet and antithrombotic drugs under clinical development are reviewed in the final portion of this chapter, and in Chapter 37, Cardiovascular Drugs in Development. The thrombolytic drugs are discussed in Chapter 19, Thrombolytic Agents.

**Platelet Physiology**

The chief function of blood platelets is to interact with the vascular endothelium and soluble plasma factors in the hemostatic process. Under normal physiologic conditions, platelets are mostly inert; an intact vascular wall prevents their adhesion to the subendothelial matrix. In response to vessel trauma, platelets will spontaneously adhere to newly exposed adhesive proteins, forming a protective monolayer of cells. Within seconds, these platelets will be activated by agonists such as thrombin, collagen, and adenosine 5'-diphosphate (ADP), causing them to change shape and to release stored vesicles. The constituents of the vesicles are mostly involved in the further activation of platelets and the propagation of the hemostatic process.

Ultimately, these activated platelets will aggregate to form a hemostatic plug, closing the vent in the endothelium and preventing further loss of blood from the site. Under certain pathologic conditions (ie, rupture of an atherosclerotic plaque), these platelet aggregates can form thrombi and be associated with multiple cardiovascular ischemic events, including unstable angina pectoris and myocardial infarction (MI). This process is discussed in the following section.

**Platelet Function**

**Platelet Adhesion**

When the endothelial intima is interrupted by vascular trauma, the subendothelial protein matrix is exposed to circulating platelets and plasma coagulation factors. The major subendothelial glycoproteins (GP) involved in platelet adhesion are von Willebrand factor, collagen, and possibly fibronectin and/or vitronectin. Platelet adhesion to the von Willebrand factor ligand at high shear rates involves the platelet surface-receptor glycoprotein GP Ib. This receptor is exposed on the surface of non-activated platelets and is the major receptor for platelet adhesion. The process of platelet adhesion in hemostasis is unique in that it occurs without prior activation by platelet activators.

**Platelet Activation**

After the platelet monolayer is formed over the endothelial lesion, specific agonists induce platelet vesicle secretion and aggregation. The most physiologically important agonists include thrombin, ADP, collagen, and thromboxane A_2 (produced from arachidonic acid) (Figure 18-1). All of these agonists probably act by a common pathway that leads to the increase of intraplatelet calcium concentrations through direct ion flux or the release of stored calcium. For example, a common pathway is the ligand-receptor activation (by G proteins) of phospholipase C that acetylyzes the conversion of phosphatidyl inositol bisphosphate to inositol triphosphate and diacylglycerol. Inositol triphosphate then leads to the mobilization of stored calcium from the dense tubular system within the platelet cytosol and degranulation of platelets (Figure 18-1).
Two important calcium-dependent processes include the phosphorylation of the myosin light chain and the activation of phospholipase A2 (PLA2).1 The phosphorylation of myosin (and actin polymerization) is involved in the physical changes that the platelet undergoes on stimulation, including the loss of its normal discoid shape, formation of pseudopodia, and centralization and exocytosis of storage granules. The activation of phospholipase A2 leads to an increase in arachidonic acid, which is converted by cyclooxygenase (COX) into thromboxane A2 (TXA2), a powerful prostaglandin agonist. The release of TXA2 (with thrombin and collagen) can lead to the release of ADP from platelet a granules. This ADP can, in turn, stimulate the arachidonic acid pathway and the further release of TXA2. In this way, the platelet can further increase its own activation via various activation mechanisms.4b

Platelet Aggregation

The final common pathway of all agonist-receptor interactions is the activation (by an unknown mechanism) of a specific receptor responsible for platelet aggregation. This receptor, GP Ibb/IIa, unlike the GP Ib receptor responsible for platelet adhesion, is active only after the platelet has been stimulated (and consequently after its intracellular calcium concentration has become increased). Also unique is that GP Ibb/IIa is found only on cells of megakaryocytic origin (ie, platelets). The receptor has a high affinity for the tripeptide sequence arginine-glycine-aspartic acid (RGD), which is found in fibrinogen, von Willebrand factor, fibronectin, and vitronectin.5 Fibrinogen, primarily because of its high concentration in the plasma, is the primary polypeptide involved in platelet aggregation. Because fibrinogen is a divalent dimer, it is able to link adjacent platelets. Other GPs, including fibronectin, von Willebrand factor, and thrombospondin, also may be involved in platelet aggregation after the initial binding to fibrinogen. The GP Ibb/IIa receptor is discussed in detail later.

The Role of Platelets in Ischemic Heart Disease

Thrombosis is often regarded as the pathologic extension of the normal hemostatic process. It involves the formation of a platelet aggregate, or thrombus, within vasculature that has not usually received external trauma. The presence of atherosclerotic vascular disease is highly correlated with the development and clinical presentation of platelet thrombi. Once formed, the thrombus may partially or totally occlude a vessel, resulting in the disruption of blood flow and tissue ischemia and necrosis. Thrombosis in the coronary arteries may directly produce the clinical conditions of unstable angina and/or acute MI.

Atherosclerosis

There are 2 distinct phases of atherosclerotic progression. The first phase involves the primary progression of growth of multifocal intimal lesions from fatty streaks to fibrous plaques. The second phase is the development of platelet thrombosis as a result of plaque rupture or ulceration.6 The second phase is most directly involved in the clinical manifestations of atherosclerosis and, therefore, is most commonly the target of pharmacologic intervention to prevent IHD.

Atherosclerosis is a chronic disease that affects only medium to large arteries, primarily the coronary and cerebral arteries, and the aorta. In a study of Macaca primates that were fed a high-lipid diet, it was determined that the initiating mechanism in the development of intimal lesions is the migration of monocytes/macrophage from the vessel lumen through an intact endothelium.
This migration occurs without any platelet interaction. Often, these infiltrating macrophages exist as lipid-filled foam cells. Within 3 months, the foam cells that have become lodged within the intima disrupt the endothelial cell layer. By the fourth month, the first sign of platelet interaction is visible; platelets have adhered to the subendothelial matrix exposed by microlesions in the endothelial layer. It therefore appears that platelets are more involved with the growth of atherosclerotic plaques than with their initiation.7

The earliest atherosclerotic lesions are the fatty streaks. The streaks appear as areas of yellow, oval discolorations ≤ 2 mm in diameter. They are composed primarily of lipid-filled foam cells (macrophages) that have infiltrated the intima. All human infants, regardless of the rate of future IHD within their population, have aortic fatty streaks by age 1.8 Fatty streaks also appear universally in the coronary arteries by age 15 and in the cerebral arteries by the third and fourth decades.

Fibrous (or raised) plaques are believed to develop from fatty streaks. Unlike the streaks, the progression to plaque development is not universal in the population. Instead, the number of raised plaques in an individual person often reflects the prevalence of IHD in his or her particular geographic population. Patients with risk factors for coronary artery disease (CAD), such as increased cholesterol, smoking, and a familial pattern and history, appear to have an increased number of raised plaques at autopsy.

The fibrous plaques appear to develop at points of hemodynamic stress along the coronary artery (and especially at points of bifurcation). They are palpable above the surface of the intima and may be as long as 2 cm in the aorta. The plaques usually consist of a cholesterol-filled center surrounded by a layer of foam cells. Overlying the lipid layer is a fibromuscular cap composed of collagen, smooth muscle, and elastin with an intact endothelial wall separating the plaque from the vessel lumen. Advanced plaques appear to have a pool of free cholesterol in their center, leading to a decrease in plaque stability.

**Figure 18-2.** Proposed outcome of atherosclerotic plaque fissuring. (Left): Initial plaque fissure. (Top right): Fissure is sealed; incorporated thrombus undergoes fibrotic organization, contributing to progression of coronary disease. Middle right: Fissure leads to intra-intimal and intraluminal thrombosis, resulting in partial or transient reduction of coronary flow as seen in unstable angina. (Bottom right): Fissure results in occlusive thrombosis, which if persistent, can lead to MI or sudden death, particularly in absence of collateral flow.

leading to the enlargement of the plaque and the appearance of “de novo” arterial stenosis on the angiogram.\textsuperscript{10}

Some plaques may heal from the fissure, whereas in other plaques, mural thrombi may develop and project into the lumen of the vessel. These thrombi have a high platelet component, causing the clot to appear white on examination. The intraluminal plaques may transiently reduce coronary blood flow leading to the ischemic condition of unstable angina, or they may break up into microemboli, causing focal areas of necrosis and possible arrhythmia. These mural thrombi have been visualized by coronary angiography in patients with unstable angina.\textsuperscript{11}

If the intraluminal clot grows rapidly, it may not allow time for the development of collateral flow. This predisposes the patient to an acute MI.\textsuperscript{12} With acute coronary syndromes, platelets can remain activated for as long as 1 month after clinical stabilization, suggesting the need for long-term antiplatelet therapy.\textsuperscript{13}

In patients who survive events caused by intraluminal thrombus formation, a natural fibrinolytic reaction normally occurs. Plasminogen is converted to the enzyme plasmin that breaks down the fibrinogen and fibrin component of the thrombus. Fibrinolytic therapy with tissue plasminogen activators has also proven effective. Yet fibrin debris that remains may contribute to further stenosis or to possible chronic total obstruction.

**Oral Antiplatelet Therapy**

The efficacy of acetylsalicylic acid, or aspirin, as an antiplatelet agent has been thoroughly investigated,\textsuperscript{14} and it remains the most widely used and cost-efficient drug in the prevention of platelet aggregation.\textsuperscript{15} Ticlopidine, an alternative drug with demonstrated antithrombotic properties in the prevention of strokes, is approved for use in aspirin-sensitive patients; however, its higher cost, additional adverse effects (particularly thrombotic thrombocytopenic purpura and agranulocytosis), and the essentially similar results obtained with aspirin, preclude its general use.\textsuperscript{16} Clopidogrel, a similar drug, is now commonly used instead of ticlopidine because it has a lower incidence of adverse effects. Until recently, dipyridamole was regarded as an antiplatelet agent, but a significant antithrombotic benefit of the drug when used alone has not been demonstrated.\textsuperscript{17}

**Aspirin**

By virtue of aspirin's antiplatelet properties, it has become an essential part of the treatment of ischemic cardiac syndromes.\textsuperscript{17} Aspirin diminishes the production of TXA\textsubscript{2} through its ability to irreversibly inhibit the COX activity of prostaglandin (PG)H synthase-1 and PGH synthase-2 known also as COX-1 and COX-2 (Figures 18-1 and 18-3).\textsuperscript{18,19}

As a result, platelets exposed to aspirin exhibit diminished aggregation in response to thrombogenic stimuli.\textsuperscript{20} Aspirin's ability to inhibit COX is impressive, as only 30 mg/d is required to eliminate the production of TXA\textsubscript{2} completely.\textsuperscript{19} The COX is irreversibly inhibited and cannot be replaced by new protein synthesis because the platelet has no nucleus. As a result, because the body's reservoir of platelets is renewed progressively over 10 days, 1 dose of aspirin exhibits detectable inhibition of platelet aggregation for more than a week, although a clinical antithrombotic effect may be of lesser duration. Additionally, there is evidence that aspirin may reduce clotting ability by inhibiting the synthesis of vitamin K-dependent factors and by stimulating fibrinolysis. These non-PG mechanisms are dose-dependent and less clearly defined.\textsuperscript{21}

In addition to inhibiting platelet COX, aspirin also inhibits the production of prostacyclin by the vascular endothelium. Prostacyclin is a substance that promotes vasodilation and inhibits platelet aggregation. Because its inhibition would theoretically promote thrombosis, it has been postulated that the beneficial effects of aspirin are reduced because of reduced prostacyclin levels.\textsuperscript{22} Un-
like platelets, however, prostacyclin production recovers within hours after aspirin administration. Various formulations of aspirin have been studied in an attempt to selectively inhibit TXA₂ without inhibiting prostacyclin. It seems, however, that even low doses of conventionally formulated aspirin will inhibit them both. Selective inhibition of TXA₂ has been achieved using a low-dose (75 mg), sustained-release aspirin preparation. Platelets in the prehepatic circulation have their COX irreversibly inhibited. Because extensive first-pass metabolism occurs, however, the endothelium in the systemic circulation is exposed to insufficient drug to inhibit prostacyclin production. Whether this is related to the now well-established clinical benefit is unknown. It has been suggested that using the lowest effective dose is the most sensible strategy to maximize efficacy and minimize toxicity. The ASA and Carotid Endarterectomy trial reported a lower risk of stroke, MI, or death in patients taking 81 or 325 mg aspirin than in those patients taking 650 or 1300 mg.

Aspirin may have beneficial actions beyond their actions on platelets. These actions also include vitamin K antagonism and acetylation of clotting factors. The drug may also affect the oxidation of low-density lipoprotein and improve endothelial function.

Aspirin in Chronic Stable Angina
In patients with stable cardiovascular disease, low-dose aspirin reduces the incidence of adverse cardiovascular events and mortality, but with an increased hemorrhagic risk.

One arm of the Physician’s Health Study examined 383 male physicians with chronic stable angina. The subjects were randomized to either 325 mg of aspirin every other day or to the placebo. Treatment was over a 5-year period. Although no change in symptom frequency or severity was noted between the 2 groups, the occurrence of a first MI was reduced by 87% in those subjects treated with aspirin. It seems likely that although there was no change in disease progression (as noted by unchanged symptomatology), the addition of aspirin reduced the risk of thrombosis in the event of plaque instability. This conclusion has been supported by data from Chesebro et al who noted that the use of aspirin and dipyridamole decreased the incidence of MI and new atherosclerotic lesions without affecting the progression of old atherosclerotic plaques. The Swedish Angina Pectoris Aspirin Trial (SAPAT) found that the addition of low-dose aspirin to sotalol treatment provided additional benefit in terms of cardiovascular events, including a significant reduction in the incidence of first MI in patients with angina.

Unstable Angina
Unstable angina represents the midpoint of the spectrum of ischemic cardiac syndromes, which spans chronic stable angina and MI. Its pathogenesis lies in the rupture of an intracoronary atheromatous plaque, which promotes platelet aggregation, thrombus formation, and luminal compromise. Theoretically, because aspirin has potent antplatelet properties, it should be beneficial in the treatment of unstable angina.

Numerous studies have examined the use of aspirin in patients with unstable angina, all of which have shown marked clinical benefit. The Veterans Administration study examined 1,384 patients with unstable angina within 48 hours of hospital admission. These patients were randomized to receive either 325 mg of aspirin per day or the placebo for 12 weeks. Death or nonfatal MI occurred in 11% of those treated with the placebo compared to only 6.3% in the aspirin group (P < .004). Although treatment was limited to 12 weeks, 1-year mortality was reduced from 9.6% in the placebo group to 5.5% in those treated with aspirin (P < .01). Cairns et al randomized 555 patients with unstable angina within 8 days of admission to either 325 mg of aspirin 4 times a day or to the placebo. Treatment was for 48 hours, and nonfatal MI or cardiac death was reduced from 14.7% to 10.5% in those treated with aspirin (P < .07). Similarly, total mortality was reduced from 10% with the placebo to 5.8% in the aspirin group (P < .04).

Theroux et al randomized 479 patients with unstable angina to 325 mg of aspirin 2 times per day or to the placebo. The patients were enrolled upon presentation to the hospital and were treated for 3 to 9 days. Nonfatal MI was reduced from 6.4% in the placebo group to 2.5% in those treated with aspirin (P < .04).

Finally, the RISC (Relationship Between Insulin Sensitivity And Cardiovascular Disease Risk) study investigated the effects of a reduced dose of aspirin in unstable angina. In the aspirin versus the placebo arm, it enrolled 388 patients to receive either 75 mg of aspirin or the placebo for 3 months. This study demonstrated a reduction in the rate of nonfatal MI or noncardiac death from 17% in the placebo group to 7.4% in aspirin group (P = .004).

It is clear from the above studies that aspirin is effective at reducing the morbidity and mortality of unstable angina with and without heparin. Specifically, nonfatal MI and cardiac death were reduced by 50% to 70%. This benefit seemed to occur across a broad spectrum of daily doses, from 1300 mg/d in the study by Cairns et al. to only 75 mg/d in the RISC trial. Because platelets are exquisitely sensitive to aspirin, this finding is not unexpected. It is recommended that patients presenting with unstable angina be treated with aspirin doses of 162 and 325 mg.

Primary Prevention of Myocardial Infarction
The rupture of an intracoronary atheromatous plaque causes the majority of MIs. This exposes subendothelial
collagen to local blood products, which results in the attraction and activation of platelets. These activated platelets release growth factors and vasoactive compounds that produce vasoconstriction, further platelet aggregation, and, ultimately, the formation of an occlusive mural thrombus.

While aspirin was shown to improve outcomes in patients with unstable angina, its benefit in primary prevention of MI was largely unknown until the results of the US Physicians’ Health Study were reported. In this study, 22,071 male US physicians were randomized to either 325 mg of aspirin every other day or to the placebo. Ninety-eight percent of those involved were free of cardiac-related symptoms, and treatment took place over a 5-year period. While the frequency of angina, coronary revascularization, or death was unchanged between the 2 groups, the incidence of MI was impressively reduced in the aspirin treated group. Specifically, the risk of fatal or nonfatal MI was reduced by 44%.

The observations made in the US Physicians’ Health Study were challenged by a similar study from Europe. The British Physicians’ Health Study was an uncontrolled trial that involved 5,139 British male physicians, two-thirds of whom were treated with 500 mg of aspirin per day. In contrast to the US study, there was no significant reduction in MI or total mortality. Criticisms of this trial were many and included its uncontrolled design, smaller sample size, higher dose of aspirin, older subjects with poorer compliance, and high confidence intervals. Its results, however, were sufficient to cast some doubt on aspirin’s utility in the primary prevention of MI. Recently it was shown that patients having a low ankle brachial index who were free of clinical cardiovascular events did not benefit from daily low-dose aspirin (100 mg).

Any doubts as to aspirin’s role in the primary prevention of MI were largely put to rest by a large observational study of US nurses and their aspirin usage. In this study, aspirin usage by 87,000 US nurses was analyzed over a 6-year period. All of the nurses involved were free of cardiac-related symptoms. The study showed that in women older than 50 years, ingestion of one to six 325-mg tablets of aspirin per week was associated with a 32% reduction in first MI. This benefit was most striking in women with risk factors for CAD including tobacco use, hypercholesterolemia, and hypertension. In women who took more than 7 tablets per week, however, there was no reduction in the rate of MI. In addition, women who took more than 15 tablets per week were at a significantly increased risk of hemorrhagic stroke. A large primary prevention trial in women demonstrated that aspirin lowered the risk of stroke without affecting the incident rate of MI.

It appears from a number of studies that 325 mg of aspirin every other day is effective at preventing a first MI in individuals, especially in men. An aspirin dose as low as 75 mg/d is the minimum dose that effectively reduces the risk of a first MI. The benefit of aspirin is most pronounced in patients who are at high risk for CAD, specifically, older individuals with multiple cardiac risk factors. The corollary of this is that the risk-to-benefit ratio for aspirin use is lowest in healthy individuals and highest in high-risk individuals. Higher doses of aspirin do not appear to confer any additional benefit and most likely impart additional risk of developing hemorrhagic stroke. Despite its proven benefit, aspirin is still being underutilized in clinical practice.

Secondary Prevention of Myocardial Infarction

Seven prospective, randomized, placebo-controlled trials have examined the use of aspirin in the secondary prevention of MI. As a cumulative total, these studies have enrolled over 15,000 survivors of MI whose treatment consisted of various aspirin regimens, with doses ranging from 325 to 1500 mg/d. Patients were enrolled from 4 weeks to 5 years post-MI. When each of these trials was examined individually, no statistically significant decrease in mortality was observed. Because the numbers of patients in each study may have been too small to provide adequate statistical power, a meta-analysis of six of the trials was performed. This meta-analysis contained 10,703 patients and showed that when aspirin was compared with the placebo, cardiovascular morbidity was reduced by 21%. In another meta-analysis from the Antiplatelet Trialists Collaboration, the risk of developing a nonfatal reinfarction was shown to be reduced by 31% and death from vascular causes was reduced by 13% in those patients treated with aspirin during the 1- to 4-year follow-up period.

Finally, in a 23-month follow-up of 931 patients with acute infarction or unstable angina, 80% of subjects were found to use aspirin on a regular basis. Their cardiac death rate was markedly reduced compared to nonaspirin users and was not explicable by imbalances in predictors of postinfarction risk, by concurrent drug therapy, or by preinfarction thrombolysis or angioplasty.

In addition to the cardiac benefits demonstrated by the above studies, aspirin also seems to reduce the risk of stroke in post-MI patients. In a subset of the Antiplatelet Trialists Collaboration, the risk of stroke in those patients treated with aspirin was examined. A 42% reduction in nonfatal strokes in the aspirin group was demonstrated, as compared to the placebo treatment. With these results in mind, treatment of post-MI patients with low-dose aspirin (perhaps 75 mg/d) seems reasonable. Although many of the above trials relied on pooled data and meta-analysis to demonstrate aspirin’s benefit in the post-MI population, the data are compelling to that effect. Aspirin does not appear to increase the risk of nonfatal cerebrovascular accident (CVA) and will most likely reduce the risk of future cardiac events. The optimal dose of aspirin for long-term postinfarction prophylaxis is unclear at this time and will need to be determined with future studies.
A meta-analysis of 5 randomized trials of primary prevention included 52,251 participants randomized to aspirin doses ranging from 75 to 650 mg/d; the mean overall stroke rate was 0.3% per year during an average follow-up of 4.6 years.60 The meta-analysis revealed no significant effect on stroke (relative risk = 1.08; 95% confidence interval, 0.95 to 1.24) contrasting with a decrease in MI (relative risk = 0.74; 95% confidence interval, 0.68 to 0.82). The authors concluded that the effect of aspirin therapy on stroke differs among individuals based on the presence or absence of overt vascular disease.

Acute Myocardial Infarction

Localized coronary thrombosis due to the rupture of an unstable, intracoronary, atheromatous plaque is thought to be responsible for more than 90% of Q-wave MI.60 Although thrombolytic agents break down the primary clot responsible for the acute event, substances liberated during this process can themselves promote platelet aggregation and reocclusion.61 Although spontaneous recanalization may occur, thrombus reformation is common and may perpetuate the ischemic process. By virtue of aspirin's potent antiplatelet properties, it is an effective agent when used either alone or with thrombolytic agents in reducing the mortality from acute MIs.

The Second International Study of Infarct Survival (ISIS-2) was a double-blind, placebo controlled trial that defined aspirin's role in the treatment of acute MI.62 ISIS-2 enrolled 17,187 patients with suspected acute MI and randomized them to either intravenous streptokinase (1.5 million units over 60 minutes), aspirin (162 mg/d for 1 month), to both, or to neither. Five weeks after randomization, aspirin reduced the risk of nonfatal reinfarction by 51% and of vascular mortality by 23% when compared with the placebo. The addition of intravenous streptokinase further reduced mortality in conjunction with aspirin. These results indicated that aspirin reduced mortality to a similar degree as did streptokinase alone and that when the two were combined, a cumulative benefit was observed. Aspirin's reduction in mortality also extended to groups treated with various heparin dosages, ranging from no heparin (288 versus 347 deaths), to subcutaneous heparin (338 versus 431 deaths), and to intravenous heparin (178 versus 238 deaths, $P < .001$). Mortality benefits were similar in both men and women and remained present after 24 months of follow-up. Importantly, treatment with aspirin did not result in any increased incidence of major bleeds (31 versus 33 bleeds) and seemed to decrease the risk of nonfatal CVA by 46% ($P = .003$). It seems clear that aspirin, with or without thrombolytic therapy, is effective at reducing the mortality and morbidity of an evolving MI.

Non-Q-wave MI results when an intracoronary occlusion is incomplete or occurs for only a short time. The pathophysiology of a non-Q-wave MI is similar to both unstable angina and to Q-wave MI in that a ruptured atheromatous plaque results in acute intracoronary thrombus formation. Although it seems likely that aspirin would confer a benefit in evolving non-Q-wave MI, no adequate trials have been performed to date in this subgroup of patients.

Current recommendations of the American College of Chest Physicians Seventh Consensus Conference are that all patients with acute MI who receive fibrinolytic therapy receive adjunctive treatment with aspirin (160 to 325 mg) on arrival at the hospital and daily thereafter. They further recommend that patients receive heparin or hirudin as an adjunct depending on their risk factor for systemic or venous thromboembolism and the fibrinolytic agent with which they are treated.63

Percutaneous Transluminal Coronary Angioplasty and Arterial Stenting

When percutaneous transluminal coronary angioplasty (PTCA) is performed, the intracoronary atheromatous plaque that is acted upon is “cracked” or “fissured” by the destructive action of balloon inflation. This results in the exposure of underlying subendothelial collagen to circulating blood products, which activates platelets and promotes thrombogenesis. It has been shown that the magnitude of platelet deposition after angioplasty is related to the depth of arterial injury64 and that in animals, pretreatment with aspirin reduces the degree of thrombus formation.65

There have been two randomized, prospective trials that have evaluated the role of aspirin in preventing abrupt closure after angioplasty.66,67 In these studies, aspirin (650 to 990 mg/d) and dipyridamole (225 mg/d) were started 24 hours preangioplasty and continued indefinitely. They demonstrated that the incidence of abrupt closure was significantly reduced when compared with the placebo. In another trial by Barnathan et al.,68 it was noted that when the coronary angiograms of patients undergoing angioplasty were analyzed retrospectively, the incidence of coronary thrombosis was significantly lower in those patients treated with either aspirin or aspirin plus dipyridamole. Finally, although aspirin does appear to lower the risk of acute thrombosis after angioplasty, it has not been shown to affect the rate of late restenosis.64 With regards to coronary artery stenting (see Chapter 29, Drug-Eluting Stents), aspirin remains an important prophylactic treatment in preventing acute thrombosis, especially in combination with clopidogrel.69 After the placement of coronary-artery stents, antiplatelet therapy with aspirin and clopidogrel was as safe and effective as aspirin and ticlopidine, while noncardiac events were significantly reduced with aspirin plus clopidogrel in a randomized trial of 700 patients with 899 lesions.68

Coronary Artery Bypass Surgery

In coronary artery bypass grafting (CABG) surgery, native coronary arteries whose blood flow is compromised
by atherosclerotic blockages are “bypassed” using either venous or arterial conduits. The arterial conduit usually consists of either the left or right internal mammary arteries and the radial arteries, and the venous conduit is usually a reversed, saphenous vein from the leg. Although this surgery is one of the mainstays of treatment for CAD, occlusion of the bypass vessels either acutely or over time is not uncommon. It has been noted, for example, that 40% to 50% of saphenous vein grafts will occlude within 10 years of their implantation.70 Reasons for graft occlusion vary with the age of the conduit. “Acute” closure (less than 1 month after placement) is usually due to thrombosis, whereas “intermediate” closure (1 month to 1 year) is caused by accelerated intimal hyperplasia. Finally, “late” occlusion (more than 1 year) results from atherosclerosis within the bypass graft.21

Multiple studies have demonstrated a decreased incidence of early thrombosis when aspirin is used in the perioperative period.72-75 Goldman et al74 randomized 50 groups of CABG patients to receive either (a) aspirin 325 mg/d, (b) aspirin 325 mg tid, (c) aspirin 325 mg tid and dipyridamole 75 mg tid, (d) sulfipyrazone 267 mg tid, or (e) the placebo. This study demonstrated a significantly decreased risk of early thrombosis in all groups treated with aspirin (73% graft patency with the placebo at 2 months versus 93% with aspirin, P < .05). The addition of dipyridamole resulted in no additional benefit and sulfipyrazone was ineffective in reducing the risk of thrombosis. Although those patients treated with aspirin had increased blood loss and need for reoperation, perioperative mortality was unchanged. The benefits noted in this study remained present after 1 year of follow-up.75 In a follow up to this study, predictors of patency 3 years after CABG were analyzed. For a patient with patent vein grafts 7 to 10 days after the operation, predictors of 3-year graft patency are more closely related to operative techniques and underlying disease and not to aspirin treatment.76

Despite the lack of effect on patency at 3 years, it is still recommended that aspirin should be given to all patients undergoing bypass surgery unless a clear contraindication exists. A dose of 325 mg/d is probably reasonable, as higher doses do not add any additional clinical benefit. The medication may be started preoperatively or within 48 hours postoperatively if preoperative administration is not possible.77,78

Transient Ischemia Attack and Stroke

The capacity of aspirin in doses of 50 to 1500 mg/d, either alone or in combination with other antiplatelet agents (dipyridamole, sulfipyrazone), to reduce the risk of recurrent CVA was studied in 10 trials (see Chapter 33, Drug Therapy of Cerebrovascular Disease) involving approximately 8,000 patients with stroke (CVA) or transient ischemic attacks (TIA).79,80 Based upon these studies, treatment of 1000 patients with aspirin for 3 years will reduce fatal and nonfatal cardiovascular events including recurrent CVA by about one-fourth.79 Optimal daily dosage of aspirin for secondary prophylaxis in cerebrovascular disease remains somewhat controversial, but doses between 300 to 1200 mg/d are the recommended dose range.80 The US Food and Drug Administration (FDA) published its rules for labeling aspirin products for over-the-counter human use and recommended aspirin doses from 50 to 325 mg/d for prevention of ischemic stroke.81 The ASA and Carotid Endarterectomy (ACE) trial suggested that low-dose aspirin is at least as effective as high-dose aspirin.82

The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study included 19,185 patients, 6,431 entering the trial with stroke. There was a statistically nonsignificant relative risk reduction of 8% for stroke favoring clopidogrel.83 The European Stroke Prevention Study 2 demonstrated that aspirin combined with sustained-release dipyridamole was more effective than either alone in reducing the risk of stroke.83 The results were independent of age. Based on this study, a combination formulation of aspirin and dipyridamole is approved for clinical use.

Systemic Lupus Erythematosus

Prophylactic aspirin should be given to all patients with systemic lupus erythematosus to prevent both arterial and venous thrombotic manifestations, especially in patients with antiphospholipid antibodies.84

Venous Thromboembolism

Aspirin use has also been shown to reduce the risk of thromboembolism after major orthopedic surgery.85 It has not been compared to low-molecular-weight heparin (LMWH) or evaluated in combination with LMWH.

Atrial Fibrillation

Aspirin has been used to reduce the hazard of thromboembolic stroke in nonvalvular atrial fibrillation (NVAF) and compared with the efficacy of warfarin.86,87 Data from randomized trials support aspirin use for thromboembolism prophylaxis in younger NVAF patients (< 60 years), especially in the absence of associated risk factors of hypertension, recent congestive heart failure, or remote thromboembolism.88 A slightly greater hazard for intracranial bleeding with warfarin might make aspirin a suitable alternative to warfarin in selected other patients.89 The clinical trial Stroke Prevention in Atrial Fibrillation (SPAF III) was designed to evaluate the relative efficacy and safety of aspirin as an adjunct to low-intensity fixed-dose warfarin in preventing thromboembolism in high-risk NVAF patients.90 The trial was stopped prematurely in high-risk patients due to an excess of strokes in
patients receiving aspirin plus low-dose warfarin. The published results thus far support the use of conventional dose warfarin in the majority of patients with atrial fibrillation (AF).

Peripheral Vascular Disease
In patients with peripheral arterial disease, the combination of oral anticoagulant and antiplatelet therapy was no more effective than antiplatelet therapy alone in preventing major cardiovascular complications and was associated with more hemorrhagic complications.90,91 Another study found a benefit for patients with stroke.92

Adverse Effects and Drug–Drug Interactions
The most common adverse effect of aspirin treatment is gastrointestinal (GI) intolerance. In the Aspirin Myocardial Infarction Study (AMIS) in which patients with known peptic ulcer disease (PUD) were excluded, 24% of those treated with aspirin (1000 mg/d) reported GI intolerance as compared with 15% in the placebo group.90 In the United Kingdom Transient Ischemic Attack Aspirin Trial (UK-TIA Trial),80 GI symptoms were reduced by 30% when the dose of aspirin was decreased from 1200 mg/d to 300 mg/d. Finally, in the Physicians’ Health Study98 (in which patients with known PUD were excluded), 325 mg of aspirin every other day resulted in only a 0.5% increase in GI symptoms when compared with the placebo. GI intolerance due to aspirin, therefore, appears to occur in a dose-dependent manner and treatment with 325 mg/d appears to be well tolerated. Two forms of COX enzymes have been identified: one that produces the “good” PGs that act in the stomach and other tissues (COX-1) and another (COX-2) that is involved in TX formation.

Agents are now available to inhibit COX-2 while sparing COX-1, which could provide a stomach-sparing aspirin. The relative risk of GI bleeding with such drugs as compared with other nonsteroidal anti-inflammatory drugs (NSAIDs) is reduced.93 However, recent studies suggest that some COX-2 inhibitors may have a prothrombotic effect in patients at risk for CAD.94 Therefore, until this issue is resolved, the COX-2 inhibitors cannot be used as aspirin substitutes for cardiovascular prophylaxis.

Bleeding complications are a common adverse effect of aspirin therapy. Specifically, the risk of developing a hemorrhagic event such as bruising, melena, and epistaxis are all increased with aspirin use. The Physicians’ Health Study96 confirmed this by reporting that 27% of those treated with aspirin (325 mg every other day) experienced bleeding complications, as compared with only 20% in the placebo group. In the UK-TIA Trial,80 there was a significant increase in the risk of GI bleeding when the dose of aspirin was increased to 1200 mg/d. For these reasons, the risks and benefits of aspirin therapy need to be weighed against one another in patients who are at increased risk of bleeding. Furthermore, the dose of aspirin used should be as low as possible because higher doses do not appear to confer additional benefits but do increase bleeding risk substantially.

Aspirin also possibly interferes with the clinical benefit of angiotensin-converting enzyme (ACE) inhibitors (see Chapter 9, The Renin Angiotensin Axis: Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers) and with furosemide in patients with heart failure.94

Aspirin Resistance
Aspirin does not completely block TXA2 in some patients, making them resistant to the protective effects of the drug. Patients taking aspirin who had high levels of TX in their urine were found to have a 3-to-5 times higher risk of cardiovascular death than patients who had lower levels.95 High levels of 11-dehydrothromboxane B2 in urine can identify patients who are resistant to aspirin.

The mechanisms for aspirin resistance appear to be multifactorial (Table 18-1) and include inappropriate dosage, type of formulation, noncompliance, diabetes mellitus, cell–cell and drug interactions, genetic polymorphisms, and CAD.95-99 It has not been determined what the best laboratory procedure is to screen for aspirin resistance.95,100,101 Those individuals at high risk for aspirin resistance might best be treated with an additional oral antiplatelet drug to achieve maximal protection against arterial thrombotic events.

Conclusion
Aspirin is effective at reducing the morbidity and mortality associated with ischemic cardiac syndromes. In particular, it is effective as primary prevention against MI in asymptomatic patients and in those with both chronic stable and unstable angina. It also reduces the risk of reinfarction in the peri- and post-MI period. Aspirin decreases the incidence of acute thrombosis after PTCA and stenting, as well as reducing the risk of bypass graft thrombosis after CABG surgery. These benefits must be weighed against the increased risk of bleeding associated with aspirin therapy. In those patients who are at a low risk for bleeding complications and who fall into one of the above categories, 325 mg of aspirin—either daily or every other day—is recommended. In patients with a higher likelihood of bleeding, these risks and benefits need to be taken into account for individualized therapy.

Dipyridamole
Dipyridamole is a pyrimidine compound that can act as both a vasodilator and an antithrombotic. The drug inhibits platelet action in vitro only at doses that are higher than those commonly used in patients, but it
Cardiovascular Pharmacotherapeutics

has been clinically effective in reducing platelet adherence to prosthetic surfaces in vivo at lower doses when combined with other agents. A number of mechanisms for its antiplatelet activity have been proposed, including either the inhibition of phosphodiesterase or the indirect activation of adenylate cyclase through its effects on prostacyclin and/or the inhibition of adenosine uptake by the vascular endothelium. The exact mechanism of action still requires further definition, although the common pathway involves elevated levels of intraplatelet cyclic adenosine monophosphate, a platelet inhibitory substance. It is also used as a provocative agent in patients undergoing diagnostic testing for CAD.

Clinical Studies
One of the drug's initial uses in humans has been as an adjunct to anticoagulant therapy in the prevention of thromboembolic events in patients with prosthetic heart valves. Although current American College of Chest Physicians' guidelines do not include dipyridamole as a first-line therapy in a patient with prosthetic heart valves, it is a useful adjunct to anticoagulant therapy. It is recommended as part of the therapy in a patient with a prosthesis-related thromboembolic event, especially in those patients with PUD where aspirin may need to be avoided. Dipyridamole is not associated with an excess of hemorrhage when combined with anticoagulant therapy. Dipyridamole has also been used as part of the therapy for patients with prosthetic grafts. Both experimental and clinical evidence suggests a superiority of an aspirin/ dipyridamole combination to either drug used alone in terms of both platelet survival and hemodialysis graft patency.

A controlled trial comparing aspirin and dipyridamole alone and in combination against the placebo for secondary prevention of ischemic stroke in 6,602 patients found an 18% reduction for aspirin alone, a 16% reduction for dipyridamole alone, and a 37% reduction with combination therapy. Although there was no effect on the death rate, there was also a significant reduction in TIs. Bleeding was significantly more common in patients receiving aspirin. A combination aspirin-dipyridamole formulation is now available for stroke prevention at an aspirin dose of 25 mg plus extended-release dipyridamole 200 mg twice daily.

Controlled trials comparing aspirin to dipyridamole in patients with stable angina are few. The limited data suggest no statistically significant difference between aspirin and dipyridamole used together as compared with aspirin alone. No trial has shown a definitive superiority of combination therapy over aspirin alone in either stable CAD, graft survival after CABG, or in the need for emergency revascularization after angioplasty.

Adverse Effects
The primary adverse effects of dipyridamole are GI and consist of nausea and vomiting. In rare cases, angina has been provoked through what is believed to be a coronary steal phenomenon.

Thienopyridines

The thienopyridine derivatives (ticlopidine, clopidogrel, and prasugrel) inhibit ADP-induced platelet aggregation. The antiplatelet effect of this class of drugs is due to the irreversible inhibition of ADP binding to the platelet P2Y12 purinergic receptors and is independent of arachidonic pathways.

Ticlopidine
Ticlopidine produces a thrombasthenia-like state, with a resultant reduction in platelet aggregation, a prolongation of the bleeding time, a decrease in platelet granule

Table 18-1. Possible Mechanisms of Aspirin Resistance (Variability in Response)

| Inadequate aspirin dose |
| Formulations of aspirin with low-to-absent bioavailability (enteric-coated or deteriorated) |
| Noncompliance with therapy |
| Drug-drug interactions with some NSAIDs (eg, ibuprofen) |
| Cigarette smoking |
| Diabetes mellitus |
| Formation of isoprostanes |
| Increased platelet sensitivity to adenosine diphosphate and collagen |
| Polymorphisms in the GP Ila/IIla receptor which affect responsiveness to aspirin |
| Inadequate blockade of erythrocyte and monocyte/macrophage activation of platelets |
| Decreased platelet sensitivity to aspirin over time (tolerance) |
| Polymorphisms of the COX-1 gene |
| Aspirin-insensitive thromboxane synthesis; inducible COX-2 or regeneration of COX-1 activity in macrophages and vascular endothelial activity cells |

NSAIDs = non-steroidal anti-inflammatory drugs; GP = glycoprotein; COX = cyclooxygenase.

release, and a reduction in platelet and fibrin deposition on artificial surfaces.

**Cerebrovascular and Peripheral Vascular Disease**

Ticlopidine has been tested thoroughly in the prevention of cerebrovascular disease. When compared with the placebo in 1,000 patients as part of a study in secondary prevention after stroke, the administration of ticlopidine resulted in a 30% reduction in the relative risk of stroke, MI, or vascular death. When compared with aspirin in the TASS study (Ticlopidine Aspirin Stroke Study), ticlopidine was found to be superior in terms of all-cause mortality as well as nonfatal stroke. This benefit persisted throughout the 5-year duration of the trial.

In patients with peripheral vascular disease and claudication, treatment with ticlopidine was associated with a reduction in mortality, MI, and CVAs. Patients with cerebrovascular and peripheral vascular disease appear to benefit from ticlopidine therapy in terms of stroke, MI, and vascular events.

The drug is approved for use in secondary stroke prevention at a dose of 250 mg twice daily.

**Cardiovascular Disease**

Ticlopidine has been used in the therapy of patients after CABG. In a randomized trial involving 173 patients, ticlopidine therapy resulted in a reduction in vein graft closure at 1 year as compared with the placebo. The graft closure rate, as assessed by digital angiography at day 10, day 180, and day 360, was decreased in the ticlopidine group as compared to the placebo group. When used in the therapy of patients with electrocardiographic evidence of unstable coronary syndromes, the addition of ticlopidine to standard therapy was associated with a reduction in vascular death and nonfatal MI, as well as the composite endpoint of both fatal and nonfatal MI. In those patients who undergo coronary stent implantation and ticlopidine and aspirin therapy have demonstrated a superiority over anticoagulant therapy with heparin and phenprocoumon. In patients undergoing stenting, ticlopidine should be administered at a 500-mg loading dose and then given 250 mg twice daily for up to 30 days.

In patients with acute MI, the drug appears to be similar to aspirin as regards subsequent mortality, recurrent acute MI, stroke, and angina. In combination with aspirin, the drug reduces the plasma levels of procoagulant tissue factor in patients with unstable angina.

**Adverse Events**

Neutropenia can occur in up to 4% of patients receiving ticlopidine. It is generally reversible, although cases of agranulocytosis have been reported. It is recommended that during the first 2 months of therapy, white blood cell counts should be checked. The most common adverse effects of the medication are GI, occurring in about 12% of patients, and include nausea, vomiting, diarrhea, and dyspepsia. A rash has been reported within the first 3 months of ticlopidine treatment. Ticlopidine is associated with a risk of thrombotic thrombocytopenic purpura estimated at 0.02%. Although this complication has also been reported with clopidogrel, ticlopidine has been supplanted by clopidogrel because of clopidogrel’s overall better safety profile.

**Clopidogrel**

Clopidogrel is a thienopyridine antiplatelet drug with a similar structure to ticlopidine. Similar to ticlopidine, clopidogrel is a prodrug that is not active in vitro but is active in vivo. Metabolism of clopidogrel by the hepatic cytochrome P450 (CYP450) enzyme system to an active metabolite is essential for its in-vivo antiplatelet action. It functions as an ADP-selective agent whose antiaggregating properties are several times higher than those of ticlopidine and are apparently due to the same mechanism of action (ie, binding to the P2Y1 receptor and thus inhibiting ADP binding to the receptor and triggering the release of thrombogenic factor-containing alpha granules). In various experimental animal models, a single oral or intravenous administration of clopidogrel inhibited ADP-induced platelet aggregation for several days and potently reduced thrombus formation. The drug is not associated with long-term tolerance.

**Clinical Trials**

Clopidogrel has been evaluated in a large phase 3 clinical trial (CAPRIE), a randomized, blinded, clinical study comparing clopidogrel 75 mg/d with aspirin 325 mg/d in 19,000 patients who had suffered a recent ischemic stroke or MI, or who had symptomatic atherosclerotic peripheral vascular disease. In this study clopidogrel was more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death. Based on this study, clopidogrel was approved for clinical use at a dose of 75 mg once daily.

In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, clopidogrel in addition to aspirin was shown to be more beneficial than aspirin alone but with a higher risk of major bleeding. For non-ST segment acute coronary syndromes, clopidogrel should be initiated with a single 300 mg loading dose and then continued at 75 mg daily. Aspirin (75 to 325 mg) once daily should be initiated and continued in combination with clopidogrel for 12 months. In CURE, most patients also received heparin acutely.

In patients aged 75 years or younger who have ST-segment elevation MI (STEMI) and who receive aspirin and standard fibrinolytic regimen, the addition of clopidogrel was shown to improve the patency rate of the
inadequate dose of clopidogrel used in individual patients. There is as yet no validated
combination with aspirin provides any clinical advantage over aspirin.137 There is also no evidence that clopidogrel used alone.135,136 In patients with stable CAD, the risk of death from vascular causes. There was no difference seen between the treatment regimens.138

In patients with AF for whom warfarin was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage.139 Warfarin is still the preferred drug over antiplatelet treatments in patients with AF.140 However, in patients with atrial fibrillation and coronary artery stents, warfarin may need to be used with one or two antiplatelet drugs.140a

The clinical benefit of clopidogrel could be attenuated by the variability of response to the antiplatelet effect of the drug in as many as 30% of patients. The possible mechanisms are listed in Table 18-2.141

One mechanism is the inadequacy of the dose being used in individual patients. There is as yet no validated platelet assay to measure clopidogrel’s antiplatelet action.141 Some investigators have suggested using higher loading doses of 600 to 1200 mg for acute coronary syndromes and higher maintenance doses of 150 mg daily.142-150 However, the results of the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) showed no difference in the primary cardiovascular outcomes when comparing the standard dose regimens of aspirin to higher dose aspirin, and the standard dose of clopidogrel to a double dose was less effective.150a,b

Another mechanism for variability in response may relate to drug–drug interactions with certain statins, especially atorvastatin.141 However the evidence is not compelling151 and there is no need to change statin doses in conjunction with clopidogrel.

Current guidelines have recommended the use of protein pump inhibitors (PPIs) to decrease the risk of GI bleeding in patients taking clopidogrel or aspirin. It has been suspected that some PPIs can interfere with the antiplatelet effect of clopidogrel.153-154b Data from recent studies suggest that some PPIs may reduce the enzymatic activity of CYP 3C19. Omeprazole is considered to be a strong inhibitor of CYP 2C19, which is necessary for clopidogrel’s activation.153 However, a recent report would suggest that there is no need to avoid concomitant use of PPIs when clinically indicated in patients receiving clopidogrel or prasugrel.153-155b

The results of 3 new studies indicate that patients with common genetic polymorphisms of CYP 2C19 resulting in reduced enzyme activity were more likely to experience recurrent cardiovascular events during clopidogrel therapy than those with normal CYP 2C19 activity.156-158 Based on these findings, it is important to maintain patients on aspirin and/or substitute prasugrel

Table 18-2. Possible Mechanisms of Clopidogrel Resistance (Variability in Response)

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate clopidogrel dose</td>
</tr>
<tr>
<td>Noncompliance with therapy</td>
</tr>
<tr>
<td>Drug–drug interactions with some HMG CoA reductase inhibitors (eg, statins) and proton pump inhibitors</td>
</tr>
<tr>
<td>Polymorphisms of the P2Y12 receptor</td>
</tr>
<tr>
<td>Interindividual differences in CYP 3A4 metabolic activity</td>
</tr>
</tbody>
</table>

for clopidogrel until appropriate pharmacogenetic studies can be done routinely to screen for the enzyme deficiency.

Prasugrel
Like clopidogrel and ticlopidine, prasugrel is a thienopyridine that selectively and irreversibly inhibits the platelet P2Y12 ADP receptor, essentially leading to an inhibition of platelet aggregation.\textsuperscript{161-162} Analogous to clopidogrel, prasugrel is an orally administered prodrug that is converted to its active metabolite by CYP-450 oxidation. However, unlike clopidogrel, which requires two enzymatic steps, prasugrel requires only one CYP-450 dependent oxidative step to generate the active metabolite.\textsuperscript{163,164} Hence, it is thought that prasugrel may have a more rapid onset of action than clopidogrel. Weerakkody et al\textsuperscript{165} set out to explore this possibility by comparing the speed of onset of platelet inhibition after loading doses of prasugrel in comparison with clopidogrel. In this design, data were pooled from three phase 1 single-center studies of patients receiving either a 60 mg loading dose of prasugrel or a 300 mg loading dose of clopidogrel. Maximum platelet aggregation was then measured by turbidometric aggregometry and a mechanistic model was used to estimate the initial rate of decrease in maximum platelet aggregation per hour. The results showed that 76 out of 76 subjects (100%) receiving prasugrel had a fast onset of platelet inhibition (maximum platelet aggregation decrease > 20%/hour) compared with only 47 out of 87 subjects (54%) receiving clopidogrel. Prasugrel was thus shown to have a consistent rapid onset of action. Irrespective of the agent given, the initial speed of the onset of platelet inhibition was highly correlated with subsequent pharmacodynamic responder status. Although this study excluded the use of aspirin in any of its patients, the results were still similar to a recent study in patients with stable cardiovascular disease who received aspirin with either 300 mg of clopidogrel or 60 mg of prasugrel.\textsuperscript{166} These studies, however, only evaluated 1 loading dose of prasugrel and clopidogrel and did not evaluate possible differences with maintenance dosing.

Another phase 1 randomized study was performed by Brandt et al\textsuperscript{167} to compare the rate of onset, magnitude, and consistency of platelet inhibition observed after loading doses of prasugrel versus clopidogrel. The results of this study showed that a 60 mg loading dose of prasugrel had a greater degree of platelet inhibition than a 300 mg loading dose of clopidogrel. The median time to achieve at least 20% of platelet aggregation inhibition was 30 minutes with prasugrel, as compared to 1.5 hours with clopidogrel. In addition, the peak inhibition of platelet aggregation was nearly twice as high with prasugrel when compared with clopidogrel. There was also a more consistent response with prasugrel and fewer nonresponders than with clopidogrel. Brandt et al postulated that the differences in the response rate between prasugrel and clopidogrel may lie in the metabolism and absorption, since the loading dose of prasugrel resulted in a consistently higher exposure to its active metabolite than did clopidogrel. In contrast to clopidogrel, prasugrel appears to be well absorbed and/or metabolized more efficiently to its active metabolite, accounting for its rapid onset of activity and relatively high efficacy.\textsuperscript{168}

Clinical Trials
Early studies suggested that prasugrel might have a more favorable effect on clinical outcomes when compared with clopidogrel. The Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-Thrombolysis in Myocardial Infarction (TIMI) 26 trial\textsuperscript{169} was a phase 2, randomized, dose-ranging, double-blind trial comparing prasugrel with clopidogrel in 904 patients undergoing elective or urgent percutaneous coronary intervention (PCI). This study was undertaken to compare the risk of bleeding events after PCI with prasugrel versus clopidogrel. Subjects were randomized to low dose (40 mg loading dose [LD] followed by 7.5 mg daily), intermediate dose (60 mg LD followed by 10 mg daily), or high dose (60 mg LD followed by 15 mg daily) prasugrel, versus the standard dose of clopidogrel (300 mg LD followed by 75 mg daily). The primary endpoint of the trial was non-CABG-related significant hemorrhage at 30 days. It was shown that there were no significant differences in bleeding complications between prasugrel- and clopidogrel-treated patients. At the highest dose of prasugrel, there was a trend observed of a higher minimal bleeding rate. There was also a lower incidence of major adverse coronary events in the prasugrel treated group, although this finding is not statistically significant. This study, however, did not set out to study the differences in the efficacy between prasugrel and clopidogrel.

The favorable results of the JUMBO-TIMI 26 trial led to a larger phase 3 clinical trial, TRITON-TIMI 38 (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38),\textsuperscript{170,171} which was designed to assess both efficacy and safety of prasugrel-treated patients versus clopidogrel-treated patients. The TRITON-TIMI 38 was a phase 3, randomized, double-blind, multinational clinical trial that randomized 13,608 patients with moderate to high risk acute coronary syndrome undergoing PCI to either prasugrel 60 mg LD followed by 10 mg daily, or clopidogrel 300 mg LD followed by 75 mg daily for up to 15 months.

The primary endpoints measured in this study included the combined occurrence rate of cardiovascular death, MI, or stroke. Major safety endpoints also evaluated the differences in the TIMI major and minor bleeding events unrelated to CABG. The results of this study showed that the primary efficacy endpoint occurred in 12.1% of patients receiving clopidogrel, as opposed to 9.9% of
patients receiving prasugrel (Figure 18-4), a difference that was shown to be statistically significant. Hence, prasugrel was associated with significantly reduced rates of ischemic events, thus supporting the study hypothesis of superior clinical efficacy when compared to clopidogrel. The prasugrel group also had significant reductions in the rates of MI (9.7% for clopidogrel versus 7.4% for prasugrel), urgent target-vessel revascularization (3.7% for clopidogrel versus 2.5% for prasugrel), and stent thrombosis (2.4% for clopidogrel versus 1.1% for prasugrel).

The reduction in the primary efficacy endpoint with prasugrel could relate in part to the more rapid onset of action of prasugrel when compared with clopidogrel. However, when comparing only endpoints occurring after day 3 of therapy, the significant reduction in the rate of ischemic endpoints persisted in the prasugrel group, suggesting a continued benefit of greater platelet inhibition during maintenance therapy as well. On the other hand, major bleeding episodes were significantly greater in the prasugrel group compared to the clopidogrel group (2.4% in prasugrel group versus 1.8% in clopidogrel group). Additionally, the rate of life-threatening bleeding, including both fatal and nonfatal bleeding, was increased in the prasugrel group when compared to the clopidogrel group. However, when the rates of certain efficacy and bleeding endpoints were included in a prespecified analysis of net clinical benefit, the findings still favored prasugrel in significantly reducing all cause mortality, nonfatal MI, nonfatal stroke, or nonfatal major bleed (13.9% in clopidogrel group versus 12.2% in prasugrel group).

In various subgroup analyses of TRITON-TIMI 38, patients with diabetes mellitus were shown to have a greater reduction in ischemic events without an observed increase in major bleeding events. In patients with STE-MI undergoing PCI, prasugrel was more effective than clopidogrel for prevention of ischemic events without an excess of bleeding. Prasugrel was also associated with fewer stent thrombi, irrespective of stent type.

Based on the results of TRITON-TIMI 38 and other clinical trials, prasugrel was approved for clinical use by the FDA.

The study investigators determined that there were 3 specific subgroups of patients who did not show a favorable net clinical benefit from prasugrel, presumably due to the increased risk of bleeding. These individuals included patients who had a previous stroke or TIA, patients 75 years or older, and patients weighing < 60 kg. Among patients without any of the risk factors described above, there was even greater efficacy observed with prasugrel and no significant difference in the rate of bleeding in the prasugrel group compared to the clopidogrel group. Thus, it would be helpful in the future to further define populations with an increased risk of bleeding associated with higher degrees of platelet inhibition before a specific flip.
recommendation regarding prasugrel can be generalized to the entire population.

A randomized, double blind, multicenter study in 10,000 patients with unstable angina is under way (TRIL-LOGY ACS) to evaluate the use of low-dose prasugrel (LD 30 mg, maintenance dose 5-10 mg depending on body weight) compared to the placebo in standard doses in patients who are being medically managed.161

Similar to aspirin, there is also a variability in the antiplatelet response to clopidogrel.17 The relative antiplatelet effects of higher clopidogrel doses than those used in TRITON-TIMI 38 in patients undergoing PCI were compared to those of prasugrel in the PRINCIPLE TIMI 44 trial (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 Trial).176 In this study the antiplatelet effects of prasugrel 60 mg LD followed by a 10 mg/day maintenance dose were compared to a clopidogrel 600 mg LD followed by a 150 mg/day maintenance dose. Greater inhibition of platelet aggregation at all time points measured from 30 minutes to 24 hours was observed in patients receiving prasugrel compared with high LD clopidogrel. During the maintenance dose phase, greater inhibition of platelet aggregation was also seen in those subjects receiving prasugrel compared with high maintenance dose clopidogrel. The trial was not powered statistically for clinical endpoints. Bleeding tended to be more frequent with prasugrel, although no significant differences were observed.

Based on the results of TRITON-TIMI 38, it appears that greater antiplatelet efficacy with drug therapy may be associated with additional clinical benefit on thrombotic events, but with an increased risk of bleeding. Future research studies may require individualized antiplatelet therapy regimens based on point-of-care testing of platelet function,177 similar to what is done with monitoring of prothrombin times in patients receiving warfarin, so as to maximize benefit of this treatment while minimizing risk. As with warfarin, too much anticoagulant activity with antiplatelet drugs resulting in bleeding will counteract the potential benefits of these antithrombotic treatments.

Prasugrel is indicated to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndromes who are managed with PCI. It is available in 5 and 10 mg tablets. The LD is 60 mg and the maintenance dose is 10 mg daily.178,179 A maintenance dose of 5 mg is recommended for patients who weigh < 60 kg. There is no dosage adjustment necessary in patients with mild to moderate renal or hepatic dysfunction. Patients should also receive aspirin 75-325 mg once daily. The drug can be used with GP IIb/IIIa inhibitors.180 Prasugrel does not seem to be affected by CYP450 genetic variants.181

The GP IIb/IIIa Integrin Glycoprotein Receptor Antagonists

Platelet aggregation is mediated by the GP IIb/IIIa receptor, a member of the integrin superfamily of membrane-bound adhesion molecules. Integrins are defined as subunit receptors composed of an α subunit (ie, GP IIb) and a β subunit (ie, GP IIa) capable of mediating adhesive interactions between cells or matrix. Although integrins are distributed widely throughout the vasculature, where they are expressed on endothelial cells, smooth-muscle cells, and leukocytes, expression of the GP IIb/IIIa integrin is restricted to platelets.182 It is the chief receptor responsible for platelet aggregation by its ability to bind soluble fibrinogen, forming bridges between platelets and leading, ultimately, to thrombus formation. GP IIb/IIIa is widely distributed on platelet surfaces (approximately 50,000 per cell) but remains unable to bind fibrinogen unless the platelet is first stimulated by agonists (such as ADP, thrombin, arachidonic acid, etc.), and undergoes a conformational change. It is believed that the adhesive binding pocket is somehow hidden until platelet activation, although this process is still unclear. Although fibrinogen is the peptide that mediates aggregation, mostly because of the large concentration of fibrinogen in plasma, GP IIb/IIIa is also capable of binding von Willebrand factor, fibronectin, and vitronectin.1 It has been demonstrated that aggregation can be supported by von Willebrand factor in the absence of fibrinogen. Therefore, these molecules may also play a role in aggregation at high shear rates such as is found in the coronary arteries.

GP IIb/IIIa, a heterodimer of two subunits, was the first integrin to be identified and has served as a model for characterization of other integrins. It has been demonstrated by electron microscopy that the receptor is composed of a globular head and two flexible tails that are imbedded in the platelet membrane. The GP IIb subunit has calcium-binding sites that have homology with calmodulin.182 In the presence of the calcium-chelating agent ethylenediamine tetraacetic acid, the receptor function is lost and the integrin dissociates into its two individual subunits. Each subunit contains a portion of the head and a single tail (Figure 18-5).

The GP IIb/IIIa domains responsible for binding adhesive proteins have been identified and in general are characterized by their ability to recognize the peptide sequence RGD. The RGD recognition sequence was originally described for fibronectin, but is now known to be present in fibrinogen, von Willebrand factor, vitronectin, and thrombospondin.183 Fibrinogen is a symmetrical protein composed of two α chains, two β chains, and two γ chains. Both of its RGD sequences are located on the α chain at residues 95 to 97 and 572 to 574. Fibrinogen also contains a 12-amino acid residue that possesses the ability
to bind to the GP IIb/IIIa receptor. This dodecapeptide (HHLGGAKQAGDV) is located at residues 400 to 411 on the fibrinogen gamma chain. It has been proposed that the RGD residues and the dodecapeptide competitively bind to GP IIb/IIIa. By initiating a conformational change in the receptor after binding, 1 recognition sequence on fibrinogen renders the other sequence inaccessible for binding. This alteration in receptor shape may be a self-regulatory mechanism of the GP IIb/IIIa receptor.

If two activated platelets with functional GP IIb/IIIa receptors each bind to the same fibrinogen molecule, a fibrinogen bridge is created between the two platelets (Figure 18-6). When this process of aggregation is repeated thousands of times, a thrombus will form. Experiments indicate that the RGD peptides bind to the GP IIIa subunit at residues 109 to 171. In contrast, the dodecapeptide binds to the GP IIb subunit at residues 294 to 314. Genetic defects in either of these two subunits can lead to the rare hemostatic disorder of Glanzmann's thrombasthenia. Patients with Glanzmann's thrombasthenia usually have a bleeding disorder during childhood. Although they have a normal platelet count, the GP IIb/IIIa receptor is either nonfunctional or absent. Platelet aggregation, in response to agonists such as thrombin, ADP, or arachidonic acid is, therefore, completely absent.

**GP IIb/IIIa Antagonists as antiplatelet agents**

As discussed earlier in this chapter, aspirin is the most common antiplatelet drug in use today. However, it is a relatively weak drug, effective against only one of the many platelet activators, TXA2. Other drugs similar to clopidogrel, ticlopidine, prasugrel, and hirudin, which are effective against ADP and thrombin, respectively, also are limited in their activity because of the platelet's ability to be activated by multiple agonists. Many patients with vascular disease take the current antiplatelet drugs and still sustain thromboembolic complications that often develop into ischemic conditions. Of importance, therefore, is the development of more effective antiplatelet agents. A drug able to inhibit platelet activation in response to all endogenous agonists would constitute a more effective therapy.

The binding of fibrinogen to activated platelets is the final step in platelet aggregation, and this binding is completely mediated by GP IIb/IIIa. Therefore, expression of the GP IIb/IIIa integrin is the final common pathway for platelet aggregation by all agonists. GP IIb/IIIa also is unique to platelets and is the most abundant platelet surface glycoprotein. These factors make GP IIb/IIIa an extremely favorable target for therapeutic pharmacologic blockade. A drug that could block the binding of fibrinogen to GP IIb/IIIa could theoretically abolish thrombosis resulting from vessel damage or atherosclerotic plaque rupture, regardless of the platelets' degree of activation. Discussed below are 3 classes of GP IIb/IIIa antagonists: disintegrins (naturally occurring GP IIb/IIIa blocking agents); monoclonal antibodies to the GP IIb/IIIa receptor; and synthetic peptide- and nonpeptide-receptor antagonists capable of blocking fibrinogen binding to platelets.

**Natural GP IIb/IIIa Antagonists: Disintegrins**

Several natural peptides derived from snake venoms have demonstrated the ability to block the GP IIb/IIIa receptor and prevent aggregation. Not surprisingly, these peptides, termed disintegrins, contain the same RGD sequence found in the endogenous adhesive proteins fibrinogen and von Willebrand factor. This tripeptide sequence enables the disintegrins to have a high affinity and specificity for all integrins, including GP IIb/IIIa. The disintegrin family includes trigramin from the snake *Trimeresurus gramineus*, bitistatin from *Bitis arietans*, and kistrin from the pit viper *Agkistrodon rhodostoma*. All of these peptides are 54 to 73 amino acids in length, and many exist in a cyclic conformation because of multiple disulfide bonds.
Bitistatin and kistrin have demonstrated the ability to inhibit platelet aggregation and subsequent thrombosis in canine models when administered in conjunction with heparin.188 Because the disintegrins have a short half-life, the antiplatelet effects are potentially reversible. Reversibility is important because of the risk of substantial, uncontrollable bleeding from tissue wounds (ie, intravenous puncture sites).

A problem with most disintegrins is that they are not specific for GP IIb/IIIa but are able to bind all RGD-dependent integrin receptors. This lack of specificity poses the potential for multiple adverse effects, including the blockade of adhesive proteins to endothelial cells and leukocytes. However, 1 disintegrin peptide has been identified that can uniquely bind to the GP IIb/IIIa receptor on the platelet membrane. Isolated from the pygmy rattlesnake Sistrurus M. barbouri, the disintegrin barbourin will not react with closely related integrins. This specificity appears to result from the substitution of a lysine (K) instead of the normal arginine (R) in the RGD sequence.189 The KGD sequence of barbourin has become the model for new, cyclic, synthetic antiplatelet peptides (discussed later in this chapter).

Although disintegrins have several properties that would be of benefit in a GP IIb/IIIa antagonist, such as high specificity (ie, with KGD) and reversibility, their use also poses problems. They tend to induce transient thrombocytopenia (abnormal decrease in blood platelets) and are highly antigenic, capable of generating an immune response. These serious adverse effects have severely limited the potential use of disintegrins as therapeutic agents.

Murine Monoclonal Antibodies (7E3)
In 1983, Coller produced a mouse monoclonal antibody against the GP IIb/IIIa integrin receptor.190 Coller later developed an additional antibody called 7E3 that more rapidly bound to ADP activated platelets.191 This antibody was subsequently used to make a human/mouse chimeric 7E3 Fab, now known as abciximab.192

Monoclonal antibodies, first produced in the 1970s by Kohler and Milstein, are populations of identical immunoglobulins derived from a single plasma cell that have been fused with an “immortal” malignant cell line. These hybridomas have the capacity to produce millions of identical antibodies with an absolute specificity for a single protein epitope.193 The Coller antibody 7E3, in its chimeric form, exhibits both a high affinity and absolute specificity for the GP IIb/IIIa receptor, two properties that made abciximab an attractive therapeutic agent for the blocking of adhesive proteins.194

Abciximab is a highly effective antithrombotic agent, specifically in preventing arterial thrombi in both canines and primates, including human beings. To eliminate the binding of fibrinogen to activated platelets, large doses of

Figure 18-6. GP IIb/IIIa structure and interactions binding platelets by divalent fibrinogen.
abciximab must be given to block GP IIb/IIIa receptor function effectively on all circulating platelets. However, by blocking all GP IIb/IIIa receptors and, consequently, inhibiting platelet aggregation, the risk of concurrent hemorrhage is increased. This bleeding risk is increased when combining antiplatelet therapy with invasive treatments such as PTCA or CABG.

Studies in baboons demonstrate that monoclonal antibodies have the potential to prevent platelet thrombus formation on synthetic fiber grafts in an arteriovenous fistula.\(^{195}\) The positive results of these primate studies highlight the potential for monoclonal antibody use in antithrombotic therapy in human beings. 7E3 has been tested in the treatment of patients with unstable angina and to prevent restenosis after coronary balloon angioplasty. Gold et al\(^{196}\) showed that 7E3 has the ability to block approximately 87% of GP IIb/IIIa receptors on platelets in human beings. In their study, a single injection of 7E3, 0.05 to 0.2 mg/kg, led to the absence of anginal symptoms (chest pain) for 12 hours in all patients tested, and in most cases (10 of 16 patients), freedom from pain for 72 hours. As expected, a large dose (0.2 mg/kg) of 7E3 prolonged the bleeding time from 6.3 minutes to > 30 minutes.

In patients with IHD who received 7E3 as a bolus injection, the effect on ADP-induced platelet aggregation and bleeding time is dose-dependent, with the maximal effect achieved at a dose of 0.25 mg/kg.\(^{197}\) A delayed and variable decrease in platelet fibrinogen levels is also observed. After an intravenous bolus dose of 0.25 mg/kg, blockade of GP IIb/IIIa receptors and inhibition of platelet function were maintained in patients receiving a maintenance infusion of 10 µg/min but not in those receiving 5 µg/min.\(^{197}\) Approximately 40% to 50% of GP IIb/IIIa receptor blockade is required for inhibition of platelet aggregation.\(^{198}\) Fluorescence flow cytometry studies reveal that platelets are uniformly coated with the drug within 30 minutes of infusion. Surface-bound antibody is still present on platelets 14 days after its administration, suggesting that antibody may be transferred to new platelets (platelet life span of approximately 10 days) or to megakaryocytes. Within 4 to 6 days of completion of a 24- to 72-hour intravenous infusion of the antibody, platelet-bound antibody concentrations are reduced by 50%, and platelet function recovers over a 48-hour period.\(^{197,199}\) After administration of an intravenous bolus, the antibody is cleared rapidly from the plasma, with an initial half-life of <10 minutes and second phase half-life of about 30 minutes. Less than 5% of the antibody can still be found in the plasma after 2 hours. Free concentrations in plasma remain relatively constant during continuous infusion of antibody at a rate of 10 µg/min for 96 hours, with concentrations in plasma levels decreasing rapidly the first 6 hours after treatment and more slowly after that.\(^{194}\) It is likely that the antibody is metabolized in a manner comparable to that of other natural proteins.

In an early randomized, placebo-controlled study of 60 patients with unstable angina, the addition of 7E3 to standard medical therapy (heparin and aspirin) appeared to be safe and effective in reducing major cardiovascular events during the hospital stay.\(^{200}\) The antibody was administered as a 0.25 mg/kg bolus followed by a 10 µg/min infusion for 18 to 24 hours until 1 hour after completion of a second angiography and percutaneous transluminal coronary angioplasty (Table 18-3).

It has been shown experimentally that approximately 70% of platelet deposition at the site of balloon injury is GP IIb/IIIa-dependent, and the remaining 30% results from non-GP IIb/IIIa-mediated platelet subendothelial adhesion.\(^{201}\) In human beings, it appears that 7E3 can result in blockade of > 80% of receptors and can reduce platelet aggregation to < 20%.\(^{202}\) The drug also can suppress the levels of circulating inflammatory markers after angioplasty.

The results of a larger study demonstrated the effectiveness of 7E3 in the prevention of postangioplasty restenosis. The Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) study highlighted the importance of the GP IIb/IIIa receptor in abrupt vessel closure after high-risk coronary angioplasty and atherectomy.\(^{203,204}\) A random population (2,099 patients) scheduled to undergo these procedures received either a bolus and infusion of the placebo; a bolus of 0.25 mg/kg 7E3 and a 12-h infusion of the placebo; or a bolus and infusion of 7E3.\(^{205}\) Results were measured as the risk of experiencing a composite primary endpoint (which included death, nonfatal MI, or unplanned invasive revascularization procedures) by 30 days. Data indicated that, as compared with those patients given the placebo, patients who received administration of the bolus and infusion of 7E3 had a 35% risk reduction in the composite-event rate. Patients who received only a 0.25 mg/kg bolus of 7E3 (and placebo infusion) still showed a 10% reduction in the risk of experiencing a primary endpoint (Table 18-3, Figure 18-7). On the basis of the results of the EPIC trial and other pharmacologic studies, the 7E3 antibody, abciximab, was approved for use in patients undergoing high-risk angioplasty. The drug is now also approved for unstable angina. The FDA-approved dose is 0.25 mg/kg bolus and 10 µg/min infusion for 18 to 24 hours before PCI and continued for 1 hour after PCI. This may not be the optimal dose, and a 12-hour infusion after PCI is recommended.\(^{206}\)

In addition, during a 6-month follow-up period, the number of ischemic events were reduced by 26% in patients who received the 7E3 antibody, suggesting a long-term benefit against clinical coronary artery stenosis.\(^{204}\)

Although these results demonstrate the importance of pharmacologic blockade of GP IIb/IIIa as therapy for ischemic events, the use of abciximab results in several negative complications. In 14% of the patients in the EPIC
A significant amount of bleeding (twice the number of major bleeding episodes in the placebo group) occurred and often required transfusion. The bleeding usually occurred at the site of vascular puncture in the groin. The increased bleeding time is compounded because the antibodies are inherently long-lived and do not dissociate from platelets during the platelets' survival time in the plasma. Thus, the inhibitory effect on systemic platelet aggregation is non-reversible and may last several days. This situation may prove to be deleterious for patients with unstable conditions that may require unplanned invasive procedures. Thrombocytopenia and pseudothrombocytopenia have been described with the use of abciximab, and altered leukocyte adhesion has been observed when it is combined with ticlopidine. Last, the use of large doses of monoclonal antibodies could stimulate the proliferation of neutralizing antibodies and, therefore, may restrict 7E3 therapy to a single use. Despite these complications, the positive results obtained by monoclonal antibody blockade of GP IIb/IIIa receptors have furthered the development of high-affinity, synthetic, peptide antagonists.

The EPILOG trial (Evaluation of PTCA to Improve Long term Outcomes by 7E3 GPIIb/IIIa Receptor Blockade Trial) evaluated the use of both high- and low-risk PTCA with 7E3. The original study design called for the
with abciximab. Specifically, the primary endpoints because of strongly favorable results in those treated trial was stopped prematurely after only 1,050 patients developed unstable angina/ECG changes the night before were randomized to standard therapy with or without the next day. Although 1,200 patients were to be enrolled, the PTCA the following day and who were scheduled for PTCA was evaluated in the CAPTURE trial (Chimeric c7E3 Antiplatelet Therapy in Unstable Angina Scheduled PTCA) and who who were scheduled PTCA was evaluated in the CAPTURE trial (Chimeric c7E3 Antiplatelet Therapy in Unstable Angina Scheduled PTCA). Abciximab appeared to be confined to patients not undergoing PCI had no effect on infarct size. In contrast to the results from the EPIC trial, bleeding complications in the 7E3/low-dose heparin group were not significantly different than with the placebo (< 2% with treatment, 3.1% placebo). The benefits provided by abciximab appeared to be confined to only those patients presenting with an elevated troponin level. In the Value of Abciximab in Patients with Acute MI Undergoing PCI after High Dose Clopidogrel Treatment (BRAVO-3) trial, the combination of clopidogrel preloading and abciximab had no effect on infarct size.

Abciximab is approved as an adjunct for preventing cardiac ischemic complications in patients undergoing PCI and in patients with unstable angina not responding to conventional medical therapy when PCI is planned within 24 hours. The safety and efficacy of abciximab use in patients not undergoing PCI has not been established. The dose of abciximab is an intravenous bolus of 0.25 mg/kg (max of 10 μg/min) with unfractionated heparin (UH) and aspirin administered 10 to 60 minutes before the start of PCI, followed by a continuous infusion of 0.125

Figure 18-7. Probability of no urgent repeated percutaneous revascularization procedures in 3 treatment groups (Kaplan-Meier plots). Events began to occur shortly after index procedure in placebo group, between 6 and 12 hours after procedure in group given bolus of c7E3 Fab, and even later in group given bolus and infusion; y axis is truncated at 97% to demonstrate differences in this end-point, which occurred with low frequency.

Reprinted with permission from EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med. 1994;330:956. Copyright © 2007 Massachusetts Medical Society. All rights reserved.
μg/kg/min to a maximum of 10 μg/min for 12 hours. In patients with unstable angina not responding to conventional medical therapy and who are planned to undergo PCI within 24 hours, abciximab may be used with a 0.25 mg/kg intravenous bolus followed by an 18- to 24-hour intravenous infusion of 10 μg/min concluding 1 hour after the PCI.

**Synthetic Peptide and Nonpeptide Antagonists**

As an alternative to monoclonal antibodies, researchers have attempted to develop small synthetic peptides with the ability to block fibrinogen from binding to the GP IIb/IIIa platelet receptor. The goal of this effort has been to create a peptide with the same affinity and specificity exhibited by monoclonal antibodies but without the adverse effects of prolonged bleeding time, immunogenicity, and irreversibility. In many cases, the synthetic peptides were modeled on the “disintegrin” or natural antiplatelet antagonists but were smaller and therefore less immunogenic. By using the RGD binding sequence found in circulating adhesive proteins, researchers developed a series of modified RGD analogues capable of binding to GP IIb/IIIa. One modification includes the addition of disulfide bonds for the creation of cyclic peptides. The cyclic conformation has not only rendered the peptides more stable in plasma, but also has imparted a higher affinity for the integrin receptor. Another modification has been to substitute lysine (K) in the RGD sequence for arginine (R). This substitution creates a peptide similar to the disintegrin barbourin (discussed earlier in this chapter), which has absolute specificity for GP IIb/IIIa integrin.

The cyclic heptapeptide epifibatide (Integrelin) is approved for use in acute coronary syndromes on the basis of the PURSUIT trial (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy trial). The recommended dose for acute coronary syndromes is an intravenous 180 μg/kg bolus followed by an infusion of 2.0 μg/min for 72 to 96 hours. The approved dose for PCI on the basis of the IMPACT-II trial (Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis II trial) is a bolus of 135 μg/kg followed by an infusion of 0.5 μg/kg/min for 20 to 24 hours. However, a dose based on the ESPRIT trial (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) is now recommended, which is two 180 μg/kg boluses 10 minutes apart and a 2.0 μg/kg/min infusion for 18 to 24 hours. The infusion rate should be decreased by 50% in patients with a creatinine clearance < 50 mL/minute. After an uncomplicated PCI, epifibatide can be abbreviated safety to < 2 hours.

The 2007 ACC/AHA (American College of Cardiology/American Heart Association) guidelines recommend that for patients presenting with unstable coronary syndromes who will be treated initially according to an invasive strategy, either an intravenous GP IIb/IIIa inhibitor or clopidogrel should be added to aspirin and other anticoagulant therapy upstream before diagnostic angiography is performed. However, recent studies have shown no benefit of using epifibatide 12 hours before angiography compared to its use after angiography. In a comparison study, there is no apparent difference in outcomes of patients treated with epifibatide compared to those treated with abciximab.

The nonpeptide tirofiban Aggrastat is approved for use in acute coronary syndromes, including those patients who are managed medically and those undergoing PTCA or atherectomy, at a dose of 0.4 μg/kg/min for 30 minutes and then 0.1 μg/kg/min for 48 to 108 hours. When tirofiban was used in patients with coronary syndromes undergoing invasive therapy, a more favorable outcome was observed compared with conservative therapy. The infusion rate should be decreased by 50% in patients with a creatinine clearance < 30 mL/minute.

An early comparison trial of two platelet GP IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization demonstrated that tirofiban offered less protection from major ischemic events than did abciximab. A more recent study comparing tirofiban to abciximab showed no difference in clinical outcomes in patients undergoing stenting for MI.

**Adverse Reactions**

The major adverse reactions with the use of GP IIb/IIIa receptor antagonists are bleeding and thrombocytopenia. Immune reactions are the cause of the thrombocytopenia and are seen with all the available agents. Some of these thrombocytopenia cases may be related to pseudothrombocytopenia that occurs as a result of artifactual platelet clumping secondary to the type of assay being used to determine platelet levels.

**Oral Glycoprotein IIb/IIIa Receptor Antagonists**

Although the peptide antagonists to the GP IIb/IIIa integrin appear to compensate for the shortcomings of the monoclonal antibodies (ie, decreased bleeding time, reversibility, and nonimmunogenicity), they have one major limitation: None is orally bioavailable in human beings. Currently, all antagonists, peptide or monoclonal antibody, must be administered intravenously. Therefore, their therapeutic use is limited to acute thrombotic situations, such as maintenance of coronary flow after angioplasty or thrombolysis (with tissue plasminogen activator or streptokinase). To be effective as preventive therapy (ie, for unstable angina and MI), an orally active form must be available. This drug must maintain low concentrations in plasma to prevent spontaneous hemorrhage but should also maximally inhibit platelet aggregation. A prototype orally active GP IIb/IIIa receptor nonpeptide...
inhibitor was developed, SC-54684A (xemilofiban); it had undergone phase 1 and 2 testing in patients, including in patients who had previously received abciximab. Xemilofiban is an ester prodrug that is converted to an active moiety (SC-54701A). However, in the EXCITE trial, when xemilofiban was used in patients undergoing PCI, there was increased bleeding and no reduction in ischemic events.

Orbofiban is an oral GP IIb/IIIa inhibitor that was studied in 10,288 patients with acute coronary syndromes. Despite a benefit that was observed among patients who underwent PCI, the trial was terminated prematurely because of an unexpected increase in 30-day mortality in the orbofiban treated group.

Sibrafiban, another oral agent, showed no additional benefit over aspirin for secondary prevention of major ischemic events after an acute coronary syndrome and was associated with more dose-related bleeding. A second sibrafiban study that combined aspirin with low-dose sibrafiban did not show improved outcomes after acute coronary syndromes and caused more bleeding as compared with aspirin alone. There was a trend toward increased mortality in this group and a significant increase in a high-dose arm.

A lotrafiban trial was also stopped because of increased mortality.

In a meta-analysis of oral GP IIb/IIIa inhibitor trials, the authors found a highly significant excess in mortality that was consistent across 4 trials with 3 different oral GP IIb/IIIa inhibitor agents and that was associated with a reduction in the need for urgent revascularization and no increase in MI. The authors believed that these findings suggest the possibility for a direct toxic effect with these agents that is related to a prothrombotic mechanism.

The several hypotheses put forward to explain the increased mortality associated with the use of oral GPIIb/IIIa inhibitors include: (a) induction of a binding configuration of the GP IIb/IIIa receptor by drug cycling on and off; (b) activation of myocyte caspase causing apoptosis; (c) increased plaque hemorrhage; and (d) a proinflammatory effect.

**Conclusion**

Antiplatelet therapy is an effective treatment for patients with coronary and cerebral vascular diseases. Aspirin is effective in reducing mortality risk in survivors of acute MI, and aspirin, ticlopidine, and clopidogrel are useful in preventing strokes in persons at high risk. Prasugrel may provide some advantages over clopidogrel in unstable coronary syndromes. The development of monoclonal antibodies and intravenous peptide and nonpeptide compounds that bind to the GP IIb/IIIa receptor in activated platelets shows great potential for treating patients undergoing coronary angioplasty to prevent short- and long-term complications and for treating patients with unstable angina and myocardial infarction. The clinical development of oral GP IIb/IIIa inhibitor agents suitable for long-term use yielded disappointing results.

**Other Anticoagulants and Direct Antithrombins**

In this section, the anticoagulant drugs heparin, heparin derivatives, and warfarin are reviewed, along with a discussion of the new direct thrombin inhibitors hirudin, Hirulog, argatroban, melagatran, and ximelagatran.

**Heparin**

**Mechanisms of Action**

Heparin, a glycosaminoglycan, is composed of alternating residues of D-glucosamine and iduronic acid. Its principal anticoagulant effect depends upon a critical pentasaccharide with high-affinity binding to antithrombin III (ATIII). When bound to the critical pentasaccharide, ATIII changes its configuration so that it can directly inhibit activated factor X (Xa). If the polysaccharide chain is long enough (> 18 saccharides), the hepant ATIII complex can also bind thrombin and inactivate its active site. Heparin catalyzes the inactivation of thrombin by ATIII (Figure 18-8) by providing a template to which both thrombin (factor IIa) and the naturally occurring serine protease inhibitor, ATIII can bind. Additionally, heparin catalyzes thrombin inactivation via a specific pathway involving heparin cofactor II, a mechanism requiring higher heparin doses but not involving the ATIII-binding pentasaccharide. In contradistinction to direct thrombin inhibitors that impede thrombin activity, heparin indirectly inhibits both thrombin activity and thrombin generation; the heparin-ATIII complex also inhibits other anticoagulation proteases, including factors IXa, Xa, Xla, Xlla.

The molecular weight of heparin ranges from 5,000 to 30,000, with a mean value of 15,000, and containing an average of approximately 50 saccharide chains. Heparin’s pharmacokinetic properties in anticoagulant activity are heterogeneous for two reasons: First, its plasma clearance is influenced by molecular size with larger-sized molecules being cleared more rapidly than smaller-sized molecules, resulting in an increased antifactor Xa to antifactor IIa (thrombin) activity ratio. Second, the anticoagulant activity of heparin is also influenced by molecular chain length; only about one-third of standard UH molecules in clinical usage are sufficiently long (containing > 18 saccharides) to possess the ability to inhibit thrombin via ATIII-mediated anticoagulant action.
Pharmacokinetics

Because it is not absorbed orally, heparin is given either subcutaneously or intravenously. When given in sufficient doses, the safety and efficacy of both routes are comparable for treating venous thrombosis if the reduced bioavailability of subcutaneous heparin is taken into account. At clinically therapeutic doses, a substantial proportion of heparin is cleared via the dose-dependent rapid pathway. Hence, the anticoagulant response to heparin is not linear but increases disproportionately both in intensity and duration with larger heparin doses. The apparently biologic half-life of heparin increases from 30 minutes to 60 minutes to 150 minutes after bolus intravenous doses of 25, 100, and 400 U/kg, respectively.

Pharmacodynamics

The intensity of heparin anticoagulant effect is monitored by the activated partial thromboplastin time (aPTT) test, which is sensitive to both antithrombin (antifactor IIa) and antifactor Ixa and Xa effects. Experimental data have suggested that an aPTT of 1.5 times control could prevent venous thrombus extension. When heparin is used clinically, however, consideration must be given to (a) interpatient variability in plasma and tissue binding that alters heparin pharmacokinetics; (b) potential increases in factor VIII (occurring as part of an acute phase reaction in seriously ill patients) that can blunt the aPTT response to a given heparin level; and (c) the variable potency of commercially employed aPTT reagents. It has been recommended that the therapeutic range for each aPTT reagent be calibrated to be the equivalent to a heparin level of 0.2 to 0.4 U/mL by protamine titration or to an antifactor Xa level of about 0.3 to 0.7 U/mL, but recent data using thromboelastography suggest guidance by aPTT rather than heparin level.

Clinical Use in Venous Thrombosis

Randomized clinical trials have established the efficacy of heparin usage in venous thrombosis. Heparin may be given in an initial intravenous bolus of 5000 U or a weight-adjusted bolus followed by at least 30,000 U/24 hours by continuous infusion with additional heparin dose adjustments to maintain a therapeutic aPTT range. Heparin's effectiveness is dependent on using an adequate starting dose and maintenance infusion that produce an adequate anticoagulant effect, measured either by aPTT or by heparin levels, provided that the heparin level is > 0.3 U/mL antifactor Xa activity.

Orthopedic and General Surgery

Heparin has been recommended for routine usage in the prevention of venous thromboembolism (VTE), especially in surgical patients undergoing elective hip or knee repair or replacement who are at high risk for perioperative venous thrombosis and pulmonary embolism (PE). The prevalence of VTE following total knee or hip replacement surgery has been summarized as between 45% and 84%, and that following hip fracture surgery as being between 36% and 60%, with a corresponding PE rate of 2% to 30% and 4% to 24%, respectively. A meta-analysis comparing the efficacy of LMWH to low-dose UH indicated that LMWH was more effective in suppressing venous thromboembolism.

Elective neurosurgery and acute spinal-cord-injury patients also have a high risk for VTE, averaging 24%. Although there has been concern regarding intracranial or intraspinal bleeding, a recent study has demonstrated the efficacy and safety of both low-dose UH and LMWH prophylaxis.

Acute Myocardial Infarction and Unstable Angina

Heparin has been used in acute MI patients to prevent VTE, mural thrombosis, and systemic embolism. Among acute MI patients not treated with antithrombotic agents, the incidence of deep-vein thrombosis (DVT) is about 24%. Subcutaneous low-dose UH in doses of 5000 to 7500 U twice daily and high-dose intravenous heparin 40,000 U/d reduces DVT without adverse bleeding events.

In the contemporary acute MI patient, heparin anticoagulation coupled with aspirin and other antiplatelet
therapy has become a mainstay of treatment. However, no benefit was seen on early coronary patency in MI patients receiving heparin before primary angioplasty. In acute coronary syndromes, it has been used to reduce the frequency of unstable angina. It has also become a standard adjunct to thrombolytic drugs despite the lack of definitive proof regarding its efficacy when it is used concurrently with either tissue plasminogen activator (t-PA), tenecteplase, reteplase, anisoylated plasminogen streptokinase activator complex (APSAC), or subsequent to streptokinase, which minimizes thrombolytic drug activation of the coagulation system during fibrinolysis. The increased plasmin generated during fibrinolytic drug therapy mediates both platelet activation and plasmin mediated-prothrombinase activity, requiring ancillary antithrombotic drug treatment.

Studies examining the efficacy of heparin therapy for the treatment of MI in the thrombolytic era are reviewed next. The SCATT (Studio sulla Calciparina nell’Angina e nella Trombosi Ventricolare nell’Infarto) study examined 711 patients randomized to receive either subcutaneous heparin or no heparin as part of the therapy for MI. Approximately half of the patients received thrombolytic therapy with streptokinase. In the heparin plus thrombolytic group and in the heparin-alone group, a reduction in mortality associated with heparin was noted. In addition, a trend toward a reduction in the number of postinfarction ischemic episodes was noted in those patients who received thrombolytic therapy plus heparin. Heparin therapy was clearly effective either alone or as an adjunct to thrombolytic therapy in the treatment of acute MI. In a larger GISSI-2 study, subcutaneous heparin therapy was not associated with a statistically significant difference in mortality, reinfarction, or unstable angina. It did, however, highlight an excess of bleeding.

The International Study Group, which incorporated some of the GISSI-2 data, examined 20,891 patients who underwent thrombolytic therapy with either APSAC or streptokinase. The group that received subcutaneous heparin experienced an excess of bleeding episodes without the benefit of a reduction in reinfarction or stroke. In addition, the Third International Study of Infarct Survivors examined 41,300 patients treated with thrombolytic therapy. The addition to aspirin of heparin resulted in an excess of transfused or major bleeding, with only a trend toward a reduction in reinfarction and with no differences in mortality or stroke. However, a meta-analysis of the data from the ISIS and GISSI trials supports a decrease in mortality during the treatment period. This mortality benefit came at the expense of increased bleeding. Taken together with a review of prior data on the use of heparin as adjuvant therapy for MI published in 1985, heparin did not appear to significantly influence the rates of reinfarction or death.

A few trials using heparin have demonstrated an improved patency rate of the infarct-related artery up to 3 days after thrombolysis for acute MI. The Heparin-Aspirin Reperfusion Trial (HART), in which 205 patients received t-PA plus either heparin or aspirin, demonstrated improved 18-hour patency of the infarct-related artery associated with heparin therapy. There were no significant differences among the two groups in terms of patency at 7 days or in terms of hemorrhagic events. Examination of the data from either the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial or the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) trials did not demonstrate an effect of heparin on mortality, reinfarction, major hemorrhage, infarct-related artery patency, or reocclusion. These angiographic trials highlighted the fact that heparin may improve coronary patency in some patients, with improvement being greatest in those patients not treated or undertreated with aspirin.

In all, the data available with heparin as adjunctive therapy for MI does not support its routine use with streptokinase. Anticoagulant therapy should be reserved for use in those patients who are at higher risk for further events—specifically, those patients who have AF or heart failure or who have suffered a large MI. The data regarding the use of heparin with t-PA is even more limited. However, the short duration of activity, the more specific fibrinolytic effect, and the angiographic data lends some support to its use with t-PA. Heparin is also useful as an adjunct therapy to antiplatelet agents in patients undergoing PCI.

Randomized clinical trials have compared the effectiveness of intravenous heparin (an indirect thrombin inhibitor) with intravenous hirudin (a direct thrombin antagonist). In the TIMI (Thrombolysis in Myocardial Infarction) 9B study, heparin (5000 U/h and 1000 U/h) and hirudin (0.1 mg/kg/h and 0.1 mg/kg/h) were found to be equally effective and to have similar major hemorrhagic adverse effects (4% to 5%) when used as adjuncts to t-PA or streptokinase to preventing unsatisfactory thrombotic outcomes in acute MI patients.

Dosing
There are several methods for optimizing intravenous heparin dose adjustments. These nomograms have been used for the treatment of both VTE and acute MI patients. A weight-based heparin nomogram has also been recommended in the current treatment guidelines for unstable angina. Such algorithms are convenient to use, are successful in achieving therapeutic aPTT levels in an expeditious manner, and reduce VTE.

Side Effects
Bleeding is the major adverse effect associated with heparin use and is partly a function of the drug's complex
pharmacokinetics, its use in severely ill patients who are often on other antithrombotic or fibrinolytic agents, and the numerous other actions of heparin on a variety of processes besides anticoagulation.279

Of special concern, however, is heparin-induced thrombocytopenia (HIT).274-277 Two mechanisms for HIT have been elucidated: an early reversible nonimmune thrombocytopenia, possibly related to weak platelet activation by the drug, and a late, serious immune thrombocytopenia with immunoglobulin G (IgG)-mediated platelet activation and thrombotic complications.249,278 Immune-related HIT was seen in 1% and 3% of patients receiving low-dose UH for 7 and 14 days, respectively, but was not observed with LMWH.272 When present, HIT becomes manifest 5 to 15 days after initiating heparin therapy but may arise within hours in patients previously exposed to heparin within the prior 3 to 6 months.249 In vitro studies suggest that LMWH can cross-react to activate platelets in serum from HIT patients.279 In 2007-2008, large amounts of contaminated heparin were imported into the United States. Many patients suffered adverse reactions with hypotension and anaphylaxis-like symptoms.279a In response to that situation, action was taken to remove the contaminated heparin from the market, and the US Pharmacopeia monograph was updated to include test methods to detect impurities, determine the potency of the drug, and harmonize with the WHO international standard unit dose. There is an approximately 10% decrease in the anticoagulant activity of the “new heparin” as compared to the “old heparin.” Both are available. Although the 10% difference will not usually be clinically important, there may be situations, such as the use of extracorporeal membrane oxygenator or cardiopulmonary bypass or life-threatening thrombotic disease, when this becomes significant.

**Shortfalls of Heparin**

The search for more potent and more direct antagonists to the clotting cascade was brought about by the realization that heparin actions are incomplete, unpredictable, and dependent upon cofactors not consistently found from patient to patient. Heparin's shortfalls have included a dependence on ATIII and cofactor II for its anticoagulant effect;280 varied activity from preparation to preparation; binding to plasma proteins, leukocytes, and osteoclasts; and an inability to inactivate clot-bound thrombin.286 Meticulous monitoring of the anticoagulant effect is necessary to retain heparin in a therapeutic range for several reasons. First, heparin is a heterogeneous mixture of molecules, each with variable biologic effects. Second, the concentrations of cofactors ATIII and cofactor II vary from individual to individual.280,281 Third, heparin can be bound by a number of plasma proteins with variable concentrations from individual to individual with a resultant difference in the amount of heparin available to exert an anticoagulant effect.282 In addition, activated platelets release platelet factor 4 and heparinase, both of which can act to counter the anticoagulant activity of heparin.282,283 Finally, much of the active thrombin is clot bound, which protects it from inactivation by heparin.281 Thus, the nidus for clot formation and propagation cannot be activated. In contrast, the direct thrombin inhibitors are ATIII independent, provide a stable, anticoagulant effect, and are able to inhibit clot-bound thrombin.281,282

**Low-Molecular-Weight Heparins (LMWH)**

LMWH are fragments of commercial-grade standard heparin produced by enzymatic or chemical depolymerization with a resultant molecular weight of 4000 to 6500 (Table 18-4). Because smaller heparin molecules (MW < 4000) are not able to bind to thrombin (factor II) and AT-III simultaneously, LMWH have a diminished ability to accelerate the inactivation of thrombin by AT-II. However, LMWH retains its ability to catalyze the inactivation of factor Xa by AT-III. Therefore, as contrasted to standard heparin (average molecular weight 12,000 to 15,000) with an anti-Xa/anti-IIa inhibitory ratio of 1:1, commercial LMWH has anti-Xa/anti-IIa ratios of 2:1 to 4:1 when tested in vitro. The persistence of anti-IIa activity by LMWH emanates from the larger oligosaccharide chains in its polydispersed spectrum.284

Other properties that distinguish LMWH from standard heparin include lack of inhibition of activity by platelet factor 4 (PF4), a potent inhibitor of standard heparin release during coagulation;285 persistence of inactivation of Xa bound to platelet membranes in the prothrombinase complex, a feature lacking in standard heparin; and lack of LMWH binding by plasma proteins, histidine-rich GP, fibronectin, vitronectin, and von Willebrand factor, as opposed to the plasma binding of standard heparin, which partially neutralizes its anti-Xa inhibition.286 In addition, UH binds to endothelium, monocytes, and osteoclasts. The diminished binding of LMWH to osteoclasts may account for the decreased incidence of osteoporosis as compared to that seen with the prolonged use of UH.

These features of LMWH, which distinguished it from standard heparin, can result in certain clinical advantages: (a) a more predictable dose response with patient variability to a fixed dose; (b) a long half-life and reduced bleeding for equivalent antithrombotic effects; (c) enhanced safety and efficacy in the treatment of patients with venous thrombosis. Table 18-4 lists several LMWHs.287

**Clinical Trials**

A meta-analysis of the relevant randomized clinical trials comparing UH with LMWH examined total mortality, pulmonary embolism mortality, rates of recurrent VTE, change in venography scores, and incidence of
bleeding.\textsuperscript{288} LMWH significantly reduced short-term and pulmonary embolism mortality, while causing less major bleeding as contrasted to UH. Longer-term mortality and serious bleeding rates were influenced by case mix and efficacy of subsequent oral anticoagulation but were still favorably influenced by LMWH as compared to UH, with a relative risk of 0.30 (95% confidence interval, 0.3 to 0.4; \( P = .0006 \)) for mortality and 0.42 (95% confidence interval, 0.2 to 0.9; \( P < .01 \)) for major bleeding.\textsuperscript{288} Additional data favoring the safety of LMWH versus UH were provided from a study of 3,809 patients undergoing major abdominal surgery with heparin prophylaxis for \( \geq 5 \) days perioperatively.\textsuperscript{289} The 4-week incidence of major bleeding was reduced from 141 to 93 (\( P < .058 \)), and major hematoma from 2.7% to 1.4%, when LMWH was compared to UH. Individual trials and a meta-analysis show that LMWH use in venous thromboembolism is associated with a decreased mortality as compared to UH. This decreased mortality incidence appears to be seen only in cancer patients, and is the subject of new trials.

**Acute Ischemic Stroke**

Thrombolytics have a place in the treatment of acute stroke, but full-dose anticoagulation with either UH or LMWH is generally not recommended, except possibly for prevention of recurrence in cardioembolic stroke.\textsuperscript{280} The International Stroke Trial (IST) compared aspirin, subcutaneous heparin, both, or neither and found no significant advantage from heparin but a higher rate of bleeding with higher doses of the drug.\textsuperscript{281}

Kay et al,\textsuperscript{282} in a randomized double-blind, placebo-controlled trial, compared the effect of two dosages of LMWH with the placebo. Three hundred and twelve patients with acute ischemic stroke were randomized within 48 hours of symptoms to high-dose nadroparin (4100 anti-Xa IU subcutaneously twice daily), low-dose nadroparin (4100 IU subcutaneously once daily), or the placebo subcutaneously for 10 days. The primary endpoint at 6 months of death and dependency of living were analyzed for 306 patients. A significant favorable dose-dependent effect of LMWH on outcomes was noted as follows: high-dose group 45%, low-dose group 52%, and the placebo 65% (\( P = .005 \)). No statistically significant difference in hemorrhagic transformation of the infarct was noted between the 3 groups. LMWH improved the 6-month outcome of acute ischemic stroke. However, it has been pointed out that these findings could not be duplicated in a very similar trial that used the same agent.\textsuperscript{280}

**Myocardial Infarction**

LMWH can be used as an alternative to weight-adjusted UH in patients with acute MI undergoing thrombolysis.\textsuperscript{293} In a recent trial, tenecteplase plus enoxaparin reduced the frequency of ischemic complications of an acute MI as compared to UH. The tenecteplase-exenaparin combination was also shown to be as effective as tenecteplase plus abciximab but easier to administer to patients.\textsuperscript{294,295}

In the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT)-Thrombolysis in Myocardial Infarction (TIMI)-25 study, it was found that patients with STEMI had better cardiovascular outcomes but increased bleeding when comparing exenaparin to UH.\textsuperscript{296,297}

Based on a recent meta-analysis, it was concluded that LMWH was more effective than UH in reducing the risk of reinfarction and death in patients with STEMI.\textsuperscript{298}

**Unstable Angina**

The use of antithrombotic agents for unstable angina, a process that results from platelet aggregation and thrombus formation, has been well studied. Gurflinkel et al,\textsuperscript{299} in a prospective, single-blind, randomized trial of patients

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**Table 18-4. Low-Molecular-Weight Heparins**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Mean &amp; Range Molecular Weight</th>
<th>Anti-Xa to Anti-IIa Ratio</th>
<th>Plasma Half-Life (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardeparin</td>
<td>Normiflow</td>
<td>5000</td>
<td>2.0/1.0</td>
<td>270</td>
</tr>
<tr>
<td>Certoparin</td>
<td>Sandoparin</td>
<td>6000 (5000–9000)</td>
<td>2.7/1.0</td>
<td>119–139</td>
</tr>
<tr>
<td>Dalteparin*</td>
<td>Fragmin</td>
<td>5000 (2000–9000)</td>
<td>3.8/1.0</td>
<td>129–180</td>
</tr>
<tr>
<td>Enoxaparin*</td>
<td>Lovenox</td>
<td>4500 (3000–8000)</td>
<td>3.2/1.0</td>
<td>132–162</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>Fraxiparine</td>
<td>4500 (2000–8000)</td>
<td>5.0/1.0</td>
<td>–</td>
</tr>
<tr>
<td>Parnaparin</td>
<td>Flaxum</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Reviparin</td>
<td>Clivarine</td>
<td>3900 (2000–4500)</td>
<td>2.8/1.0</td>
<td>111</td>
</tr>
<tr>
<td>Tinzaparin*</td>
<td>Innohep</td>
<td>4500 (3000–6000)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*FDA approved.*
with unstable angina, compared the effects of nadroparin calcium, an LMWH (214 IU/kg anti-Xa subcutaneous twice a day) and aspirin, versus UH and aspirin (200 mg/d), versus aspirin (200 mg/d) alone in 211 patients. Primary outcomes were recurrent angina, acute MI, urgent revascularization, major bleeding, and death. There was a significant benefit with the use of LMWH and aspirin versus UH and aspirin in the rate of recurrent angina, 21% versus 44%, respectively.

FRISC (Fragmin During Instability with CAD) was a multicenter study that randomized 1,506 patients with unstable angina to LMWH (120 IU/kg subcutaneously every 12 hours up to day 6 and then 7500 U every day at home until day 40) or the placebo. At day 6, there were differences between the LMWH and the placebo groups in the occurrence of new MI and death (1.8% and 4.7%, respectively) and severe angina (7.8% and 13.9%, respectively). The benefit continued through day 40. By day 150 no differences were noted between the two groups. FRISC (Fragmin in Unstable Coronary Artery Disease), another multicenter, randomized study, enrolled 1,482 patients with unstable angina. Patients were randomized to UH (5000 U intravenous bolus, 1000 U/infusion, and then 1250 U subcutaneous twice a day) versus LMWH (120 IU/kg every 12). Therapy continued for 6 weeks. The initial data at 7 days indicated that there were no differences between groups in death, MI, urgent revascularization, non-Q-wave MI, or unstable angina. In a study of thrombolytic therapy with enoxaparin plus aspirin versus UH plus aspirin, enoxaparin plus aspirin was more effective in reducing the incidence of ischemic events in patients with unstable angina or non-Q-wave MIs in the early stage. This greater efficacy was sustained at a 1-year follow-up. A recent meta-analysis shows no difference in efficacy or safety between UH and LMWH in aspirin-treated patients with acute coronary syndromes. Both therapies halve the risk of MI and death. There is no evidence to support the use of LMWH after 7 days.

The American College of Chest Physicians Consensus Conference now recommends that unstable angina be treated with aspirin or an alternative antiplatelet agent combined with intravenous heparin (about 75 U/kg intravenous bolus, initial maintenance 1250 U/h intravenous, aPTT 1.5 to 2 times control) or LMWH (dose regimen from trial), dalteparin (120 IU/kg subcutaneous every 12 hours), enoxaparin (1 mg/kg subcutaneous twice a day), nadroparin (either 86 anti-Xa IU/kg twice a day for 4 to 8 days or the same dose given intravenously then subcutaneously twice a day for 24 days) for at least 48 hours, or until the unstable pain pattern resolves. The newest ACC/AHA guidelines for managing acute coronary syndromes also recommend LMWH as preferable to UH.

The SYNERGY (Superior Yield of New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial found that enoxaparin was not inferior to UH in the setting of an early invasive strategy for patients with non-ST segment elevation acute coronary syndromes. The primary efficacy endpoint in the study was death or nonfatal MI 30 days after enrollment.

Prevention of Venous Thromboembolism after Knee Arthroplasty

In patients undergoing major knee surgery, 60% to 70% develop DVT. Proximal DVT occurs in 20% of these patients. Initially, pneumatic compression cuffs and warfarin were used as prophylaxis. In a double-blind, randomized trial, Levine et al compared the use of ardeparin (Normiflo), an LMWH, and compression stockings with stockings alone for the prevention of thromboembolism postoperatively. The study group received ardeparin 0.005 mL/kg subcutaneously every 12 hours. At day 14, venography was performed. Of the patients receiving LMWH, 28 of 90 (31%) were found to have DVT and 2 (2%) were proximal DVT, whereas 60 of the 104 patients with compression stockings alone (58%) developed DVT and 16 (15%) were proximal. One patient in each group developed PE. There was no difference in the rate of major bleeding between groups. LMWH was found to be safe and effective.

Leclerc et al compared the use of the LMWH enoxaparin with the placebo in patients undergoing knee replacement. The incidence of distal and proximal DVT in the placebo group was 45% and 20%. The LMWH group had only a 19% incidence of distal DVT and no proximal DVT.

In a recent randomized, double-blind trial by Leclerc, enoxaparin and warfarin were compared. Patients undergoing knee replacement were randomized to enoxaparin (30 mg subcutaneously every 12 hours) or warfarin (dose adjusted to keep the international normalized ratio [INR] between 2.0 and 3.0). The primary endpoint was the incidence of DVT as per bilateral venography. The secondary endpoint was the incidence of hemorrhage. The incidence of DVT was 36.9% for the enoxaparin group and 51.7% for the warfarin group. There was no difference in the incidence of major bleeding, 1.8% versus 2.1%, respectively, or proximal DVT.

Other studies have compared LMWH to warfarin in patients undergoing knee arthroplasty (Table 18-5). All but one of the studies showed that fixed-dose LMWH was more effective than adjusted-dose warfarin in preventing DVT postoperatively. Hull et al compared Logiparin (tinzaparin) subcutaneously every day to warfarin. The incidence of DVT was 45% versus 55%, respectively. The high incidence of DVT in the LMWH group was believed to be secondary to the daily dosing required instead of the usual twice-a-day dosing regimen. The American College
of Chest Physicians Consensus Conference reviewed 6 randomized trials that directly compared oral anticoagu-
lants with LMWH in total knee replacement and found
total DVT rates of 46.2% and 31.5%, respectively, with
some increase in bleeding.253 However, because 1 high-
quality study found a 3-month cumulative incidence of
only 0.8%,310 it was concluded that adjusted-dose warfa-
rin was also effective after total-knee replacement.

Acute Proximal Deep-Vein Thrombosis

Acute proximal DVT is associated with the risk of PE and
recurrent thromboembolism. Management of this condi-
tion has traditionally required a hospitalization of 5 to 7
days for treatment with UH and initiation of oral anti-
cogulation with warfarin. Recent studies compared the use
of LMWH to UH in hospital for the treatment of proximi-
al DVT. Hull et al randomized 418 patients to receive
either UH or LMWH (Logiparin, now called tinzaparin,
175 U/kg subcutaneously once daily) and demonstrated
a significantly lower recurrence and bleeding rate with
LMWH, as well as a decreased mortality rate.311 Subse-
quent studies took this type of treatment to the outpatient
setting. Levine et al132 randomized 253 patients to receive
UH intravenously and 247 patients to receive LMWH
(enoxaparin 1 mg/kg subcutaneous twice a day) for the
management of acute proximal DVT. There was, however,
no statistically significant difference in recurrent throm-
boembolism or major bleeding between the two groups.
There was a major difference in the average length of hos-
pitalization, 1.1 days for the LMWH group and 6.5 days
for the UH group. Similarly, Koopman et al133 random-
ized 198 patients to receive UH intravenously and 202
patients to receive weight-dosed nadroparin-Ca (Fraxi-
parine) subcutaneously twice a day. Rates of recurrent
thromboembolism and major bleeding were low and
similar between the two groups. Again, there was a sig-
nificant reduction in the length of hospitalization for the
LMWH group.

The outpatient treatment of proximal DVT with
LMWH is safe and effective. Gould et al conducted a
meta-analysis of 11 randomized, controlled studies com-
paring LMWH to UH for the acute treatment of DVT
and confirmed the finding of Hull et al that there was a
significant decrease in mortality with LMWH and simi-

Table 18-5. Comparative Studies of Warfarin and Low-Molecular-Weight Heparin after Knee Arthroplasty

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensity</th>
<th>DVT n/n (%)</th>
<th>Proximal DVT n/n (%)</th>
<th>Wound Hematoma n/n (%)</th>
<th>Major Bleeding n/n (%)</th>
<th>Regimen</th>
<th>DVT n/n (%)</th>
<th>Proximal DVT n/n (%)</th>
<th>Wound Hematoma n/n (%)</th>
<th>Major Bleeding n/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al509</td>
<td>INR 2.0–3.0</td>
<td>152/277 (55)</td>
<td>34/277 (12)</td>
<td>19/324 (6)</td>
<td>321 (1)</td>
<td>Tinzaparin 75 U/kg/d</td>
<td>116/258 (45)</td>
<td>20/258 (8)</td>
<td>28/317 (9)</td>
<td>9/317 (3)</td>
</tr>
<tr>
<td>RD Heparin Group552</td>
<td>PTR 1.2–1.5</td>
<td>60/147 (41)</td>
<td>15/147 (10)</td>
<td>NA</td>
<td>NA</td>
<td>Ardeparin 90 U/kg/d</td>
<td>41/149 (28)</td>
<td>7/149 (5)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Heit et al304</td>
<td>INR 2.0–3.0</td>
<td>81/222 (36)</td>
<td>15/222 (7)</td>
<td>NA</td>
<td>NA</td>
<td>Ardeparin 50 U BID</td>
<td>58/230 (25)</td>
<td>14/230 (6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Leclerc308</td>
<td>INR 2.0–3.0</td>
<td>109/211 (52)</td>
<td>22/211 (10)</td>
<td>18/334 (5)</td>
<td>6/334 (2)</td>
<td>Enoxaparin 30 mg BID</td>
<td>76/206 (37)</td>
<td>24/206 (12)</td>
<td>18/336 (5)</td>
<td>7/336 (2)</td>
</tr>
</tbody>
</table>

LMWH = low molecular weight heparin; DVT = deep vein thrombosis; PTR = prothrombin time ratio; INR = international normalized ratio; NA = not available

Values are the number of patients with events/number of patients studied (%).

lar rates of recurrence and bleeding. Subtraction analysis suggests that this decrease in mortality was seen only in cancer patients with DVT, and new trials are addressing this issue.

Restenosis after Percutaneous Transluminal Coronary Angioplasty

Anticoagulants are important after PTCA because they reduce thrombus formation, which is responsible for acute closure and late restenosis. Heparin inhibits smooth-muscle cell migration and proliferation in vitro. It alters the binding of specific growth factors such as platelet-derived growth factor and epidermal growth factor. In experimental animal models, heparin has reduced neointimal hyperplasia and restenosis following vascular injury. Three clinical trials analyzing the effects of LMWH on restenosis were done. The ERA (Early Rheumatoid Arthritis) Trial, a double-blind multicenter study, examined the effects of enoxaparin 40 mg subcutaneous every day versus the placebo for 1 month post-PTCA. The angiographic and clinical restenosis rate at 6 months was similar for both groups. The restenosis rate was 52% for the LMWH group and 51% for the placebo group. The EMPAR (Enoxaparin and Maxepa for the Prevention of Angioplasty Restenosis Trial) studied the effects of LMWH and omega-3 polyunsaturated fatty acid on restenosis. The angiographic restenosis rate at 4 months was 47% for the treatment group and 46% for the placebo group. FACT (Fraxiparine Angioplastie Coronaire Transluminale), a multicenter double-blind randomized trial, compared Fraxiparine with aspirin post-PTCA. The 3-month angiographic restenosis rate was similar for both groups, 41% and 38%, respectively. There was no difference in the 6-month clinical-event rates for death, acute MI, and repeat revascularization. One study examined whether intramural enoxaparin before balloon-expandable stenting decreases the in-stent restenosis rate when compared to the use of intravenous unfractionated heparin. Late lumen loss and in-stent stenosis were lower in the enoxaparin group than in the heparin group.

In elective PCI, it was shown that a single intravenous bolus of 0.5 mg/kg of enoxaparin was associated with reduced rates of bleeding and a dose of 0.75 mg/kg yielded rates similar to those for UH with more predictable anticoagulation levels. Enoxaparin was also shown to be safe in patients with renal dysfunction.

Management of Intermittent Claudication

Several small studies have demonstrated clinical improvement using LMWH in patients with intermittent claudication and Raynaud’s phenomenon. Mannarino et al randomized 44 patients into a double-blind controlled study evaluating LMWH versus the placebo. Patients were treated for 6 months with daily subcutaneous injections of either LMWH or the placebo. After 6 months of treatment, the LMWH group had a 25% improvement in pain-free walking time (P < .05) with no adverse bleeding effects. Although patients were clinically improved, no angiographic changes were found. Calabro et al randomized 36 patients in a double-blinded study to receive either LMWH or the placebo for a period of 6 months. Patients receiving LMWH had statistically significant increases in claudication time and absolute claudication distance and in the time interval free of pain. These small studies showing clinical improvement using LMWH versus the placebo suggest that LMWH may have a role in the management of intermittent claudication (see Chapter 34, Drug Treatment of Peripheral Vascular Disease), but larger and more definitive studies are needed.

Another small study tested the hypothesis that LMWH would be more effective than aspirin and dipyridamole in maintaining graft patency in patients undergoing femoropopliteal bypass grafting. Patients were randomized to receive either a daily injection of 2500 IU LMWH or 300 mg aspirin with 100 mg dipyridamole for 3 months. Ninety-four patients were randomized to LMWH and 106 were randomized to aspirin and dipyridamole. Patients were stratified according to indication for surgery and were followed up for 1 year. Benefit was confined to those having salvage surgery. For those having surgery for claudication, there was no significant benefit. No major bleeding events occurred in either group. The authors concluded that LMWH is better than aspirin and dipyridamole in maintaining femoropopliteal-graft patency in patients with critical limb ischemia undergoing salvage surgery. This study also suffered from small numbers of patients, and LMWH has not yet gained a standard role in the management of intermittent claudication.

Thromboembolic Prophylaxis in Patients with Atrial Fibrillation

The increased risk of arterial embolism associated with chronic AF is well known. Both aspirin and oral anticoagulation with warfarin reduce the incidence of embolic events in patients with chronic nonrheumatic AF. Harenberg et al randomized 75 patients with nonrheumatic AF to receive either the LMWH CY 216 or to receive no specific treatment. Patients with a history of cerebral or peripheral embolism were included in the study. Overall mortality in the control group was 43% and 7.5% in the treatment group. The number of embolic events was reduced in the treatment group from 20% to 8.6%. The most striking difference was seen in the group of patients with a history of prior cerebral embolism. In the 15 patients from this subset who were treated with LMWH, one extracerebral nonfatal embolism occurred, while 3 of the 7 patients with prior stroke who received no treatment experienced fatal reembolism. No major bleeding complications were reported in either group. Further studies to evaluate the efficacy and safety of LMWH ver-
sus oral anticoagulation are necessary, particularly in patients with prior embolic events. There is no evidence that LMWH is superior to aspirin for the treatment of acute ischemic stroke in patients with AF. The use of LMWH as bridging therapy to warfarin with cardioversion or other procedures is attractive from an economic point of view. This approach has been carried out in small trials, but it requires further study.

Thromboprophylaxis for Hemodialysis

Standard UH is used to prevent clotting in the membrane filter during hemodialysis. As many azotemic patients have increased risk for bleeding complications, due to abnormal platelet function, an alternative to UH is being sought in LMWHs in the hope of reducing bleeding complications in hemodialysis patients. Several preliminary studies have demonstrated adequate antithrombosis with fewer hemorrhagic effects. An additional benefit of LMWH prophylaxis is a decrease in lipid blood levels. Schmitt and Schneider switched 22 patients on chronic hemodialysis from UH to the LMWH dalteparin. They found significant decreases in total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and a minor decrease in high-density lipoprotein cholesterol levels. Triglycerides increased during the first 2 months of LMWH therapy but then normalized to previous levels. Hyperlipidemia presents a high risk for developing cardiovascular disease, and LMWH may become the antithrombotic of choice in hemodialysis patients if further trials indicate its safety, efficacy, and significant lipid-lowering effects. Recent small studies have found no difference in lipid profiles over 24 weeks of LMWH or UH for hemodialysis, and small or no differences in anticoagulant efficacy, so that the increased cost of LMWH has resulted in UH still being the standard product used for both standard and venovenous hemodialysis.

Angina

Preliminary studies suggest that LMWHs may play a role in the control of stable angina, but no definitive recommendation can be made just yet. Melandri et al conducted a randomized, double-blind, placebo-controlled trial of 29 patients with stable exercise-induced angina proven angiographically CAD. Patients aged 40 to 79 years received either 6400 U of the LMWH parnaparin or the placebo subcutaneously. All patients were treated with beta-blockers and calcium-channel blockers, nitrates, and aspirin. Treadmill exercise testing was conducted at the beginning and repeated at the end of the 3-month treatment period with myocardial ischemia being defined as ST depression > 1 mm. Exercise time to ischemia (ST depression) was increased in the treatment group from 285 to 345 seconds. There was no significant increase in the placebo group. The time to the onset of symptoms was nonsignificantly increased in the treatment group, although there was a significant improvement (P = .016) in terms of the Canadian Cardiovascular Society classification for angina reflecting subjective improvement in symptoms.

Dosages

The dosing regimens for enoxaparin are as follows: for DVT prophylaxis, 40 mg subcutaneously (SC) once daily for up to 12 days; for DVT prophylaxis in knee replacement surgery, 30 mg SC every 12 hours for up to 14 days; for DVT prophylaxis in hip replacement surgery, 30 mg SC every 12 hours or 40 mg SC once daily for up to 14 days; for DVT prophylaxis in medical patients, 40 mg SC once daily for up to 14 days; for in-patient treatment of acute DVT with and without PE, 1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily (with warfarin) up to 17 days; for out-patient treatment of acute DVT without PE, 1 mg SC every 12 hours (with warfarin) up to 17 days; for unstable angina and non-Q wave MI, 1 mg/kg SC every 12 hours (with aspirin) for 2-8 days; for acute STEMI in patients < 75 years, 30 mg single intravenous bolus plus 1 mg/kg SC dose followed by a 1 mg/kg SC dose every 12 hours for at least 8 days (with aspirin); for an acute STEMI in patients older than 75 years, 0.75 mg/kg SC every 12 hours (no bolus) at least 8 days (with aspirin). For elective PCI, an intravenous dose of 0.5 mg was found to be safe.

The dosing regimens with dalteparin are as follows: for prophylaxis of ischemic complications in unstable angina, 120 IU/kg of body weight but not more than 10,000 IU SC every 12 hours with concurrent aspirin for 5 to 8 days; for prophylaxis of DVT undergoing hip replacement, 5000 IU 10-14 hours before surgery, 2500 IU within 2 hours before surgery, 2500 IU 4 to 8 hours after surgery, and 5000 IU daily in the postoperative period for 5 to 10 days; for prophylaxis of DVT following abdominal surgery, 2500 IU SC once daily starting 1 to 2 hours prior to surgery and repeated once daily postoperatively for 5 to 10 days; in higher risk patients, 5000 IU SC the evening before surgery, then once daily postoperatively for 5 to 10 days; in medical patients with severely restricted mobility during an acute illness, 5000 IU SC once daily for 12 to 14 days. Patients who have DVTs and cancer can also benefit from receiving treatment with long-term (up to 6 months) dalteparin.

Adverse Effects

LMWH has been associated with less major bleeding than UH in patients with an acute DVT. Patients receiving LMWH can develop HIT. Non-dialysis patients with a creatinine clearance < 30 mg/min may need to have
adjustments made in their LMWH dose, although recent data show relative safety with enoxaparin.320

Cost-Effectiveness
Cost minimization analyses have addressed the issue of the higher cost of LMWH versus UH.334,335 These analyses show that the higher medication cost of LMWH was outweighed by the reduction in cost attributable to a reduced incidence of DVT, PE, and major and minor bleeding associated with LMWH, both for general and orthopedic surgical patients undergoing perioperative heparin thromboembolic prophylaxis.334,336 The cost of LMWH may be less of an issue now that a generic form of enoxaparin is available.

Danaparoid
The heparin analogue danaparoid sodium is a mixture of sulfated glycosaminoglycans of porcine origin. Danaparoid consists of heparan sulfate (≈ 84%), dermatan sulfate (≈ 12%), and a small amount of chondroitin sulfate (≈ 4%).337 The drug is FDA-approved for prophylaxis of postoperative DVT in patients undergoing elective hip replacement surgery. In contrast to LMWHs, which have an 80% to 90% incidence of cross-reactivity in HIT, danaparoid has a cross-reactivity rate of approximately 10%. Although danaparoid is effective for total DVT prophylaxis, it does not offer a significant advantage over comparators for prophylaxis of the more clinically important proximal DVT. For this reason, its high cost prohibits routine use for this indication. It has been used as an option in patients who have documented HIT and still require anticoagulation. However, new agents (see below) have now been approved that have no cross-reactivity with the antibodies found in HIT. The drug is no longer available for clinical use in the United States.

Direct Thrombin Inhibition
The rationale for developing direct thrombin inhibitors came from the realization that: (a) the acute coronary syndromes, MI, and unstable angina are the result of plaque rupture and in situ thrombosis;338,339a and (b) thrombin plays a central role in the activation of clotting factors V and VIII, platelet activation and aggregations, cross-linking of fibrin, and stabilization of the hemostatic plug. Therefore, investigators have looked to thrombin and thrombin-inhibitors as prime targets for anticoagulant drug therapy.

Brief Review of Thrombin's Action
Thrombin is a key regulator of the hemostatic process responsible for the conversion of fibrinogen to fibrin. Thrombin is generated from prothrombin through the action of activated factors V, X, calcium, and phospholipid. Thrombin not only acts to catalyze the conversion of fibrinogen to fibrin, it also acts with factor XIII to cross-link and stabilize the clot. It amplifies the clotting cascade by activating other clotting factors, and acts as a potent agonist for platelet activity and recruitment. In terms of its interaction with the endothelial surface, it can act as a vasodilator in areas where the endothelial surface has not been damaged, but it can also be a potent vasoconstrictor when it comes into contact with injured or denuded endothelial surfaces. This action is dependent on endothelin release. In addition, it stimulates the release of platelet-derived growth factor, interleukin 1, and, therefore, may be an important mediator of smooth-muscle growth and proliferation;339,340 thus, it possibly plays an important role in subacute coronary artery closure and in postangioplasty restenosis.

Hirudin (Lepirudin and Desirudin)

Properties and Mechanism of Action
Hirudin is a 65-amino-acid polypeptide that was originally isolated from leech salivary glands and is now available as a recombinant product derived from yeast.340a

Hirudin is a specific inhibitor of thrombin that binds to both the active and substrate recognition sites of thrombin.340b The attachment of hirudin to thrombin is not limited to these two sites, and other areas of contact have been described.341a Hirudin is specific for thrombin and does not inhibit other serine proteases.341 While binding is not covalent, the process of deattachment is slow and, for most purposes, is irreversible. This is in contrast to many of the other direct thrombin inhibitors, where binding to thrombin is not as extensive. Lepirudin is one of several recombinant hirudins. It is FDA-approved for use in patients with HIT342,343 and for patients with coronary syndromes without ST elevation. Desirudin, another recombinant analog of hirudin, is approved for use in DVT prevention.343a,b

Myocardial Infarction
In TIMI 5, hirudin was associated with a significant reduction in the composite endpoint of death, reinfarction, congestive heart failure or shock.344 Hirudin use was associated with improved patency of the infarct-related artery at 18 to 36 hours. Major hemorrhage occurred in 23% of heparin-treated patients, and in 17% of hirudin-treated patients. The Hirudin for Improvement of Thrombolysis (HIT-III) trial also showed a low incidence of spontaneous hemorrhage and low incidence of reoclusion with low doses of hirudin.345 The HIT-III trial also showed that higher doses of hirudin were associated with cerebral bleeds. The TIMI 6 data confirmed the results of TIMI 5, with favorable trends in the incidence of death, reinfarction, and shock without increases in major hemorrhage.346 In the phase 3 clinical trials TIMI 9A and GUSTO 2A, an excess of cerebral hemorrhage associated with hirudin was
revealed without a clear mortality benefit. More recently, the GUSTO 2B data did not reveal an advantage of hirudin over heparin in the composite endpoint of death or reinfarction at 30 days. However, treatment with hirudin resulted in fewer adjustments of anticoagulant doses, and a significant reduction in the combined endpoint at 48 hours. In patients with unstable angina, hirudin improved the minimal luminal diameter of the culprit artery to a greater extent than does heparin, and slightly reduced the incidence of MI. Results from the Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) trial suggest that hirudin may be useful when compared with heparin in preventing cardiovascular death, MI, and refractory angina, with relative safety in patients who have unstable angina or acute MI without ST-segment elevation who are receiving aspirin. Based on OASIS-2, the drug is approved for this indication.

Percutaneous Transluminal Coronary Angioplasty

There have been a number of trials comparing heparin to hirudin and Hirulog in patients undergoing angioplasty. In a pilot trial involving 113 patients, coronary flow 24 hours postprocedure was 100% for hirudin and 91% for heparin. The endpoint of ischemia on 24-hour Holter monitor; MI; and the composite endpoint of death, MI, and CABG were reduced in the hirudin group. The Hirudin in a European Trial vs Heparin in the Prevention of Restenosis after PTCA (HELVETICA) involved more than 1,000 patients and compared angiographic evidence of restenosis at 6 months postangioplasty. This trial revealed no significant differences in restenosis. However, the incidence of death, MI, and repeat intervention within the first 24 hours was less with hirudin. The rates of major bleeds were similar. Hirulog was shown to reduce bleeding complications after angioplasty but was ineffective in reducing important clinical events.

Monitoring Therapy and Dose

There are a number of issues that should be considered in the dosing and monitoring of hirudin activity. Hirudin levels can be monitored using both the aPTT and the thrombin time. The thrombin time is the most accurate indicator of hirudin activity. However, the assay system may be too cumbersome for routine clinical use. The aPTT system is the most widely used system despite the fact that the aPTT values may not be completely reliable. A number of studies have found that the aPTT is insensitive at both high and low doses of hirudin. In addition, the dose range of heparin that has been effective in the treatment of cardiovascular disease was determined empirically, which may not be true for hirudin. Antithrombotic doses of hirudin that appear to be equipotent with heparin prolong the aPTT to a lesser degree in animal and human models. However, clinical studies in man have demonstrated efficacy for hirudin, as well as Hirulog. Weight-adjusted dosing with a target aPTT of 65 to 90 seconds was effective and safe in the TIMI 6 trial. In TIMI 9A, a hirudin dose of 0.6 mg/kg bolus with an infusion rate of 0.2 mg/kg/h was excessive. GUSTO 2B evaluated a dose of hirudin at 0.1 mg/kg bolus and infusion of 0.1 mg/kg/min and found that it was safe and effective but not superior to heparin. The dosage regimen approved for clinical use in the United States for patients with HIT and associated thromboembolic disease is 0.4 mg/kg as a bolus dose followed by a 0.15 mg/kg/h infusion for 72 hours to maintain the aPTT between 60 and 100 seconds, although many clinicians find this to be too high a starting dose. Also, hirudin induces antibodies that prolong its half-life.

Adverse Effects

The major reported complication with hirudin has been bleeding. Initial trials have demonstrated efficacy and safety of use as compared with heparin. Unlike heparin, however, hirudin does not have a commercially available antagonist. If significant bleeding occurs, the clinician should be familiar with the therapies available to neutralize the effects of hirudin. Some studies have suggested that activated prothrombin complex concentrates may be useful. The mechanism of this reversal has not been elucidated; presumably, the production of thrombin generated by the activated complexes overcomes the effects of hirudin. Recombinant factor VIIa also restores platelet function and can reverse the bleeding caused by hirudin. Lastly, either monoclonal antibodies or plasma infusions have been used to neutralize the effects of hirudin. In addition, physical methods of removing hirudin from the circulation are available; these include hemofiltration and hemodialysis. Hirudin is cleared by the kidneys and should not be used in patients with renal dysfunction.

Bivalirudin (Hirulog)

Bivalirudin has been used as an adjunct to thrombolytic therapy, with initial results indicating favorable trends in terms of vessel patency, clinical events, and bleeding complications. The drug is FDA-approved for use as an anticoagulant in patients with unstable angina undergoing PTCA, on the basis of trials showing that it is as effective as heparin, while causing less bleeding. The recommended dose of bivalirudin is 1 mg/kg as an IV bolus followed by a 4-hour infusion at a rate of 2.5 mg/kg/hour. After the completion of the initial 4-hour infusion, an additional infusion may be initiated at a rate of 0.2 mg/kg/hours for up to 20 hours.

Properties and Mechanisms of Action

Hirulog binds at the active and substrate recognition sites of thrombin and does not exhibit multiple areas of
contact. In addition, there is evidence that the drug is degraded at the active site, making it a less potent thrombin inhibitor.361

Unstable Coronary Syndromes and Acute Myocardial Infarction
In patients undergoing PTCA for unstable or postinfarction angina, bivalirudin with provisional GP IIb/IIIa blockade was as effective as heparin but was associated with lower rates of moderate bleeding, including in those patients with renal dysfunction.365-367 Among moderate to high risk patients with unstable coronary syndromes undergoing PCI, coronary reserve was found to be greater with bivalirudin than the GP IIb/IIIa blocker eptifibatide.368 In the Acute Catherization and Urgent Intervention Triage Strategy (ACUITY) trial in patients with moderate or high-risk acute coronary syndromes who were undergoing invasive treatment with GP IIb/IIIa inhibitors, bivalirudin was associated with rates of ischemia and bleeding that were similar to those of heparin. With the use of bivalirudin alone, the rates of ischemia were similar and there were significantly lower rates of bleeding.369,370 In patients with stable and unstable angina who underwent PCI after treatment with clopidogrel, bivalirudin did not provide a net clinical benefit but was associated with a reduced incidence of major bleeding.371 Bivalirudin has also been shown to be effective when used alone compared with heparin plus GP IIb/IIIa inhibitors in patients with acute ST-segment elevation MI undergoing PCI.372-374 Bivalirudin alone was associated with less bleeding. Bivalirudin has also been used as alternative anticoagulation during cardiopulmonary bypass in patients with HIT.375

Monitoring Therapy and Dose
The current recommended dose of bivalirudin in the setting of PCI in patients with and without HIT is an intravenous dose of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/hour for the duration of the PCI procedure. Five minutes after the bolus dose has been given, an ACT should be performed and an additional 0.3 mg/kg should be given if necessary. Continuation of the infusion can be done for 4 hours postprocedure. After 4 hours, an additional intravenous infusion of the drug may be initiated at a rate of 0.2 mg/kg for up to 20 hours.

Argatroban
Properties and Mechanisms of Action
Argatroban is a potent intravenous direct thrombin inhibitor that binds to the catalytic site of thrombin.376 With a relatively short intravenous half-life, it binds rapidly and reversibly to both clot-bound and soluble thrombin. The drug is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT376-378 and for patients at risk for HIT undergoing PCI.379 The safety and effectiveness of argatroban for cardiac indications outside of PCI in patients with HIT have not been established, which limits its clinical use compared to other direct thrombin inhibitors.

Monitoring Therapy and Dose
Before administration of argatroban, heparin should be discontinued and baseline measurement of the aPTT should be made. The recommended initial dose of argatroban in patients without hepatic impairment is 2 µg/kg/min as a continuous infusion. The drug should be adjusted to maintain an aPTT at 1.5 to 3 times the baseline value for a mean of 5 to 7 days.379

Ximelagatran
Ximelagatran is an orally active direct thrombin inhibitor that had initially shown a great deal of promise with its rapid onset of action, favorable pharmacokinetic profile and, unlike warfarin, a lack of drug–drug and drug–food interactions.380 In various phase 3 clinical trials, the drug was shown to be more efficacious than warfarin and enoxaparin in preventing VTE after knee or hip replacement surgery381,382 and as effective as warfarin in providing stroke prevention in patients with NVAF.380 The drug had been approved for use in Europe for the prevention of VTE in orthopedic patients; however, it was withdrawn from the world market because of hepatotoxicity.

Factor Xa Inhibition
Fondaparinux
Properties and Mechanism of Action
The direct thrombin inhibitors do not affect thrombin generation and may not inhibit all available thrombin. The inhibition of factor Xa can prevent thrombin from being generated and disrupts the thrombin feedback loop, which amplifies additional thrombin production. A novel approach to factor Xa inhibition has been taken by synthesizing the critical pentasaccharide of heparin that is the binding site of heparin to ATIII. The drug is currently approved as an SC injection for the prophylaxis of DVT, which may lead to PE in patients undergoing hip fracture therapy, hip replacement therapy, and knee replacement therapy and in patients undergoing abdominal surgery who are at risk for thromboembolic complications. The drug is also approved for the treatment of acute DVT when administered in conjunction with warfarin and for the treatment of acute PE when administered in conjunction with warfarin when initial therapy is administered in the hospital. Although not an FDA-approved indication, the drug is recommended as an alternative to UH, enoxaparin, and bivalirudin as an initial anticoagulation approach with antiplatelet drugs for unstable coronary syndromes.

Clinical Trials
In patients undergoing orthopedic surgery, 2.5 mg of fondaparinux SC once daily starting 6 hours
postoperatively showed a major benefit over enoxaparin without increasing the risk of bleeding. Once-daily SC fondaparinux was shown to be at least as effective and safe as twice-daily enoxaparin in the initial treatment of symptomatic DVT.

Recently it was shown that fondaparinux at a dose of 2.5 mg once daily SC for 45 days was effective for the treatment of patients with acute symptomatic superficial vein thrombosis of the legs.

Once-daily SC fondaparinux without monitoring was shown to be at least as effective and as safe as adjusted-dose UH in the initial treatment of stable patients with acute PE.

In patients undergoing PCI, fondaparinux in doses of 2.5 and 5 mg was comparable to UH in clinical safety and efficacy outcomes and when combined.

In patients with acute coronary syndromes, fondaparinux was found to be comparable to enoxaparin in reducing the risk of ischemic events at 9 days with a reduced incidence of major bleeding.

In patients with STEMI, fondaparinux significantly reduced mortality and reinfarction without increasing bleeding and strokes compared with the placebo or UH at 30 days. In patients undergoing PCI in the same trial, fondaparinux was inferior to heparin in preventing clots from forming in catheters. The use of supplemental UH at the time of catheterization seemed to reduce the risk of this complication.

The 2007 ACC/AHA guidelines recommend fondaparinux as a treatment for patients with unstable angina and non-STEMI who are to be managed conservatively or with an early invasive strategy, unless CABG is planned.

Idraparinux

Idraparinux is a long-acting pentasaccharide that is administered SC once weekly. It is now being studied in clinical trials versus standard therapy for treatment of pulmonary embolism and with warfarin for stroke prevention in AF.

In patients with DVT, once weekly idraparinux for 3-6 months had similar efficacy to that of standard treatment (heparin plus vitamin K antagonist). The primary efficacy outcome was the 3-month incidence of symptomatic recurrent VTE. In patients with PE, idraparinux was less efficacious than standard therapy.

Idraparinux linked to biotin is being studied. It has the advantage of having an antidote, since avidin binds to the biotin and removes the anticoagulant molecular from the circulation.

Oral Anticoagulants

Warfarin

Mechanism of Action

Warfarin is a vitamin K antagonist that blocks the cyclic interconversion of vitamin K(2) and its 2,3 epoxide by inhibiting two regulatory enzymes, vitamin K epoxide reductase and vitamin K reductase. Vitamin K(2) is an essential cofactor for the carboxylation of glutamate residues on N-terminal portions of inactive coagulant proenzymes (factors II, VII, IX, X) in a reaction that is catalyzed by a vitamin K-dependent carboxylase. Because γ-carboxylation of vitamin K-dependent coagulation enzymes is a requisite step in the ability of the enzymes to bind metals, undergo conformational changes, bind to cofactors, and become activated, warfarin impedes the activity of these essential reactions in the coagulation pathway.

Pharmacokinetics

Warfarin, a racemic mixture of R and S isoforms, undergoes rapid and extensive gastrointestinal absorption, reaching maximal plasma concentrations in 90 minutes. In the blood, it has a half-life of 36 to 42 hours.
and is extensively bound to plasma proteins, principally albumin. Only 1% to 3% of warfarin circulates in the free state, but it rapidly accumulates in the liver where it is metabolized microsomally to inactive catabolites; the R isomers are metabolized to warfarin alcohols and excreted in the urine; and the S isomers are oxidized and eliminated via the bile. Numerous drugs and disease entities that alter warfarin absorption, plasma protein binding, liver microsomal activity, or basal vitamin K levels can increase or decrease warfarin anticoagulant sensitivity.400 (see Chapter 29, Drug-Eluting Stents). Because many of these agents may be prescribed concurrently with warfarin, adjustment in the daily anticoagulant dose will be necessary to avoid inadequate or excessive anticoagulation. A dietary inventory, including all drug and vitamin supplementation, is equally important because massive amounts of dietary vitamin K can increase warfarin resistance; dietary vitamin K deficiency, malabsorption problems, liquid paraffin laxatives, and hypocholesterolemic bile-binding resins can reduce warfarin absorption or increase warfarin excretion; and large doses of vitamin E used as an antioxidant can antagonize vitamin K action.396 Moreover, variations in dose response to warfarin can occur during extended periods of anticoagulation (variations that may have one or several patient, medication, or laboratory causes).396,398

New data on genetic polymorphism of vitamin K epoxide reductase and cytochromes have led to new recommendations about warfarin dosing.394

Laboratory Monitoring of Warfarin

Historically, the most commonly used test to monitor warfarin anticoagulation has been the prothrombin time. This test is sensitive to reduced activity of factors II, VII, and X but not to reduced activity of factor IX.399 Interpretation of the prothrombin time results, while satisfactory for individual patient measurement, has been complicated, however, because thromboplastin reagents in standard usage vary in their sensitivity to the reduction of vitamin K-dependent clotting factors.399,400 Hence, the prothrombin-time result can reflect very different degrees of anticoagulation when different thromboplastins are used as reagents.

Efforts to resolve the problem of variability in thromboplastin sensitivity led to the adoption of the INR system, based upon a World Health Organization International Reference Thromboplastin Reagent. The INR is the prothrombin time ratio obtained by testing a given anticoagulated patient plasma sample using the WHO Reference Thromboplastin. The INR for any prothrombin time ratio measured with any thromboplastin reagent can be calculated if the International Sensitivity Index (ISI) of the reagent is known, where INR = patient prothrombin time in sec/control prothrombin time in sec18-21,400 Figure 18-9 shows the relationship between prothrombin time ratio and INR for thromboplastins reagents of differing ISI. The INR value is the preferred method for expressing the degree of anticoagulation with warfarin, for comparing various results of clinical trials using warfarin, and for setting standard ranges of anticoagulation for specific clinical entities.401

Certain caveats regarding the use of an INR measurement system should be kept in mind, however:402 (1) During induction of warfarin anticoagulation, the prothrombin time may more accurately define warfarin effect because the INR standard is based on ISI values derived from patients anticoagulated for at least 6 weeks, when factors II, VII, and X are all decreased in activity. During the initial 2 to 3 days of warfarin therapy, the prothrombin time increase is mainly attributable to decreased functional factor VII and, to a lesser extent, factor X. (2) The naturally-occurring anticoagulant protein C is also decreased by warfarin anticoagulation. During the early stages of warfarin anticoagulation, protein C falls rapidly just as factor VII does. Thus, there is a period when the full impact of anticoagulation is not manifest but a natural protective mechanism has been diminished. This is particularly important when considering switching from argatroban or lepirudin to warfarin anticoagulation in the treatment of HIT.403 In such situations, warfarin anticoagulation should be delayed and proceed slowly. (3) Individual thromboplastin reagents vary in their sensitivity to differing proportionate reductions in the activity of the 3 of 4 vitamin K-dependent procoagulant factors impeded by warfarin. (4) The calculated INR value is less accurate when the prothrombin time is measured with insensitive thromboplastin having high ISI values.404 Despite these limitations, expert panels continue to recommend the INR as a grading system for warfarin dosing during both induction and maintenance anticoagulation, especially when sensitive thromboplastin (INR ≤ 1.5) reagents are used, careful calibration of laboratory automated clot detectors are employed, and mean normal prothrombin time is calculated according to recommended guidelines.402,405

Warfarin Dosing: Initiation of Treatment

Upon inception of warfarin, a measurable anticoagulation effect is delayed until circulating factors II, VII, and X are cleared and replaced by dysfunctional vitamin K-dependent factors with fewer carboxylglutamate residues.405 An initial anticoagulant effect will occur within 24 hours as factor VII (half-time 6 to 7 hours) is cleared. Peak anticoagulation action of warfarin is delayed for 72 to 96 hours because of the longer half-time of factors II (50 hours), IX (24 hours), and X (36 hours).293 Warfarin suppression of the anticoagulant activity of proteins C (half-time 8 hours) and S (30 hours) may also contribute to the initial delay in anticoagulant effect.396
Selection of an initial warfarin dose will depend upon an appraisal of the age and nutritional status of the patient and concomitant medical conditions and drugs that could alter warfarin impact on anticoagulation. Expedient but safe anticoagulation is also an economic concern for hospitalized patients with decreased inpatient length of stay. For rapid effect, a dose of 10 mg warfarin can be given on day 1. If the INR is < 1.5 on day 2, an additional 10 mg can be given. If the INR is >1.5 on day 2, then a smaller warfarin dose may be given (5.0 to 7.5 mg). By day 3, an INR of < 1.5 suggests a higher-than-average maintenance dose (≥ 5 mg); an INR of 1.5 to 2.0 suggests an average maintenance dose (4 to 6 mg); and an INR of ≥ 2.0 suggests a lower-than-average maintenance dose is needed. When urgent anticoagulation is required, intravenous heparin and direct thrombin inhibitors should be utilized concurrently for 3 to 4 days.

When less-urgent outpatient anticoagulation is desired, warfarin can be initiated at 5 mg/d. In many patients, an INR of 2.0 can be attained in about 4 to 5 days. Daily maintenance doses will depend upon the clinical condition being treated and the targeted INR range.

**Warfarin Dosing: Maintenance Therapy**

Chronic warfarin therapy is used in the prevention of venous and arterial thromboembolism. Specific clinical indications, generally recommended, INR ranges, and duration of therapy are outlined in Figure 18-10 and are summarized in greater detail in a consensus report on antithrombotic therapy and a detailed report of anticoagulation in patients with artificial cardiac valves. The use of specialized anticoagulation clinics can enhance the quality of care receiving warfarin treatment by assuring that the INR remains within the desired range. Thromboembolic strokes arising from inadequate anticoagulation and serious bleeding adverse events stemming from excessive anticoagulation are thereby kept to a minimum.

Persistent questions regarding the optimal benefit-risk ratio of specific or combined drug therapy with warfarin and aspirin in the treatment of arterial thromboembolism have been recently addressed. Three hundred and seventy cardiac surgical patients receiving a mechanical or tissue valve replacement were randomized to 100-mg delayed-release enteric aspirin or the placebo, in addition to warfarin adjusted to an INR of 3.0 to 4.5. Combined aspirin-warfarin therapy reduced total and cardiovascular mortality and major systemic and cerebral emboli, with an additional overall risk reduction of 61% (9.9% per year for the placebo-warfarin, 3.9% per year for aspirin-warfarin), albeit with increased minor bleeding events. The average INR values in these patients was 3.0 to 3.1, and the average warfarin dose was 5.5 to 5.8 mg/d. Low-dose aspirin and low-dose warfarin studies have been carried out to test the efficacy and safety of such combinations with no apparent benefit seen. Clinical experience with well-controlled adequate warfarin anticoagulation continues to be the mainstay of treatment for prosthetic valve patients and for patients with rheumatic mitral valve disease who have either a history of systemic embolism or who have paroxysmal or chronic AF. Warfarin is also recommended as a prophylaxis in patients with nonrheumatic AF. Consensus recommendations have stratified such patients according to the presence of risk factors for embolization, including left ventricular systolic dysfunction, history of prior embolism, hypertension, or age older than 75 years. Warfarin is recommended for patients with any of these high-risk factors, while aspirin or warfarin is recommended for lower-risk patients.

Further studies using a case-control methodology indicate that among patients with nonrheumatic AF, warfarin anticoagulation prophylaxis is highly effective against ischemic stroke at an INR of ≥ 2.0. Adjusted odds ratio for ischemic stroke rose to 1.5 at INR 1.8 and more precipitously at lower INRs. Secondary stroke prevention in nonvalvular AF patients was also found to be effective at INR of ≥ 2.0, while hemorrhagic risk increased at INRs above 4.5. In older patients, low-intensity warfarin (INR 1.5 to 2.1) appears to be safer than conventional-intensity treatment. While higher INRs are required for mechanical heart valves, adverse bleeding events also increase at INR levels of ≥ 4.5.

**Clinical Recommendation for Myocardial Infarction**

Data from the prethrombolytic era demonstrates significant reductions in PE, stroke, and, in 1 case, reductions in mortality associated with anticoagulant use after MI. A meta-analysis of several trials from this era reveals reductions in the combined endpoint of mortality and nonfatal
reinfarction. The ASPECT trial demonstrated a 50% reduction in reinfarction, and a 40% reduction in stroke associated with the use of warfarin after MI. A number of studies from the thrombolytic era support the use of warfarin after MI, particularly in the prevention of embolic events in those patients who are at high risk (anterior wall MI, AF, significant left ventricular dysfunction). The Warfarin Aspirin Reinfarction Study (CARS) examined the effect of low-dose warfarin in combination with aspirin in the long-term treatment of the postinfarction patient. Warfarin doses of up to 3 mg/d in combination with aspirin 80 mg/d did not improve mortality when compared to aspirin 160 mg/d. In fact, the combination group showed a stroke rate that was higher than that observed in the aspirin group alone. At this juncture, we would recommend the use of oral anticoagulants in those patients who have suffered an anterior MI, have significant left ventricular dysfunction, AF, or history of a thromboembolic event.

Unstable Angina

The Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial showed that the long-term combination of aspirin plus warfarin was superior to aspirin alone in preventing ischemic events.

Prosthetic Valves

There are clear indications for anticoagulation after the placement of prosthetic heart valves. For those patients with bioprosthetic heart valves in the aortic position, we do not recommend routine anticoagulation. However, evidence exists for a high rate of embolic events in the first 3 months, and some recommend anticoagulants for the first 3 months postoperatively. For those patients with bioprosthetic valves in the mitral position, the rate of embolic events range from 0.4% to 1.9% per year in those patients without AF, without prior history of emboli, and without enlarged atria. However, given a thromboembolic rate of up to 80% within the first 3 months of replacement, all patients should be anticoagulated for the first 3 months after mitral valve replacement. However, it remains unclear whether these patients should be anticoagulated long-term. If AF has become evident, left atrial thrombus is present, or there is a history of embolic events, then these patients should probably be anticoagulated.

Those patients with mechanical heart valves should be anticoagulated regardless of location. Those patients with a prosthetic valve in the mitral position are more likely to have a thromboembolic event as compared to those patients with a prosthetic valve in the aortic position. Other risk factors for high rates of thromboembolic events include patients with prior thromboembolic events, AF, enlarged left atria, ball-and-cage type valves, and dual-valve replacement. Given that there are data for the different types of valves, each with its own optimal regimen, our recommendations are bound to be oversimplified. For those patients without a prior embolic event, we recommend a prothrombin time ratio of 2.5 to 3.5, with a slightly higher INR for those patients with a ball-and-cage valve. For those patients with a prior embolic event, aspirin at an initial dose of 80 mg or dipyridamole at a dose of 400 mg/d should be added. Although the risk of bleeding will be greater, if significant bleeding occurs in patients with prosthetic valves, anticoagulation can be stopped for up to 2 weeks with a low risk of thromboembolism.

Atrial Fibrillation

There have been several randomized, placebo-controlled trials of anticoagulant therapy in AF. The current recommendations for anticoagulant therapy can be divided into several major groups. Those patients with valvular disease and AF should be anticoagulated. Those patients < 75 years with NVAF without structural heart disease or risk factors for heart disease, can be managed without anticoagulant therapy, and, in many cases, without aspirin. Those patients who are older than 75 years should be anticoagulated. However, the decision to treat should be balanced with the risk of an age-related increase in bleeds. For those patients who are between the ages of 65 and 75, the presence of risk factors plays a major role in the decision to anticoagulate. Those patients with either a prior thromboembolic event, hypertension, diabetes mellitus, existing CAD, or reduced left ventricular function are at increased risk of a thrombotic event. Those patients with none of these risk factors are at a risk of thromboembolic events of 2% to 4% per year, and the benefit of therapy with oral anticoagulants as compared to aspirin is much reduced. In the Stroke Prevention in Atrial Fibrillation Trial II, there was no significant difference between aspirin therapy and warfarin therapy for some patients. However, it was recently shown that warfarin is more effective than the combination of aspirin plus clopidogrel. Lastly, patients with AF-complicating thyrotoxicosis are at increased risk of thromboembolism and should be anticoagulated.

Angioplasty and Thrombolysis

In a clinical trial of warfarin started before PCI and continued for 1 year, there was also a reduction in early and long-term ischemic events.

Adverse Effects

The main complication associated with warfarin therapy is bleeding. The risk of bleeding is directly related to the intensity of therapy, with higher anticoagulant levels being associated with the greatest risk of hemorrhage. The risk of bleeding is also reported to be associated with...
Advancing age, prior history of GI bleeding, prior stroke, and concomitant use of aspirin and other NSAIDs.\textsuperscript{396,413} If bleeding does occur, anticoagulation can be stopped. In addition, vitamin K in oral parenteral formulations can be used as an antidote. The effectiveness of this treatment has never been shown.\textsuperscript{440}

Other adverse events with warfarin have been described, the most important of which is warfarin-induced skin necrosis.\textsuperscript{441} The mechanism is still unclear; however, an association with both protein C and protein S deficiencies have been described.\textsuperscript{443} In addition, a similarity between these lesions and those seen in neonatal purpura fulminans (complicating homozygous protein C deficiency) has been noted. The lesion is caused by thrombosis of venules and capillaries in subcutaneous fatty tissue. In this group of patients, anticoagulation with warfarin must be overlapped with heparin, and warfarin therapy is begun at very low doses (0.03 mg/kg).\textsuperscript{441} Long-term warfarin therapy has also been shown to increase the risk of osteoporotic fractures in the elderly;\textsuperscript{462} and to increase the risk of cardiac valve calcification.\textsuperscript{443} Lastly, warfarin therapy should be avoided in pregnancy. Specifically, it is associated with birth defects, central nervous system abnormalities, and fetal bleeding.\textsuperscript{444} The FDA modified the warfarin prescribing label to suggest that, but did not mandate warfarin pharmacogenetic testing. However, current data do not suggest this approach in routine clinical practice.\textsuperscript{445,446}

**Antiplatelet Drugs in Development**

This section reviews specific inhibitors of TXA\textsubscript{2} synthesis and/or action and the other antiplatelet strategies (Table 18-6 and Figure 18-3).

**Inhibitors of Thromboxane \( \text{A}_2 \) Synthesis and Action**

In platelets, cell-membrane phospholipids serve as the precursor to arachidonic acid formation through the action of PLA\textsubscript{2}. Although the actual phospholipids that serve as the arachidonic acid precursor have never been properly established, arachidonic acid is stereospecifically numbered at the 2 position. Therefore, it is accepted that arachidonic acid is derived from the \( S \_2 \) position of intracellular phospholipids. The enzyme \( \text{COX} \) oxygenates arachidonic acid to prostaglandin \( \text{G}_2 \) (PGG\textsubscript{2}), which is rapidly converted to prostaglandin \( \text{H}_2 \) (PGH\textsubscript{2}) by the peroxidase activity of \( \text{COX} \). From here, PGH\textsubscript{2} undergoes cell-specific isomerization and or reduction to create the major biologically active prostanoids PGD\textsubscript{2}, PGE\textsubscript{2}, PGF\textsubscript{2}, prostacyclin (PGI\textsubscript{2}), or TXA\textsubscript{2}. TXA\textsubscript{2} is the predominant COX product formed from arachidonic acid in human platelets. TXA\textsubscript{2} is neither stored in platelets, nor is it formed in the absence of activation.\textsuperscript{447}

Arachidonic acid metabolism also takes place in the vessel wall, where the major product is PGI\textsubscript{2}. PGI\textsubscript{2}'s actions include that of a platelet inhibitor and vasodilator. Arachidonic acid metabolism is identical in the vessel wall to its metabolism in platelets except for the last step, which in endothelium leads to PGI\textsubscript{2} (by PGI\textsubscript{2} synthase) formation, and in platelets leads to TXA\textsubscript{2} formation (by TX synthase).

TXA\textsubscript{2} mediates its actions by binding to specific receptors located on platelet membranes. At one time it was thought that all of the biological activities of the arachidonic acid cascade were attributable to TXA\textsubscript{2} and that PGH\textsubscript{2} was confined to the role of a simple metabolic precursor. However, it has become clear that PGH\textsubscript{2} can exert the same effects as TXA\textsubscript{2} on platelets. In fact, the affinity of PGH\textsubscript{2} for the thromboxane receptor is actually greater than is the affinity of TXA\textsubscript{2}, and it is actually a more powerful platelet aggregator. The importance of this unique quality of PGH\textsubscript{2} will become apparent later when TX synthase inhibition is discussed. While it would appear that PGH\textsubscript{2} exerts its action by binding to the TXA\textsubscript{2} receptor, a distinct receptor subtype specific to PGH\textsubscript{2} cannot be ruled out.\textsuperscript{448}

Binding of TXA\textsubscript{2} to the TXA\textsubscript{2}/PGH\textsubscript{2} receptor elicits biological responses in platelets. TXA\textsubscript{2} is both a potent platelet-aggregating substance and a vasoconstrictor. It is thought to stimulate platelet aggregation by mobilizing intracellular calcium from the dense tubular system. This release of calcium has two distinct biological phases. The first phase is that it further activates PLA\textsubscript{2}, causing enhanced activation of arachidonic acid that leads to increased production of TXA\textsubscript{2}. The second phase is that it activates the myosin light chain leading to platelet contraction. This leads to secretion of ADP and serotonin; two strong platelet aggregators. It is also thought that

### Table 18-6. New Antiplatelet Treatments

| 1. | Thromboxane (TXA\textsubscript{2}) synthase inhibitors |
| 2. | Thromboxane receptor inhibitors (TXA\textsubscript{2}/PGH\textsubscript{2}) |
| 3. | Dual TXA\textsubscript{2} synthase--TXA\textsubscript{2}/PGH\textsubscript{2} receptor inhibitors |
| 4. | Platelet glycoprotein Ib integrin inhibitors |
| 5. | von Willebrand factor inhibitors |
| 6. | P2Y\textsubscript{12} antagonists |
| 7. | Prostacyclin and analogues |
| 8. | Protease-activated receptor antagonism |
| 9. | Nitroester of aspirin (NCX4016) |
| 10. | Trapidil |
| 11. | Triflusal |
TXA₂ inhibits the production of adenylate cyclase, which leads to a reduction of intracellular cyclic adenosine monophosphate (cAMP). cAMP inhibits both platelet secretion and aggregation by reducing intracellular calcium levels, and its concentration depends on the activity of both adeny1 cyclase and phosphodiesterase. Any reduction in adeny1 cyclase activity or inhibition of phosphodiesterase would lead to decreased intracellular cAMP and increased platelet activity. The latest findings in the field of PGI₂ and TXA₂ modulators under clinical evaluation have been recently reviewed.449

As discussed earlier, aspirin exerts its antiplatelet effects by acetyling, and thereby inactivating, the enzyme COX that inhibits TXA₂ production. Because platelets do not contain a nucleus and cannot generate more COX, the inhibition of TXA₂ is permanent for the life of the platelet. The antiplatelet benefit of aspirin is complicated by its capacity to block COX in the endothelium, thus preventing the production of PGI₂. Endothelial cells can regenerate COX within a few hours after being inhibited by aspirin. It has been reported that 95% inhibition of the capacity to produce TXA₂ must be achieved before a therapeutic antiplatelet effect is achieved. This, then, requires an aspirin dose above that necessary to preserve PGI₂ production. The optimal drug is one that inhibits platelet TXA₂ while preserving PGI₂ production in the vascular endothelium. An even better approach would be to use a drug that inhibits platelet TXA₂ production and increases production of PGI₂ by directly inhibiting TXA₂ synthase, thus shunting the substrates to be acted upon by PGI₂ synthase and increasing the production of PGI₂. The following discussion will describe this pharmacologic approach taken to directly inhibit TXA₂ synthase or to directly block the actions on the TXA₂ receptor itself.

Thromboxane Synthase Inhibitors

To make inhibition of TXA₂ more specific, drugs were designed that are specific inhibitors of TX synthase, the enzyme that converts PGH₂ into TXA₂. By inhibiting production of TXA₂ without interfering with the production of PGH₂, these drugs indirectly increase the formation of endothelial cell-produced PGI₂. Adding to the anti-thrombotic effect, this production of PGI₂ precursors by activated platelets occurs at the site of vessel injury where they can exert their greatest influence.

Activated platelets release PGH₂, which is taken up by endothelial cells and converted to PGI₂ by PGI₂ synthase. It was suggested that normal patients treated with TX synthase inhibitors had as much as a threefold increase in circulating PGI₂.440 Despite this laboratory finding, early clinical studies with these drugs have been disappointing. In 1990, Fiddler and Lumley reviewed the clinical studies of TXA₂ synthase inhibitors and TXA₂ receptor blockers that had been tested over the previous 10 years. The prototype TXA₂ synthase inhibitor dazoxiben was studied in several separate trials in patients with stable angina; trials showed little or no clinical benefit.450 It should be noted, however, that TXA₂ and its metabolites do not appear to be elevated in patients with stable angina, possibly accounting for the negative findings.450 Three small studies demonstrating the effect of dazoxiben on peripheral vascular disease showed mixed results at best. These results are disappointing, especially because Reilly et al had demonstrated previously an increased production of TXA₂ in 9 patients with peripheral vascular disease.451 They also demonstrated that the administration of a TXA₂ synthase inhibitor displayed incomplete inhibition of TXA₂ synthesis and evidence for continued platelet activation in vivo. Studies using dazoxiben have been performed in a variety of clinical situations, including cardiopulmonary bypass, hemodialysis, adult respiratory distress syndrome, and Raynaud’s disease with similar disappointing results. One of the explanations given for the failure of thromboxane synthase inhibitors to provide clinical benefit is that certain endoperoxides accumulate in the presence of thromboxane synthase inhibition (such as PGH₂), which can substitute for TXA₂ and cause platelet aggregation. The affinity of PGH₂ for the platelet receptor is higher than the affinity of TXA₂, and it is even more potent than TXA₂ in inducing platelet aggregation. Because the receptor that TXA₂ acts on is also acted on by PGH₂ (with greater affinity), it has been named the TXA₂/PGH₂ receptor.

TXA₂/PGH₂ Receptor Antagonists

Whether or not TXA₂/PGH₂ receptor blockade offers any significant clinical advantage was also reviewed by Fiddler and Lumley.450 They reported on a number of TXA₂/PGH₂ receptor blockers in a variety of clinical conditions thought to be associated with increased TXA₂ production. Receptor antagonists showed no clinical benefit with exercise-induced angina. This result is consistent with a 1986 report that showed a lack of elevation of TXA₂ metabolites in these patients. In addition, the drug BM13.177 (a TXA₂/PGH₂ receptor antagonist), when administered intravenously, actually induced resting myocardial ischemia in 50% of patients studied. This was thought to be due to a coronary steal mechanism.452

In peripheral vascular disease, AH23848 (a TXA₂/PGH₂ receptor antagonist) was compared with aspirin in a double-blind, placebo-controlled trial in which platelet accumulation on mature Dacron aortobifemoral grafts was evaluated. Because TXA₂ and its metabolites are elevated in this disease state, it would seem likely that a TXA₂ receptor blocker would inhibit peripheral vascular disease. Unlike aspirin, AH23848 significantly reduced platelet deposition on the grafts.453

A novel TX receptor antagonist, S18886, has been shown to inhibit not only TXA₂, but other eicosanoids not
affected by aspirin such as isoprostanes and hydroxyeicosatetraenoic acid. Thus, this drug also shows promise in attenuating inflammatory processes by specific eicosanoids that could lead to atherosclerotic plaque rupture that other antiplatelet drugs have not yet targeted.

**Dual TXA<sub>2</sub> Inhibition and TXA<sub>2</sub>/PGH<sub>2</sub> Receptor Antagonism**

Two independent studies were done with compounds designed to have a dual effect—TXA<sub>2</sub> synthase inhibition and TXA<sub>2</sub>/PGH<sub>2</sub> receptor antagonism. The compounds were shown to both inhibit the production of TXA<sub>2</sub> and to increase the production of the antithrombogenic prostaglandin PGI<sub>2</sub>. The compounds were also shown to inhibit platelet aggregation, induced by various pro-aggregatory stimuli. Hoet et al studied a combined TXA<sub>2</sub>/PGH<sub>2</sub> receptor antagonist and TXA<sub>2</sub> synthase inhibitor (R68070), and compared it with aspirin in an in vivo setting. They found that while aspirin and R68070 both significantly inhibited TXA<sub>2</sub>-dependent reactions, R68070 was more powerful than aspirin in prolonging the bleeding time. In addition, serum PGI<sub>2</sub> was completely inhibited by aspirin, while being stimulated by R68070. These results suggested that R68070, by virtue of its ability to increase PGI<sub>2</sub> production, could be a more powerful platelet inhibitor than aspirin.

Timmermans et al compared the standard therapy of aspirin and a calcium-channel antagonist with ridogrel (a dual TXA<sub>2</sub> synthase inhibitor/receptor blocker) in 30 patients undergoing PTCA. Each patient was given ridogrel during PTCA and then followed up at 6 months. None of the patients had early reocclusion, as opposed to 5.6% of patients treated with the standard therapy who underwent PTCA during this period. Serum TXA<sub>2</sub> was almost completely suppressed, and PGF<sub>2</sub> was significantly elevated as early as 2 hours after receiving ridogrel. Subsequent studies using dual-TXA<sub>2</sub> synthase inhibitor/receptor blocker drugs for preventing postangioplasty re-stenosis have shown no apparent benefit.

Clearly, there need to be more in vivo human studies that test the effects of TXA<sub>2</sub> inhibition and its effects on thrombolysis. There is already a great abundance of information characterizing aspirin and its effects on thrombolysis. As mentioned previously, ISIS-2 convincingly demonstrated the benefit of aspirin as cojoint treatment in patients undergoing thrombolysis. If TXA<sub>2</sub> synthase inhibitors/receptor blockers are going to have a major role in this field, there must be studies comparing the effects of TXA<sub>2</sub> synthase inhibition/receptor blockade with aspirin. The Ridogrel Versus Aspirin Patency Trial (RAPT) compared the efficacy of ridogrel with that of aspirin for enhancing coronary reperfusion in approximately 900 patients with acute MI receiving thrombolytic therapy. Coronary patency as determined by angiography did not differ greatly in the two groups (70.5% versus 73.7%). However, over a long-term follow up, there was a significant (32%) decrease in the incidence of new ischemic events in the patients who took ridogrel in contrast to the patients who took aspirin. These results indicate that ridogrel is not superior to aspirin in potentiating thrombolysis and preventing rethrombosis, but it may be more effective than aspirin in preventing new ischemic events in the weeks to months after MI. Although ridogrel did not prove to be superior to aspirin in the setting of an acute MI, it is safe and well tolerated. Therefore, ridogrel could be a perfectly acceptable alternative to aspirin in patients with an acute MI who cannot tolerate aspirin because of allergy. However, for patients who have no adverse reaction to aspirin, ridogrel has no apparent benefit. A study by Tranchesi et al confirmed the findings of the RAPT study.

**Miscellaneous Uses**

There have been a number of recent reports assessing the role of TXA<sub>2</sub> synthase inhibitors/ receptor blockers in other cardiovascular diseases. Ritter et al studied the effects of ridogrel in patients with uncomplicated essential hypertension. Although excretion of TXA<sub>2</sub> metabolites was decreased and vasodilatory prostaglandin metabolites were increased, blood pressure did not differ significantly between ridogrel and the placebo treatment periods. This study confirmed the findings of an earlier study by Kudo that showed that OKY-0469, a TXA<sub>2</sub> synthase inhibitor/receptor blocker, had no effect on blood pressure but did augment the hypotensive effect of captopril.

TXA<sub>2</sub> may, by virtue of its being a potent vaso- and bronchoconstrictor as well as platelet aggregator, be an important mediator in circulatory shock. Patel et al studied the effects of SQ-29548, a potent TXA<sub>2</sub> receptor blocker, in a rat model of circulatory shock. They found that in combination with leukotriene receptor antagonism, SQ-29548 caused a significant prolongation in survival time and a prolongation of circulatory compensation.

**Glycoprotein Ib Antagonists**

Circulating platelets will adhere to the subendothelial vasculature matrix during vascular injury by the attachment of the platelet GP Ib glycoprotein to von Willebrand factor. The binding of GP Ib receptors can also make the GP IIB/IIIa receptors functional for platelet aggregation. The vascular biology of the GP Ib-IX-V complex was recently reviewed. The authors point out that the GP Ib-IX-V complex regulates shear dependent adhesion and aggregation of platelets and may provide a suitable target for therapeutic intervention.

Monoclonal antibodies against both GP Ib have anti-thrombotic actions in animal models. Clinical studies still need to be done.

Another novel approach to inhibit thrombogenesis may be by targeting adhesive proteins, such as P-selectin, and their interaction with leukocytes and tissue factor.
Antiplatelet and Other Antithrombotic Drugs

Anti-von Willebrand Factor Agents

Von Willebrand factor (vWF) has been shown to be a well-established clinical biomarker for the presence of atherosclerotic disease and a prognostic indicator of outcomes both during and after an acute event.\textsuperscript{468-470} Since it is also recognized as a mediator of these events,\textsuperscript{471} inhibiting vWF provides a unique antithrombotic approach to treat patients with acute coronary syndromes.\textsuperscript{471a}

ARC1779 is a therapeutic aptamer antagonist of the A1 domain of vWF, the ligand for receptor GP 1b on platelets. Aptamers are oligonucleotides with drug-like properties that share attributes of monoclonal antibodies.\textsuperscript{472} The agent is being developed as a novel antithrombotic agent for intravenous use in patients with acute coronary syndromes.\textsuperscript{473} Since vWF is active only in the presence of shear forces found in the arterial side circulation,\textsuperscript{474,475} an antagonist of vWF should act with special specificity, avoiding some of the hemorrhagic consequences of available antiplatelet drugs.

The pharmacokinetics, pharmacodynamics, safety, and tolerability of ARC1779 were evaluated in a randomized, placebo-controlled phase 2 study in healthy volunteers.\textsuperscript{473} ARC1779 was shown to produce dose- and concentration-dependent inhibition of vWF activity and platelet function, with a pharmacokinetic profile suitable for use in patients with acute coronary syndromes. In the study there were no deaths, serious adverse effects, or premature discontinuation of therapy; Spontaneous bleeding was not observed. A study of ARC1779 in patients with thrombotic microangiopathy has been terminated (clinicaltrials.gov).

New P2Y\textsubscript{12} Antagonists

AZD6140 (Ticagrelor)

AZD6140 is the first drug in a new class of oral antiplatelet agents known as cyclopentyl triazolopyrimidines.\textsuperscript{476-476b} AZD6140 is a reversible inhibitor of the platelet P2Y\textsubscript{12} receptor, leading to an inhibition of ADP-induced prothrombotic events. This drug has novel pharmacologic properties when compared to the thienopyridines (irreversible P2Y\textsubscript{12} receptor inhibitors), completely inhibiting ADP-induced platelet aggregation ex vivo (Figure 18-11).\textsuperscript{477} Unlike the thienopyridines, AZD6140 is orally active in its parent form, without the need for metabolic activation. Thus, this drug offers several advantages when compared to the standard irreversible inhibitors of the P2Y\textsubscript{12} receptor by providing a more rapid and complete antiplatelet effect.\textsuperscript{454,477a} Additionally, a reversible P2Y\textsubscript{12} receptor antagonist may have a clinical advantage for patients awaiting CABG where rapid recovery of platelet function is necessary, unlike the 5 day irreversible antiplatelet action seen with thienopyridines. The FDA recently turned down the drug for U.S. marketing. The drug was approved in Europe.

A randomized, double-blind study, the phase 2a Dose-finding Investigative Study to assess the Pharmacodynamic Effects of AZD6140 in Atherosclerotic Disease (DISPERSE) trial,\textsuperscript{476} was designed to assess the pharmacodynamics, pharmacokinetics, safety, and tolerability of combining AZD6140 with aspirin versus clopidogrel with aspirin in patients with known atherosclerotic disease. Patients were randomized to receive 1 of 4 dose regimens of AZD6140 (50 mg twice/day, 100 mg twice/day, 200 mg twice/day, or 400 mg once daily) or clopidogrel 75 mg daily for 28 days. Patients receiving AZD6140 achieved significantly greater inhibition of platelet aggregation.
at 200 mg twice/day or 400 mg once daily compared to clopidogrel. AZD6140 also inhibited ADP-induced platelet aggregation at 2 hours postdose after initial dosing and at steady state. In contrast, clopidogrel minimally inhibited platelet aggregation after 24 hours. The magnitude of inhibition at steady state was greater with AZD6140 than with clopidogrel, except in the 50 mg dose. However, several adverse effects were noted with AZD6140 in this study that may limit the overall clinical usage of the drug. The incidence of bleeding was increased with the 3 higher doses of AZD6140 compared with clopidogrel. In addition, the incidence of dyspnea appeared to increase with each incremental dose of AZD6140, although none of the reported episodes were considered to be serious.

The DISPERSE-2 trial was a phase 2 study designed to evaluate the clinical safety of 90 mg twice/day and 180 mg twice/day of oral AZD6140 versus 75 mg daily of clopidogrel in patients presenting with non-ST elevation acute coronary syndrome. In the doses used, AZD6140 inhibited platelet aggregation more than clopidogrel. In addition, AZD6140 further suppressed platelet aggregation in clopidogrel-treated patients. This study found similar rates of bleeding with both AZD6140 and clopidogrel. There was no significant difference in ischemic events, although the lowest rates were observed in patients receiving 180 mg twice/day of AZD6140.

In a post hoc analysis of continuous electrocardiograms, mostly asymptomatic pauses > 2.5 seconds were more common, especially in the AZD6140 180 mg twice/day group compared to clopidogrel. The results of a recently completed trial in patients with acute coronary syndromes with or without ST-segment elevation, PLATO (Platelet Inhibition and Patient Outcomes Trial) demonstrated that treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, MI, and stroke without an increase in the rate of overall bleeding. However, nonprocedure-related bleeding, dyspnea, and bradycardia were more common, especially in patients receiving 180 mg twice/day of AZD6140.

The Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) study is the first to demonstrate that ticagrelor overcomes nonresponsiveness to and high platelet reactivity during clopidogrel therapy. The antiplatelet effect of ticagrelor is essentially uniform and high in both clopidogrel responders and nonresponders.

NCX-4016 is an NO-releasing aspirin formulation that was initially designed to protect the gastric mucosa, and thus eliminate an unfavorable adverse effect of aspirin. The potential benefits of this drug include all of the major benefits of aspirin combined with NO, that include its gastroprotective, antithrombotic, antiatherogenic, and vasodilatory effects. It is well known that NO induces vasodilation through the synthesis of cGMP from guanylate cyclase in vascular smooth muscle cells, but it has also recently been shown to inhibit platelet aggregation, inflammation, apoptosis, and cellular proliferation. In contrast to aspirin, NCX-4016 has also been shown to inhibit shear stress-induced platelet activation and to inhibit the formation of superoxide and reactive oxygen species in the vascular wall. Finally, NCX-4016 has been shown to inhibit platelet activation in vitro more effectively than aspirin, to inhibit smooth muscle cell proliferation, to exert an endothelial cell protective activity and to suppress the function of several inflammatory cells involved in atherothrombosis.

A study by Fu et al compared the cardioprotective effects of NCX-4016 and aspirin in an anesthetized rat model of myocardial ischemia/reperfusion. In this study, the rats were given either aspirin or NCX-4016 orally for 7 consecutive days prior to 25 minutes of myocardial ischemia, followed by 48 hours of reperfusion. The results showed that NCX-4016–treated animals had a lower mortality rate (18.2% versus 27.3%), decreased infarct size, and improved ischemia/reperfusion-induced myocardial contractile dysfunction when compared with aspirin. The investigators demonstrated that there was no appreciable difference in systemic blood pressure and heart rate between the two groups; thus, any benefit in the NCX-4016 treated group could not be attributed to drug-induced hemodynamic alterations.

In clinical studies, there has been some evidence that NCX-4016 may be a useful adjunct for preventing restenosis after PCI, while also having significant anti-hypertensive effects. Lorusso et al evaluated the functional effects of an NO-releasing aspirin on vein grafts of diabetic and nondiabetic patients undergoing CABG. NO-releasing aspirin induced a significant and comparable vascular relaxation in all venous segments of diabetic and nondiabetic patients. This study confirmed the impairment of endothelium-dependent vasodilative property of venous grafts in diabetic patients. NO-releasing aspirin, and NCX-4016 in particular, could represent a promising therapy for diabetic patients undergoing elective CABG. Furthermore, it was shown that NCX-4016 decreased fasting hyperinsulinemia and insulin resistance in patients with normal glucose tolerance. These observations have led to further research.
Factor enhancing thrombin’s ability to cleave PAR1. PAR4, thrombin signaling in human platelets by serving as a co-

has also been suggested by the authors to play a role in inhibition of thrombin-induced platelet activation. GP Ib both PAR1 and PAR4 simultaneously led to a synergistic platelet actions of PAR1 antagonism. Thus, inhibition of concentration of thrombin but lost its effectiveness when

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us in the absence of TXA2 and ADP activation, making these activated platelets refractory to many of the antiplatelet agents currently in use.491 Thus, there has been much interest over the past decade to elucidate the receptors necessary for thrombin-induced platelet activation and for developing novel therapeutic strategies in inhibiting platelet activation. 491a Kahn et al492 demonstrated that thrombin activates platelets through proteolytic acti-

vation of two protease-activated receptors (PARs): PAR1 and PAR4. Activation of either receptor was sufficient to trigger platelet secretion or aggregation. Furthermore, PAR1 mediates platelet activation at low concentrations of thrombin, whereas PAR4 only mediates platelet activation at high concentrations of thrombin. Since the dis-

covery of specific thrombin receptors on platelets that mediate platelet activation, there has been much interest in the clinical development of thrombin receptor antagonists (PAR antagonists).

In light of these results, Wu et al491 set out to compare the effects of PAR1 antagonists, PAR4 antagonists, and both PAR1/PAR4 antagonists on thrombin-induced human platelet activation. They concluded that PAR1 antagonism inhibited platelet activation during a low concentration of thrombin but lost its effectiveness when higher concentrations of thrombin were used. Moreover, antagonism of PAR4 alone had little or no effect on platelet aggregation but did significantly enhance the anti-

platelet actions of PAR1 antagonism. Thus, inhibition of both PAR1 and PAR4 simultaneously led to a synergistic inhibition of thrombin-induced platelet activation. GP Ib has also been suggested by the authors to play a role in thrombin signaling in human platelets by serving as a co-

factor enhancing thrombin’s ability to cleave PAR1. PAR4, however, is activated independently of GP Ib. As a result, it may be necessary to block all 3 receptors in order to completely inhibit thrombin-induced platelet activation. The study also demonstrated that P-selectin expression in thrombin-stimulated platelets can be synergistically inhibited by combined PAR1/PAR4 antagonism. This would be clinically relevant as platelet P-selectin has been implicated in causing myocardial injury following the re-

perfusion of ischemic myocardium.493

Due to the potential for potent platelet inhibition with blockade of thrombin-induced platelet activation, additional animal and clinical studies are necessary. There are currently phase 2 and 3 trials underway evaluating the effects of two PAR1 antagonists, E5555 and SCH530348. In one of these trials, oral SCH530348 (vorapaxar) was found to be well tolerated and did not cause increased bleeding even when administered with aspirin and clopidogrel.494 Additionally, the TRANSCENDENCE-PCI (Thrombin Receptor Antagonist for Clinical Event Reduction Over Standard Concomitant Therapies) trial is a multicenter, randomized, double-blind, placebo controlled study to evaluate the effects of SCH530348 compared with GP IIb/IIIa inhibitors with respect to the incidence of major and minor bleeding episodes.44 These results will shed further light on the safety and efficacy of thrombin receptor blockade and its role as a novel antiplatelet drug approach.

Protease Activated Receptor Antagonists

Thrombin is a key enzyme in the blood coagulation cascade and been shown to be the most potent platelet ac-

tivator. Moreover, thrombin-induced platelet aggregation can occur in the absence of TXA2 and ADP activation, making these activated platelets refractory to many of the antiplatelet agents currently in use.491 Thus, there has been much interest over the past decade to elucidate the receptors necessary for thrombin-induced platelet activation and for developing novel therapeutic strategies in inhibiting platelet activation. 491a Kahn et al492 demonstrated that thrombin activates platelets through proteolytic acti-

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Cilostazol, a specific inhibitor of phosphodiesterase-3 (see Chapter 34, Drug Treatment of Peripheral Vascular Disease), is an effective inhibitor of agonist and shear-stress-induced platelet aggregation.495 Cilostazol has similar antiplatelet effects to ticlopidine. In combination with aspirin, it appears to be as effective as aspirin plus ticlo-

pidine after primary angioplasty and stent implantation.496 When added to aspirin and clopidogrel, cilostazol was shown to improve the long-term outcome after PCI.497 In combination with high-dose clopidogrel, it was shown to have additive benefit.498

Trapidil (triazolopyrimidine) is an antiplatelet agent that also acts as a platelet-derived growth factor agonist. It has been used with aspirin to reduce cardiovascular events in MI patients after thrombolysis or angioplasty.499

Triflusal is an antiplatelet drug that is similar and struc-
turally related to aspirin but has several notable differenc-
es in its mechanism of action. In a clinical trial following acute MI, it had comparable efficacy and fewer complica-
tions than aspirin.500
New Anticoagulation Approaches

A new generation of anticoagulants are being developed (Tables 18-7 and 18-8), some of which may be approved for clinical use.

Oral Anticoagulants

UH and warfarin were discovered over 60 years ago and for the past 40 years were the only anticoagulants available for clinical use.501,502 The LMWHs were subsequently introduced in the 1970s, and in recent years, parenteral direct thrombin inhibitors and the indirect factor Xa inhibitor, fondaparinux, were also introduced. Warfarin is the only available oral anticoagulant and its use is complicated by a slow onset of action, unpredictable pharmacokinetics that require close monitoring the drug’s effect, and multiple drug–drug interactions.

There is an urgent need to develop an oral anticoagulant that should be effective while bypassing many of the clinical barriers and inconvenience of warfarin.503 An ideal drug should have a rapid onset of action, should avoid the need for a concurrent parenteral agent with its first dose, should exhibit minimal food–drug or drug–drug interactions, and should possess predictable pharmacokinetics independent of gender, race, ethnicity, or other genetic polymorphisms. Such characteristics should allow for fixed dosing and should eliminate the need for permanent monitoring. There are several newly developed oral anticoagulants being investigated in clinical trials for various indications. These new anticoagulant drugs can be divided into groups based on the part of the anticoagulation cascade they affect and include factor IXa inhibitors, factor Xa inhibitors, and direct thrombin inhibitors and are described below (Figure 18-12).

Direct Thrombin Inhibitors

Melagatran is a potent thrombin inhibitor. Although melagatran has complete SC bioavailability and low interindividual variability with parenteral administration, its oral bioavailability is low. To improve the oral bioavailability of melagatran, it was converted into an orally absorbable prodrug, ximelagatran. In phase 3 clinical trials, the drug, in a fixed dose without monitoring, was shown to be as effective as the combination of warfarin and enoxaparin for the treatment of venous thromboembolism of DVT504 and for reducing the risk of stroke when compared to warfarin in patients with NVAF.505,506 In patients who had survived an MI, the combination of ximelagatran and aspirin was more effective than aspirin alone in preventing recurrent cardiovascular events.507 Although it was with-
Antiplatelet and Other Antithrombotic Drugs

The results of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial were recently reported on.512,512a In this noninferiority trial, 18,113 patients who had AF and were at risk for stroke were randomized in a blinded fashion to receive fixed doses of oral dabigatran (110 or 150 mg twice daily) or in an unblinded fashion to receive adjusted dose warfarin. The median duration of patient follow up was 2.0 years. The primary endpoints were stroke or a systemic embolism.

The rates of the primary outcome were 1.69% per year in the warfarin group as compared to 1.53% (noninferiority) in the group that received 110 mg of dabigatran, and 1.1% per year (superiority) in the group that received 150 mg of dabigatran. The rates of major bleeding were 3.36% per year in the warfarin group compared to 2.71% in the group that received 110 mg dabigatran and 3.11% in the group that received 150 mg dabigatran. There was a mortality advantage in the 150 mg dabigatran treatment group. In conclusion, dabigatran given at a dose of 110 mg twice daily was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin but with a lower risk of bleeding. Dabigatran administered at a dose of 150 mg twice daily compared to warfarin was associated with lower rates of stroke and systemic embolization but similar rates of major bleeding. Based on the results of the RE-LY trial, the FDA has approved the 75 mg and 150 mg doses of dabigatran for stroke prevention in patients with AF.

AZD0837 is a new oral direct thrombin inhibitor that is being evaluated for clinical use in a once-daily extended-release formulation. It is a prodrug that has an active metabolite. The drug is being evaluated in patients with chronic AF to see whether the drug will cause fewer embolic events with chronic use when compared to vitamin K antagonists.513

Odiparcil is an oral indirect thrombin inhibitor that inhibits the propagation of coagulation by increasing the activation of heparin cofactor II, a natural anticoagulant in the body that inhibit thrombin.514 The drug is currently being compared to warfarin for the prevention of DVT in patients following hip or knee replacement surgery.

**Oral Factor Xa Inhibitors**

The orally administered factor Xa inhibitors are small molecular entities that reversibly bind to the active sites of factor Xa.18 These drugs have a high oral bioavailability and a rapid onset of action.

Rivaroxaban is a once-daily oral direct factor Xa inhibitor that has been shown to be effective and safe as a prophylaxis for venous thromboembolism in patients undergoing knee and hip replacement.515-516a It has been compared to enoxaparin 30 to 40 mg in multiple safety and efficacy studies using a dose of 10 mg once daily and found to be more effective than enoxaparin with a two-fold higher bleeding risk.517-520 The drug has received a favorable review for approval by the FDA for prophylactic use against DVT in patients undergoing hip or knee replacement surgery.

In a phase 2 study, twice-daily rivaroxaban in doses of 10, 20, or 30 mg has been compared to enoxaparin followed by a vitamin K antagonist for the treatment of hepatotoxicity, its use opened the way to develop other agents within this class.

Dabigatran etexilate is a prodrug hydrolyzed to its active metabolites by esterase-catalyzed hydrolysis in the plasma and liver.508 The active drug inhibits both clot-bound and fluid-phase thrombin. The drug reaches a peak plasma level in 2 hours after dosing and the plasma levels increase in a predictable fashion with increases in the oral dose. The drug is cleared by the kidney and has a half-life of 14 to 17 hours, allowing for once- or twice-daily dosing.

Dabigatran at a dose of 220 mg/daily was shown to be comparable to enoxaparin 40 mg daily in preventing DVT and all-cause mortality in patients undergoing total hip or total knee replacement.509,510 In these studies, dabigatran was generally well tolerated with no difference in the bleeding risk compared to enoxaparin. In another study in patients undergoing knee surgery, dabigatran appeared to be less effective than enoxaparin.511 However, a higher dose of enoxaparin was used compared to previous studies.509,510

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In a phase 2 study, twice-daily rivaroxaban in doses of 10, 20, or 30 mg has been compared to enoxaparin followed by a vitamin K antagonist for the treatment of...
a proximal DVT.\textsuperscript{521} Major bleeding was seen with rivaroxaban. Another study evaluated a once-daily dose of rivaroxaban 10, 20, 30, or 40 mg and found no increased bleeding risk.\textsuperscript{522}

Other comparative trials are evaluating the efficacy and safety of rivaroxaban in the prevention of stroke in patients with AF;\textsuperscript{524,525} for a secondary prevention against proximal VTE in long-term treatment, for VTE prophylaxis in medically-ill patients, and for reducing morbidity and mortality in patients with acute coronary syndromes as compared to aspirin or aspirin plus a thienopyridine.\textsuperscript{515,523,524} Precautions must be exercised when the drug is used in patients with moderate to severe renal or hepatic dysfunction and in patients receiving strong CYP3A4 inhibitors/inducers.\textsuperscript{515} The most common adverse effects are bleeding, nausea, vomiting and constipation.

Apixaban is another oral direct factor Xa inhibitor that demonstrates both antithrombotic and clot regression activity.\textsuperscript{524} The drug exhibits stable pharmacokinetics, a fast onset of action, and high bioavailability and shows minimal potential for drug–drug interactions. It is eliminated by nonrenal mechanisms.

Apixaban is being studied in patients with AF for prevention of strokes, prevention of DVT in patients with acute medical illness, treatment of DVT and PE, and for preventing DVT in patients with advanced malignancy.\textsuperscript{524}

The results of the Apixaban Dose Orally Versus Anti-coagulant with Enoxaparin 2 (ADVANCE 1) were recently reported on.\textsuperscript{525} In this double-blind, double-dummy study, 3195 patients undergoing total knee replacement received 2.5 mg of apixaban orally twice daily or 30 mg of enoxaparin subcutaneously every 12 hours. Both medications were started 12 to 24 hours after surgery and continued for 10 to 14 days. Bilateral venography was then performed. The primary efficacy outcome was a composite of both asymptomatic and symptomatic DVT, nonfatal pulmonary embolism, and death. Patients were followed for 60 days after anticoagulation was stopped. Compared to enoxaparin, apixaban did not meet the statistical criteria for noninferiority, but apixaban was associated with less bleeding and a similar adverse effect profile.\textsuperscript{525} Additional studies are in progress evaluating apixaban versus enoxaparin in patients undergoing total hip and total knee replacement. Two studies showed apixaban twice daily started on the morning after a total knee replacement was as effective a treatment to prevent DVT as enoxaparin without increased bleeding.\textsuperscript{528,529}

Apixaban has also been studied in patients after acute coronary syndrome, with concurrent antiplatelet therapy in the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE).\textsuperscript{527} In this double-blind, placebo-controlled dosing study, 1,715 patients with ECG-documented acute coronary syndromes were randomized to receive the placebo or 1 of 4 doses of apixaban: 2.5 mg twice daily, 10 mg once daily, 10 mg twice daily, or 20 mg once daily. The authors concluded from the results of the study that there was a dose-related increase in bleeding and a trend towards reduction in ischemic events. In this study, the safety and efficacy of apixaban may have varied depending on the antiplatelet therapy.

Other studies with apixaban include the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) that will help determine whether apixaban is noninferior or superior to warfarin in preventing stroke and systemic embolism.\textsuperscript{527} Another study, AVERROES, is comparing apixaban to aspirin in AF patients to prevent stroke in those who failed or are unsuitable for vitamin K antagonist treatment.\textsuperscript{527b} Preliminary results show that apixaban is more effective than aspirin in preventing strokes and systemic blood clots.\textsuperscript{527a} A study with apixaban was recently terminated because of increased bleeding.\textsuperscript{527}

**Other Oral Anti-Thrombin Agents**

LY517717 is now being evaluated in patients undergoing knee and replacement surgery, and it appears to be comparable to enoxaparin in preventing DVT.\textsuperscript{524,528}

YM-150 is being evaluated in phase 2 trials, compared to warfarin and enoxaparin, in patients undergoing hip and knee replacement to prevent DVT, and in patients with NVAF, compared to warfarin, to prevent stroke.\textsuperscript{524}

DU-176b is being compared to dalteparin for preventing DVT in patients undergoing hip replacement and for reducing emboli and strokes compared to warfarin in patients with NVAF.\textsuperscript{524} Edoxaban, the free base of DU-176b, is in early clinical trials.\textsuperscript{528a,529}

Betrixaban is a long-acting agent that is not excreted by the kidney and lacks major interactions with the CYP450 system.\textsuperscript{529} In doses of 15 or 40 mg twice daily, it has been compared to enoxaparin 30 mg twice daily and demonstrates comparable safety. Larger trials are now in progress.

TAK-422 is in phase 2 clinical trials in patients for the prevention of arterial and venous disease.\textsuperscript{530,530a}

**Oral Heparin**

An additional approach to oral anticoagulation is the development of agents that enhance the intestinal absorption of heparin. These agents have been administered to humans and show anticoagulant activity.\textsuperscript{531} The same approach to an oral LMWH might show promise.

**Factor Xa Inhibitors**

Factor Xa plays an important role in the intrinsic coagulation pathway and therefore has been a potential target in the development of novel anticoagulants. Various parenteral factor Xa inhibitors have been developed, and an
orally active formulation (TTP-889) has been evaluated in patients undergoing surgical repair of a fracture. It was not found to be effective.532 RB007 was effective. 532a

Parenteral Agents in Development

Direct and Indirect Factor Xa Inhibitors

Parenteral direct and indirect factor Xa inhibitors are available (Table 18-9). Fondaparinux is an indirect factor Xa inhibitor, and longer-acting agents that can be dosed subcutaneously once a week are being investigated. One of these agents, idaparinux, was shown to cause increased bleeding in a clinical drug comparator trial.533 Additional development of the drug has been terminated. Idrabiotaparinux is a biotinylated equivalent of idraparinux, and there is an antidote available for the drug, which is not the situation with either fondaparinux or idraparinux.532 Phase 3 studies with idrabiotaparinux are now in progress in DVT prevention, DVT treatment, and stroke prevention in patients with AF.

Otamaxiban is a direct parenteral factor Xa inhibitor that is being developed for use in patients with unstable coronary syndromes.534 In patients with non-ST-elevation, otamaxiban infusions were shown to have a potential benefit in reducing ischemic events while having a safety profile similar to UH plus eptifibatide.535 The drug is also being studied in patients undergoing percutaneous coronary intervention and compared to UH.536

DX-9065a is a nonpeptide arginine derivative that binds to the active site of factor Xa and inhibits factor VIIa within the factor VIIa/TF complex. Because it binds to factor Xa, the drug has a very long half-life. In patients with unstable coronary syndromes managed with standard antithrombotics, the use of intravenous NAPc2 was well tolerated and reduced ischemia.542

Factor VIIa Inhibitor

Factor VIIa inhibitor exerts its anticoagulant effect by competing with factor VIIa for tissue factor binding. The drug, combined with heparin, has been shown to be more effective than heparin alone.

Protein C

Protein C is a natural anticoagulant that when activated selectively degrades the coagulation cofactors Va and VIIIa, thereby inhibiting thrombosis.543 Activated protein C interrupts the feedback actions of thrombin on the coagulation cascade. The action of activated protein C is enhanced by protein S, another vitamin K-dependent plasma protein.544 A deficiency or reduced response to activated protein C is associated with an increased risk for vascular diseases.

Table 18-9. Comparison of Indirect and Direct Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Indirect (eg, fondaparinux)</th>
<th>Direct (eg, rivaroxaban, apixaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitory mechanism</td>
<td>AT dependent, catalytic</td>
<td>Non-AT dependent; stoichiometric</td>
</tr>
<tr>
<td>Drug target</td>
<td>Free Xa</td>
<td>Free and tissue bound Xa</td>
</tr>
<tr>
<td>Binding</td>
<td>Reversible</td>
<td>Irreversible</td>
</tr>
</tbody>
</table>

Protein C can be isolated from plasma or obtained by use of recombinant technology. Its antithrombotic activity has been demonstrated in animals, but it is associated with significant bleeding.545

A novel protein C activator has been identified, which, when infused into monkeys, can cause dose-dependent, reversible anticoagulation without consumption of fibrinogen, coagulation factors, or platelet activation, and without prolongation of the bleeding time.

Reduced levels of activated protein C are found in the majority of patients with sepsis. In sepsis, due to the inflammatory cytokines (tumor necrosis factor-α, interleukin-β, interleukin-6), thrombomodulin is downregulated, resulting in a decreased level of activated protein C, thereby increasing thrombosis and decreasing fibrinolysis. It is also found that activated protein C has anti-inflammatory properties by inhibiting production of inflammatory cytokines.546 Recombinant activated protein C is approved for clinical use to reduce the coagulation and inflammatory changes in severe sepsis, while reducing mortality.547

**Thrombomodulin**

Thrombomodulin is an endothelial cell-surface protein that complexes with thrombin, causing it to lose its coagulant activity while promoting the production of the endogenous anticoagulant protein C.536,548 Thrombomodulin is present on the endothelial cells of most blood vessels including those of the heart. Studies show that mutations in the promoter region of the thrombomodulin gene may constitute a risk factor for arterial thrombosis.549 Novel recombinant soluble human thrombomodulin, ART-123, activates the protein C pathway in healthy volunteers,550 and prolongs the thrombin time, prothrombin time, and aPTT. It has been used in patients undergoing elective hip replacement with prophylactic benefit shown in DVT.536

**New Low Molecular Weight Heparins**

A group of new LMWHs are being evaluated for cancer-associated thrombosis (AVE5026, an ultra-LMWH with enriched anti Xa activity). Bemiparin is another ultra-LMWH under investigation.

**Combined Factor IXa/IIa Inhibitors**

A group of synthetic combination agents are being evaluated (EP42675 and hexadecasaccharide SR12381A).

**Conclusion**

A large number of new oral antithrombotic drugs are being evaluated as potential replacements for warfarin and heparin in the prevention of veno- and arterioembolic diseases. The new oral thrombin and factor Xa inhibitors produce more predictable anticoagulant responses than warfarin and eliminate the need for routine monitoring and frequent dose adjustments.551 These agents have shown comparable or superior efficacy compared to warfarin and LMWH in the prevention of DVT in patients undergoing various orthopedic surgical procedures, in the treatment of DVT and the prevention of pulmonary embolism, and in reducing the risk of stroke in patients with NVAF. The drugs are also being studied in patients with unstable coronary syndromes. Compared to warfarin, these drugs have clear pharmacodynamic and pharmacokinetic benefits over available antithrombotic agents, and if the bleeding risks are acceptable, they may provide welcome additions to the therapeutic armamentarium for managing, preventing, and treating veno- and arterial-thromboembolic diseases.

*Note: References for this chapter can be found here: www.cvpct3.com*
Thrombolytic agents are drugs administered to patients for dissolution by fibrinolysis of established blood clot by activating endogenous plasminogen. Although some of these agents have been available for more than 60 years, it was not until the 1980s that they came into widespread use for the treatment of patients with acute myocardial infarction (AMI) and other thrombotic states.

Thrombolytic agents act by converting the proenzyme plasminogen to the active enzyme plasmin (Figure 19-1) by cleavage of the Arg-Val peptide bond. Plasmin lyses fibrin clot and is a nonspecific serum protease that is capable of breaking down plasminogen factors V and VIII. The action of plasmin is neutralized by circulating plasma inhibitors, primarily α2 antiplasmin. Endogenous thrombolysis is also inhibited by the plasminogen activator inhibitor (PAI-1). Thrombolytics can also affect platelet function in response to pathologic shear stress by inhibiting platelet aggregation in stenotic arteries.

Specific Thrombolytic Agents

Streptokinase

Streptokinase is a single-chain polypeptide derived from beta-hemolytic streptococci. It is not an enzyme and thus has no enzymatic action on plasminogen. It binds with plasminogen in a 1:1 ratio, resulting in a conformational change in the plasminogen, which thus becomes an active enzyme. This active plasminogen-streptokinase complex catalyzes the conversion of another plasminogen molecule to active plasmin. This activation of plasminogen is enhanced in the presence of fibrinogen but also other coagulation proteins, resulting in a systemic fibrinolytic state. In contrast to plasmin, the plasminogen-streptokinase complex is not rapidly neutralized by α2 antiplasmin.

Anistreplase

Anisoylated plasminogen streptokinase activator complex (APSAC) is a second-generation agent consisting of streptokinase bound in vitro to plasminogen by the insertion of an anisoyl group. This results in a much more stable enzyme complex, protecting it from plasmin inhibitors and resulting in a prolonged half-life, thus permitting the agent to be administered as a single bolus. APSAC is currently unavailable in the United States.

Urokinase

Urokinase was formerly available in both single- and double-chain forms. The double-chain form was originally isolated from urine and subsequently from human kidney cells in culture. Urokinase activates plasminogen directly and has no specific affinity for fibrin, activating both fibrin-bound and circulating plasminogen. Because urokinase is a naturally occurring product, it is not antigenic and is not neutralized by antibodies. Urokinase is no longer available in the United States.

Tissue Plasminogen Activator (tPA)

Single-chain tPA, also known as alteplase, occurs naturally but is synthesized for commercial use using a recombinant DNA technique. A double chain form of tPA, duteplase, was also synthesized and appeared to have similar activity when tested in vitro, but this form is not commercially available. The tPA molecule has a binding site enabling it to bind specifically to fibrin in thrombus. Therefore, it should theoretically be clot-specific and not
result in activation of generally circulating plasminogen. PAI-1 is important, and under natural conditions neutralizes endogenous tPA but not with administration of therapeutic doses of tPA.6

The currently available thrombolytic agents are listed in Table 19-1. The doses listed are for patients with AMI.7

**Retepase**

Reteplase, recombinant plasmin activator, or reteplase, is a deletion mutant of naturally occurring tPA that has a kringle-2 domain and lacks the finger, epidermal growth factor, and kringle-1 domain. Its slower clearance permits reteplase to be given as a double bolus injection.

**Tenecteplase (TNK-tPA)**

TNK-tPA is a genetically engineered variant of tPA with amino acid substitution at 3 sites. These substitutions lead to a longer half-life, increased fibrin specificity, and an increased resistance to PAI-1.8,9 The longer half-life of TNK-tPA makes it the only thrombolytic agent currently available that can be given as a single bolus injection.

**Fibrin Specificity**

An agent that is fibrin-specific is activated in the presence of fibrin clot and will not indiscriminately activate circulating plasminogen. Agents that are non–fibrin specific will activate circulating plasminogen, which is not indiscriminately clot bound. This may result in depletion of circulating plasminogen and lead to “plasminogen steal,” leaching fibrin-bound plasminogen from the clot and reducing the intensity of the thrombolysis.10

**Use in Acute Myocardial Infarction**

Enthusiasm for the use of thrombolytic agents with the ensuing trials only became popular after the pathophysiology of AMI was understood. Davies and Thomas observed in pathologic specimens that most cases with AMI were due to sudden occlusion of a coronary artery by a thrombus at the site of a ruptured atherosclerotic plaque.11 DeWood and colleagues confirmed this by demonstrating an occlusive thrombus in over 85% of coronary angiograms performed in patients within the first 3 hours of presentation with a transmural MI.12 A decade earlier, Reimer et al established that in dogs, a “wavefront” of MI progressed from the subendocardium to the subepicardium with a longer duration of temporary occlusion of a circumflex coronary artery.13 Rentrop and colleagues demonstrated the successful dissolution of the offending coronary thrombus with the use of intracoronary streptokinase.14,15 Subsequent trials utilizing intracoronary administration of streptokinase revealed significant improvement in survival, particularly in those patients in whom the thrombus was successfully lysed.16-18 However, it was not until intravenous thrombolytic agents were administered that large multicenter trials could be successfully undertaken.

**Effect on Mortality**

Intravenous administration of thrombolytic agents has been shown to significantly reduce the mortality rate of AMI long term.18 The results of the larger multicenter, randomized trials in which different intravenous thrombolytic agents were used are shown in Table 19-2.

The first large-scale trial conducted by the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) in 1986 convincingly showed that intravenous streptokinase administered within 6 hours of AMI significantly reduced the 21-day mortality by 18%.19 A similar 25% reduction in vascular mortality with the use of intravenous streptokinase was shown in the Second International Study of Infarct Survival (ISIS-2).20 In this trial, patients were admitted with symptoms suggestive of AMI; only 55% had significant ST-segment elevation. One smaller trial, the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM), showed no significant survival benefit despite improved ventricular function and smaller infarct size in the thrombolysed group.21 In the APSAC Interventional Mortality Study (AIMS), patients with AMI and ST-segment elevation were ran-
Thrombolytic Agents

Randomized within 6 hours of onset of symptoms. The trial was terminated prematurely because of the significant 47.5% reduction in mortality in the actively treated group.

The effect of tPA on mortality was studied in the Anglo-Saxon Scandinavian Study of Early Thrombolysis (ASSET) using the then-standard 3-hour dosing regimen and randomizing the patients within 5 hours of the onset of symptoms. As with the ISIS-2 trial, no electrocardiographic (ECG) criteria were required for enrollment. Consequently, only 72% of these patients were considered to have an AMI, yet there was a significant 26% reduction in mortality in patients receiving tPA.

Because of the proven efficacy of thrombolytic agents, it would be unethical to test new agents against the placebo. Therefore, thrombolytic agents are now tested for equivalency or superiority with standard thrombolytic agents.

### Comparison of Thrombolytic Agents

The early mortality rates comparing thrombolytic agents used in the treatment of AMI are shown in Table 19-3.

### Streptokinase versus tPA

In the GISSI-2 and ISIS-3 trials, the mortality rates were similar in the groups of patients who received streptokinase and tPA. In the ISIS-3 trial, the mortality rate in one-third of patients who also received APSAC was similar. However, in these 2 trials, conducted predominately in Europe, heparin was administered subcutaneously and not intravenously, as is customary in the United States. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) Trial, there was a 14% relative and a 1% absolute reduction in mortality rate in patients assigned to receive tPA compared with those receiving streptokinase. In this trial, tPA was administered using an accelerated protocol in which a thrombolytic agent was administered over 1½ hours, with two-thirds of the dose being given in the first 30 minutes rather than the conventional 3 hours. The tPA utilized in the ISIS-3 trial was duteplase rather than the standard alteplase, but the 90-minute patency rate is regarded as being similar.

### Double Bolus versus Continuous Infusion of tPA

In the continuous infusion versus double bolus administration of alteplase (COBOLT) trial, over 7000 patients were randomized to receive tPA either in the form of double boluses separated by 30 minutes or a 90-minute continuous infusion. The 30-day mortality was 7.98% for the patients receiving double boluses versus 7.44% for those receiving continuous infusion. Therefore, the double bolusing of alteplase failed to show equivalency to the
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90-minute front-loaded infusion despite its superiority in achieving 90-minute patency.31

**Reteplase versus Streptokinase and tPA**

In the INJECT trial (International Joint Efficacy Comparison of Thrombolytic), reteplase was shown to be at least equivalent to streptokinase.32 The size of the trial was not large enough to determine whether the 0.5% lower mortality in patients treated with reteplase was significant. The early mortality rate in patients treated with reteplase and front-loaded tPA was shown to be similar in the GUSTO-3 trial33 despite the apparent superiority of 90-minute patency rates when these 2 agents were specifically tested.

**TNK-tPA versus tPA**

Single-bolus TNK-tPA was compared with front-loaded tPA in the ASSENT-2 trial (Assessment of the Safety and Efficacy of a New Thrombolytic).34 The results shown in Figure 19-2 confirm the equivalence of the 2 agents. The rate of intracerebral hemorrhage was 0.9% and similar for both agents, whereas there were significantly less noncerebral bleeding complications in patients receiving TNK-tPA. The ease of administration of TNK-tPA has made its use more convenient than that of conventional tPA, with the sole advantage of tPA being that it can be discontinued should major hemorrhage occur within the first 90 minutes of its infusion.

**The Effect of Time on Efficacy**

In the GISSI-1 trial, there was a nearly 50% reduction in mortality when streptokinase was administered within 1 hour of the onset of symptoms; a 23% reduction in mortality when thrombolytic agent was administered within 3 hours; and a 17% reduction in mortality between 3 and 6 hours.19 There was no significant reduction in mortality when streptokinase was administered between 6 and 12 hours after the onset of symptoms.19 However, in the AIMS trial, there was a similar reduction in mortality when the APSAC was administered within 4 hours or between 4 and 6 hours after the onset of symptoms, but the relatively small number of patients randomized in the trial makes these results less meaningful.23 In the ASSET

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**Table 19-2. Early Mortality Following Thrombolysis**

<table>
<thead>
<tr>
<th>Thrombolytic Agent</th>
<th>Trial</th>
<th>n</th>
<th>Control</th>
<th>Agent</th>
<th>Survival Benefit %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>ISAM</td>
<td>1741</td>
<td>7.1</td>
<td>6.3</td>
<td>11 (NS)</td>
</tr>
<tr>
<td></td>
<td>GISSI-1</td>
<td>11,806</td>
<td>13.0</td>
<td>10.7</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>ISIS-2</td>
<td>17,187</td>
<td>12.0</td>
<td>9.2</td>
<td>25</td>
</tr>
<tr>
<td>APSAC</td>
<td>AIMS</td>
<td>1004</td>
<td>12.2</td>
<td>6.4</td>
<td>47</td>
</tr>
<tr>
<td>tPA</td>
<td>ASSET</td>
<td>5011</td>
<td>9.8</td>
<td>7.2</td>
<td>27</td>
</tr>
</tbody>
</table>

n = number of patients randomized in trial; NS = not significant

**Table 19-3. Early Mortality Comparing Different Thrombolytic Agents**

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Streptokinase</th>
<th>tPA</th>
<th>Reteplase</th>
<th>Tenecteplase</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-3</td>
<td>41,299</td>
<td>10.9</td>
<td>10.3</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-2</td>
<td>12,490</td>
<td>8.6</td>
<td>9.0</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GUSTO-1</td>
<td>41,021</td>
<td>7.3</td>
<td>6.3</td>
<td>9.02</td>
<td>.001</td>
<td></td>
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<tr>
<td>INJECT</td>
<td>6,010</td>
<td>9.53</td>
<td>7.24</td>
<td>7.47</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GUSTO-3</td>
<td>15,059</td>
<td>6.18</td>
<td>6.15</td>
<td>NS</td>
<td></td>
<td></td>
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<td>ASSENT-2</td>
<td>16,949</td>
<td>6.18</td>
<td>6.15</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = number of patients in trial; NS = not significant; tPA = tissue plasminogen activator
Thrombolytic Agents

In the trial in which tPA was administered, there was a similar reduction in mortality in patients who received thrombolysis within 3 hours or between 3 and 5 hours.\(^{24}\) In the ISIS-2 trial, the greatest reduction in vascular mortality (35%) occurred when streptokinase was administered within 4 hours of the onset of chest pain, yet there was still a significant reduction in mortality in those patients who were randomized between 5 and 24 hours.\(^{17}\) In the South American EMERAS (Estudio Multicéntrico Estreptokinasa Repúblicas de América del Sur) Trial, there was no improvement in survival when streptokinase was administered between 7 and 12 hours or up to 24 hours following chest pain.\(^{35}\)

The Late Assessment of Thrombolytic Efficacy (LATE) study was designed to prospectively randomize patients to receive tPA between 6 and 24 hours after the onset of chest pain.\(^{36}\) However, only 55% of the patients had significant ST-segment elevation. There was a significant relative reduction (25.6%) in the 35-day mortality rate in patients randomized to receive tPA between 6 and 12 hours compared with the placebo (8.9% versus 12.0% respectively). There was no significant difference in mortality when these patients were randomized between 12 and 24 hours after the onset of symptoms. However, if patients whose thrombolysis was delayed more than 3 hours after being initially assessed in the hospital were excluded from the study, patients who received their thrombolytic agents between 12 and 24 hours after the onset of symptoms had a 22.4% reduction in mortality.

Therefore, it has become standard practice to administer thrombolytic agents up to 12 hours following the onset of chest pain in patients with AMI. Whether patients should receive thrombolytic agents if they present 12 to 24 hours after the onset of chest pain is controversial. However, patients who have continued chest pain beyond 12 hours, staggered onset of pain, or those at higher risk with, for example, anterior wall or complicated inferior wall MI, can be considered for late administration of these agents.

It is not clear why patients benefit from late thrombolysis, as it is assumed that myocardial necrosis would have been completed within 6 hours. Therefore, its benefits may be attributed to a reduction in post-MI remodeling and ventricular arrhythmias. In addition, infarction may not be complete if significant collateral blood flow is present to maintain viability beyond 6 hours or if the occluded coronary vessel is intermittently or partially spontaneously reperfused.

Prehospital Thrombolysis

It has been convincingly shown that the benefit of reperfusion therapy is dependent on the time elapsed between the onset of symptoms and the initiation of treatment\(^{36}\) and more so with thrombolysis than percutaneous angioplasty. A meta-analysis of prehospital compared with in hospital fibrinolysis showed a 17% relative reduction in mortality.\(^{37}\)

In the Comparison of Angioplasty and Prehospital Thrombolysis In Acute Myocardial infarction (CAPTIM) study,\(^{38}\) 840 patients were randomized; 460 were enrolled within 2 hours of onset of symptoms. The patients received thrombolysis 55 minutes earlier than angioplasty, and they had a nonsignificant lower mortality (2.2% versus 3.6%, \(P = .007\)). Therefore, prehospital thrombolysis may be a very reasonable alternative to primary angioplasty in patients who present early, eg, within 3 hours of onset of symptoms. However, the benefit from prehospital thrombolysis has not been shown in clinical trials.\(^{39-41}\)

**Patency**

The mechanism whereby thrombolysis improves survival is by achieving and maintaining patency of the infarct related artery. Early or 90-minute patency has been shown to be an important determinant of survival following thrombolysis.\(^{16,42-44}\) The TIMI (Thrombolysis In Myocardial Infarction) grade classification\(^{40}\) is generally used to evaluate patency: grade 0-no perfusion; grade 1-penetration without perfusion; grade 2-partial perfusion with
a rate of entry or clearance of contrast material beyond the occlusion that is impaired; and grade 3-complete reperfusion.

The patency rates (TIMI grades 2 and 3) at 90 minutes from grouped studies are shown in Table 19-4. Treatment with the front-loaded or accelerated tPA regimen is associated with high patency rates, while streptokinase is associated with the lowest patency rates. Administration of double bolus tPA, reteplase, and TNK-tPA resulted in similar patency rates. By 2 to 3 hours, there was no significant difference in the patency rates between the different agents, and by 24 hours, there was no further change in the patency rates.

It was shown in analysis of 3,913 patients from a series of TIMI trials that TIMI flow grade 2 or 3 at 60 minutes after thrombolysis occurred in patients who received their therapy 2.8 hours after the onset of their chest pain, whereas those with TIMI grade 0 or 1 were at 3.3 hours (Figure 19-3). A delay beyond 4 hours was associated with a reduced patency and TIMI frame count. There was a small yet significant reduction in left ventricular ejection fraction in patients whose time from symptom onset was > 4 hours compared with less (55.3% versus 58.8%).

Reocclusion and Reinfarction

Reocclusion and reinfarction following successful thrombolysis carries a significant increase in morbidity and mortality.

For a definitive diagnosis of reocclusion to be made, angiograms must be performed immediately following thrombolysis and at a later date, generally prior to hospital discharge. The diagnosis of reinfarction is often difficult, as it may immediately follow successful thrombolysis. In a meta-analysis combining the results of randomized trials, Granger et al reported a reocclusion rate of 13.5% when patients received tPA and intravenous heparin compared with 8.0% when non–fibrin specific thrombolytic agents (streptokinase, APSAC, and urokinase) were used. Therefore, it was somewhat surprising to observe the lower reported rates of reinfarction in those patients who received tPA with subcutaneous heparin compared with streptokinase in the GISSI-2 and ISSI-3 trials. Since more than 50% of the reocclusion occurs within 24 hours, it is possible that these events were undetected in clinical trials. However, there was no difference in the reocclusion rates reported with streptokinase compared with tPA in the GUSTO angiographic sub-study.

Reocclusion after successful thrombolysis was recorded in 9.2% of patients in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) I, II, and III trials but was recorded at 16.9% in those patients who required emergency angioplasty following thrombolysis. The reocclusion was clinically recognized in 58% of the patients and was associated with deleterious effects, whether silent or clinically evident. The mortality rate was 4.5% if the infarct-related artery remained patent and 11.0% if the artery reoccluded.

Patients who reinfarcted while in hospital were generally managed by performing immediate angioplasty without repeat administration of a thrombolytic agent. However, should performing an angioplasty not be feasible or appropriate, it has been reported the patient can receive a second dose of a thrombolytic agent. Streptokinase

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### Table 19-4. Patency Rates (TIMI Grades 2 and 3) at 90 Min after Thrombolysis with Different Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>n</th>
<th>TIMI Grades 2 and 3 (%)</th>
<th>TIMI Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>283</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>tPA: 3-h infusion</td>
<td>1648</td>
<td>70</td>
<td>52</td>
</tr>
<tr>
<td>tPA: front loaded</td>
<td>629</td>
<td>83</td>
<td>65</td>
</tr>
<tr>
<td>tPA: double bolus</td>
<td>84</td>
<td>93</td>
<td>88</td>
</tr>
<tr>
<td>Reteplase</td>
<td>157</td>
<td>83</td>
<td>60</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>148</td>
<td>79</td>
<td>63</td>
</tr>
</tbody>
</table>

*n = number of patients randomized; tPA = tissue plasminogen activator*
nase resistance titers increase by the fifth day after admin-
istration of either streptokinase or APSAC and remain
risen for at least a year. Therefore, if a patient has received
either of these 2 agents in the previous year (and prob-
ably further back), it is advisable that tPA or reteplase be
used. Recurrence of reinfarction after thrombolysis with
tPA or streptokinase was successfully treated with tPA in
85% of patients (two-thirds within 1 hour of completion of
thrombolysis) without an increase in bleeding comp-
lications, but reocclusion occurred in more than half of
these patients.

In a nonrandomized study of 2,301 patients who rein-
farcted in the GUSTO-I and ASSENT-2 trials, it was re-
ported that the 30-day mortality was similar in those who
received repeat thrombolysis or revascularization (11% versus
11%), whereas the mortality in patients who were
 treated conservatively was higher (28%). Patients who
developed early recurrence of infarction while in hospital are managed by performing immediate
angioplasty without repeat administration of a thrombo-
lytic agent. Repeat thrombolysis has not been shown to
be effective.

Completeness of Reperfusion

In the Western Washington Trial, in which intracoronary
streptokinase was administered, the 30-day survival was
significantly improved in those patients receiving throm-
bolysis compared with controls (3.7% versus 11.2% re-
spectively), but by 1 year there was no difference in the
survival. However, when the survival was analyzed for
completeness of reperfusion, there was a significant im-
provement in survival in those patients who had com-
plete reperfusion (and presumably TIMI grade 3 flow)
compared with patients with partial (presumably TIMI
grade 2 flow) or no reperfusion (98% versus 77% versus
85% respectively), suggesting that partial reperfusion
could possibly be harmful.

The Thrombolysis Trial of Anistreplase in Acute Myo-
cardial Infarction (TEAM-3 Trial), in which APSAC or
tPA was administered and the patients studied 30 hours after administration of their thrombolytic agents, patients
with TIMI grade 3 perfusion had better left ventricular
systolic function and a trend toward lower mortality com-
pared with patients with TIMI grade 2 and TIMI grade 0
or 1.

The angiographic substudy of the GUSTO Trial reported
that the 24-hour mortality was 2.93% and highest in
patients who had TIMI grade 2 at 90 minutes post-
thrombolysis. The mortality was 0.89% and was the lowest
in patients with TIMI grade 3 flow and 2.35% in patients
with TIMI grade 0 or 1 flow. In this angiographic sub-
study, in which 1,210 patients were randomized to have
a 90-minute coronary angiogram, 54% of the patients
who received tPA had TIMI grade 3 flow compared with
31% of patients who received streptokinase. However, ir-
respective of the treatment regimen the patient received,
the 30-day mortality was 4% in patients with TIMI grade
3 flow and 8.4%, 9.2%, and 7.8% in patients with TIMI
grade 0, 1, and 2 grades, respectively. When the 90-min-
ute patency data and the corresponding 30-day mortality
from the angiographic substudy were extrapolated to the
41,021 patients in the main GUSTO trial, the investiga-
tors were able to accurately predict the mortality in the
different subgroups of the thrombolytic regimen.

Therefore, it appears that the 90-minute patency rate
following thrombolysis, and in particular the TIMI grade
3 flow, can predict an improved survival compared with
patients with TIMI grade 2 flow who may have no differ-
ce in survival than patients who have TIMI grade 0 or 1
flow.

Subsequently it has been shown that the TIMI frame
count, which is based on the number of angiographic
frames needed for contrast to traverse the artery (each
frame is 1/30th second) is a more accurate assessment of
flow. Therefore, there is a spectrum of myocardial viability
of patient survival within the group of patients with
TIMI grade 3 flow. The delay in flow through a patent coro-
nary artery is a consequence of downstream microvascular
obstruction. Therefore, patients with a lower TIMI frame
count following thrombolysis have a better survival.

Thrombolysis in Clinical Subgroups

Anterior Wall Myocardial Infarction

The mortality rate of patients with anterior wall MI has
been significantly reduced by thrombolysis, with a 37%
reduction in mortality in the ISMI-2 trial and a 21% re-
duction in mortality in the GISSI-1 trial. These reduc-
tions in rates were significantly greater with anterior wall
MI than inferior wall MI. In the GUSTO-1 trial, it was
shown that there was a significant 18% reduction or a 1.9%
absolute reduction in mortality in patients with anterior
wall MI who received tPA compared with those receiving
streptokinase, whereas the 11% reduction in mortality in
patients with inferior wall MI who received tPA as op-
posed to streptokinase was of borderline significance.

Inferior Wall Myocardial Infarction

Inferior wall MI is generally associated with a lower
mortality rate because of the smaller mass of myocardium supplied by the right coronary artery. Therefore, it
is not surprising that there was no statistical difference
with regard to mortality in the individual trials among
patients treated with thrombolysis compared to the pla-
cebo. However, when the data were pooled, there was
a significant 22% relative reduction in mortality, from
8.7% to 6.8%, with the use of thrombolytic agents.
a more recent overview that included patients in the ISIS-3,26 EMERAS,35 and LATE36 trials, the reduction in mortality was only 11% in patients randomized to receive thrombolysis.

Patients with inferior wall MI with the highest mortality are most likely to derive the greatest benefit from thrombolysis; these include patients with right ventricular infarction, accompanying anterior ST-segment depression, and heart block. Therefore, the use of thrombolytic agents should be considered in all patients with an inferior wall MI, particularly those who are considered to be at highest risk.

Non-Q-Wave Myocardial Infarction
Approximately 50% of patients presenting with AMI do not have ST-segment elevation or left bundle branch block. Administration of thrombolytic agents to patients in the GISSI-119 and ISIS-2 trials20 who presented with ST-segment depression did not result in improvement in survival despite a significant mortality in these groups (16% to 20%). This question was specifically addressed in a prospective manner in the TIMI-IIIB trial,63 where patients who presented with non-Q-wave MI or unstable angina pectoris with ST-segment depression or T-wave inversion were randomized to receive tPA or the placebo. The mortality rate was not significantly different in the tPA group versus those receiving the placebo (10.9% versus 8.9% respectively). It is possible that thrombolytic agents may actually be harmful in patients with non-Q-wave MI, as thrombolytic therapy has a prothrombotic action—activating platelets and exposing thrombin, thus resulting in progression of the partially occluded coronary artery to complete occlusion. In a post hoc analysis of the LATE Study,64 it was found that thrombolysis was beneficial to patients presenting 6 hours after the onset of chest pain with non-Q-wave MI. However, the authors themselves caution against accepting these results without further prospective testing in a larger number of patients.

Left Bundle Branch Block
The diagnosis of AMI in the presence of left bundle branch block may be masked; even using the criteria developed from the GUSTO-1 Study,64 the sensitivity of diagnosis was as low as 36%. Unfortunately, relatively few patients with left bundle branch block have been randomized in the megatrials. In an overview of all the fibrinolysis trials, only 2,032 patients with bundle branch blocks were enrolled.62 There was a significant reduction in 35-day mortality in patients having thrombolysis compared with those receiving the placebo (18.7% versus 23.6%, respectively). However, it has become standard practice to administer thrombolytic agents to all patients with presumed new left bundle branch block and typical symptoms of AMI.

Cardiogenic Shock
Patients with cardiogenic shock have generally been excluded from most of the thrombolysis trials. Therefore, there are limited data concerning the efficacy of these agents. In the GISSI-1 trial,69 there was no significant difference in the survival of patients who presented in cardiogenic shock, whether they received thrombolysis or the placebo. In the ISIS-2 trial,20 patients who were hypertensive with a systolic blood pressure < 100 mm Hg had a 24% significant relative reduction in 5-week mortality of 28.5% with streptokinase compared to 37.5% in the control group. In an overview of the megatrials of patients presenting with blood pressure <100 mm Hg, the 35-day mortality was 28.9% in patients receiving thrombolysis compared with 31.5% of those in the control group.61

A problem in treating patients in cardiogenic shock with streptokinase is that the patients are already hypertensive before administration of a drug, which itself may cause a decrease in blood pressure. However, in the GUSTO-1 trial,21 patients treated with tPA were much less likely to develop cardiogenic shock, whereas those who were in cardiogenic shock at the time of randomization and who received streptokinase with intravenous heparin had a better 30-day mortality of 54%, compared with 59% in those patients receiving tPA. The poor results with administration of thrombolytic agents in patients with cardiogenic shock are probably related to the low patency rates achieved even with the use of intracoronary streptokinase.15 The low patency rate has been attributed to the poor delivery of thrombolytic agents to the occluded coronary vessel in the presence of cardiogenic shock, but this does not explain the poor results with administration of intracoronary thrombolysis. Because of the high mortality associated with thrombolysis and administration of thrombolytic agents, it has become standard practice not to use thrombolytic agents and to transfer these patients directly to the cardiac catheterization laboratory for immediate angiography and coronary revascularization.68

In all subsequent trials, patients with cardiogenic shock have been excluded from receiving thrombolysis.

Elderly Patients
There is a general reluctance to use thrombolytic agents in the elderly because it is widely believed that the complication rate from their use is higher among these patients and that their effectiveness is inferior in the elderly.69-71 In addition, a higher percentage of elderly patients will have contraindications to thrombolytic therapy, including severe hypertension, recent cerebrovascular accident and bleeding disorders, or too late an arrival in an emergency department.

Streptokinase is the only thrombolytic agent that was administered to patients aged 70 years or older in these
early trials. In the GISSI-1 trial, there was a significant reduction in mortality compared with controls among patients younger than 65 years who were treated with streptokinase. Although the mortality rate was lower among patients older than 65 or 75 years who were thrombolysed, the reduction in mortality was not significantly different. However, the number of lives saved was more than 4 patients per 100 among the elderly who were treated and only 2 in the younger group. The ISIS 2 trial was the only study in which a greater mortality in the elderly was reported, but the total number of patients in this age group was small and results were not statistically significant. By far, the largest number of elderly patients were randomized in the ISIS-2 trial; here the mortality rate was significantly reduced among the elderly, particularly when aspirin was combined with streptokinase. In the ASSET trial, in which patients received either tPA or the placebo, all patients were < 75 years. In this trial, a reduction in mortality for patients < 66 years was not significant, but it was highly significant for those older than 65 years. The results of the ISIS-2 trial were similar to those of the ASSET trial in that the mortality rate was reduced in patients randomized to receive APSAC, but it was significant only in the older and not in the younger patients. In this trial, all patients were < 70 years and the numbers were relatively small.

Three large trials directly compared the outcome of streptokinase with tPA. In the GISSI-2 trial, 22.5% of the 12,490 patients were older than 70 years, but the results were not separately analyzed according to age. In the ISAR trial, 26.1% of the 41,299 patients were 70 years or older. The results were also not separately analyzed according to age.

In the GUSTO trial, in which 12% of the 31,021 patients were older than 75 years, there was no significant difference in the mortality of 19.3% in the patients receiving tPA compared with 20.6% with streptokinase. In the angiographic substudy, regional left ventricular dysfunction was greater in the elderly patients older than 75; in contrast to the younger patients, this dysfunction was maintained at follow-up despite patent of the infarct-related artery. This has led the authors to speculate that a more rapid progression or impaired recovery of ischemic injury occurs in the elderly.

A recent observational study of 7,864 Medicare patients who had received thrombolytic treatment revealed that patients older than 75 years had a higher 30-day mortality than those who did not receive thrombolysis (18.0% versus 13.6%). This study has been criticized, as there were significant imbalances between the groups, which were, however, adjusted for prognostic factors. Selection for treatment was based on physician preferences, and only one-third of the ECG-eligible patients were included in the study. The Fibrinolytic Therapy Trialist (FTT) reviewed 58,600 patients who were randomized to thrombolytic trials and showed that among the 5,788 patients older than 75, there was a nonsignificant difference in mortality benefit in those patients who received thrombolytic therapy compared with those who did not (24.3% versus 25.3%).

Therefore, elderly patients with AMI can benefit significantly from the administration of thrombolytic agents, but it should be remembered that the incidence, albeit small, of intracerebral hemorrhage increases with age (see “Intracranial Hemorrhage,” below) and that thrombolytic agents should generally be reserved for those patients who are at high risk, presenting with large anterior wall MI and/or complicated inferior wall MI.

Combination of Fibrinolytic Agents and Platelet Glycoprotein IIb/IIIa Receptor Inhibitors

The use of a fibrinolytic agent alone or with conventional use of aspirin and heparin has achieved a ceiling of approximately 60% TIMI grade 3 flow at 90 minutes. This is less than that achieved with primary percutaneous transluminal coronary angioplasty (PTCA) at 80% to 95%. Since AMI is associated with a thrombus rich in both fibrin and platelets, recent trials have added platelet glycoprotein IIb/IIIa receptor antagonists to a thrombolytic agent to improve the reperfusion rate without significantly increasing bleeding events. These agents may not only potentiate fibrinolysis but also reduce distal microembolism and platelet-leukocyte clumping.

In the IMPACT trial (Integrin Receptor Blockade with Integrelin in Acute Myocardial Infarction), Integrelin was added to full-dose frontloaded tPA and resulted in a 66% TIMI grade 3 flow at 90 minutes compared with 39% in those patients who received tPA alone. Abciximab was used with a lower dose of reteplase (5 mu + 5 mu in the SPEED trial) in the Emergency Department) resulting in a 61% grade 3 TIMI flow at 60 minutes compared with 47% in those patients receiving full-dose reteplase. Abciximab has also been used with lower-dose tPA (5-mg bolus plus 35-mg infusion over 60 minutes) in the TIMI 14 study. This resulted in a 76% TIMI grade 3 flow at 90 minutes compared with 50% in those patients receiving front-loaded tPA. This combination of thrombolytic and GP IIb/IIIa inhibitor resulted in an even more pronounced difference at 60 minutes. The combination of streptokinase and abciximab has not been shown to be effective and resulted in a significant increase in bleeding complications.

Despite the superior early patency rates in patients receiving the combination of thrombolytic and platelet GP IIb/IIIa inhibitor, when 16,588 patients were randomized to receive reteplase with or without abciximab in the
GUSTO V trial, there was no difference in the 30-day mortality (5.6% versus 5.9%). In the ASSENT-3 trial, 6,095 patients were randomized into 3 groups: full dose TNK-tPA with unfractionated heparin or low-molecular-weight heparin, and half-dose TNK-tPA with abciximab. The rate of in-hospital refractory ischemia and reinfarction was higher in the group receiving unfractionated heparin and similar in the groups receiving low-molecular-weight heparin or abciximab, but the 30-day mortality rates were not different among the 3 groups. There was no difference in the incidence of intracranial hemorrhage, but major hemorrhage was significantly greater in the patients receiving abciximab (4.3%) compared with those receiving unfractionated heparin (2.2%).

Other Adjunctive Antithrombotic Therapies

Successful thrombolysis paradoxically results in conditions that favor rethrombosis. In the process of thrombolysis, thrombin bound to fibrin is exposed to reperfused blood on the thrombus surface. This clot-bound thrombus activates fibrinogen and platelets, which are major contributors to rethrombosis and hence reocclusion of successfully thrombolysed coronary arteries.

The objective of adjunctive treatment is to improve patency and reduce the high incidence of reocclusion following successful thrombolysis by inhibiting thrombin activity and platelet function. It is not clear whether adjunctive therapy can enhance thrombolysis itself.

Aspirin and Other Antiplatelet Drugs

Aspirin inhibits platelet aggregation by irreversibly inhibiting cyclooxygenase and the consequent production of thromboxane A₂. Aspirin has been convincingly shown to reduce mortality and presumably prevent reocclusion after successful thrombolysis. In the ISIS-2 Trial, there was a 23% reduction in mortality among patients receiving aspirin alone compared with the placebo, and this was similar to the 25% reduction in mortality among those who received streptokinase alone. When aspirin is combined with streptokinase, there is an additional 19% reduction in mortality. Since aspirin administration following thrombolysis decreased late but not early mortality, it is postulated that the mechanism whereby it is beneficial is in preventing reocclusion, and consequently reinfarction, rather than by accelerating thrombolysis.

Thromboxane is one of the many activators of the GP IIb/IIIa receptors on the platelet surface that permit the binding of fibrinogen to platelets and the consequent aggregation. Therefore, aspirin is a relatively weak antiplatelet drug in comparison with the recently developed and more powerful GP IIb/IIIa receptor inhibitors.

Clopidogrel is an orally active antiplatelet agent that blocks ADP-induced platelet activation and independent cyclooxygenase inhibition of aspirin. In the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY TIMI 28) study, 300 mg clopidogrel followed by 75 mg daily was compared to the placebo in 3,491 randomized patients younger than 75 years who had received thrombolysis. This did not result in an increased rate of ST-segment resolution at 90 or 180 minutes. Late patency was assessed with angiography after 3½ days. The composite endpoint of occluded coronary artery, death, and reinfarction was significantly reduced from 21.7% in the placebo group to 15.0% in the clopidogrel group. Therefore, clopidogrel, because of its delayed onset of activity, does not seem to enhance fibrinolysis but primarily prevents reinfarction. There was no increased bleeding in the patients receiving clopidogrel.

It became standard practice to administer 300 mg followed by 75 mg daily of clopidogrel to all patients younger than 75 years who receive thrombolysis. Patients older than 75 years should probably receive 75 mg as an initial loading dose and a subsequent maintenance dose.

Heparin and Other Antithrombin Drugs

The anticoagulant affect of heparin is primarily related to its antithrombin activity. Therefore, heparin has been administered to improve patency, particularly following thrombolysis with tPA, but it is also used with streptokinase. Heparin has been shown to improve patency, but it is not clear that it improves mortality and reduces reinfarction. In the TAMI study, patency at 90 minutes following thrombolysis with tPA was 79% whether the patients received heparin or not. This led the authors to conclude that heparin did not facilitate the fibrinolytic effect of tPA. In the Heparin Aspirin Reperfusion Trial, coronary artery patency in 205 patients who had been thrombolysed was assessed at 18 hours after patients had received either aspirin or heparin. The patency rate was 82% in the heparin group and significantly greater than that in the aspirin group, but a low dose of aspirin (80 mg) was used. In the European Cooperative Study Group 6 trial, the patency rate at the mean of 81 hours following thrombolysis with tPA was 80% in those patients who received both aspirin and heparin and was significantly greater than the 75% in patients who received aspirin alone. It is concluded that intravenous heparin in a 5000-U bolus followed by 1000 U/hour increases patency during the first few days following thrombolysis with tPA, probably by preventing rethrombosis.

The effect of heparin on mortality is less convincing. In the GISSI-2 study, patients received aspirin with ei-
coronary angiography and angioplasty, thus benefiting the patient receiving enoxaparin. The major bleeding rate was significantly 0.8% higher in the patients receiving enoxaparin, but the stroke rate was the same.

The dose of enoxaparin prescribed is a 30-mg bolus given intravenously followed 15 minutes later by a subcutaneous injection of 1.0 mg/kg for 12 hours. For patients older than 75 years, the dose is adjusted as enoxaparin is primarily excreted by the kidneys and the danger of bleeding is higher. Therefore, no bolus is given and the maintenance dose is 0.75mg/kg.

Coronary Angioplasty and Thrombolysis

Fibrinolysis-Facilitated Percutaneous Coronary Intervention

The routine administration of a thrombolytic agent shortly before a planned angioplasty for ST elevation MI has not generally been thought of as advantageous. In a meta-analysis102 of 4 trials in which 2,679 patients were randomized, no benefit was shown to those patients receiving fibrinolysis. Facilitated angioplasty was evaluated in a large randomized trial, ASSENT-4PCI,103 where 1,667 patients were scheduled to have primary angioplasty but a delay of 1 to 3 hours was anticipated. One group received TNK-tPA and both groups had angioplasty with a median delay of 115 and 107 minutes. The primary endpoint of death, congestive heart failure or shock within 90 days, was reached in 19% of patients assigned to the group receiving thrombolytic therapy and 13% to those who had primary angioplasty. The trial was prematurely stopped by the data monitoring committee before the anticipated 4,000 patients were randomized. Therefore, it is not recommended that facilitated angioplasty be performed.

Rescue Angioplasty

Rescue angioplasty has been performed with unsuccessful fibrinolysis associated with failed ST-segment resolution and chest pain 60 to 90 minutes after thrombolytic therapy. In a meta-analysis of 5 trials where a total of 920 patients were randomized, a 37% nonsignificant reduction in mortality occurred (P = .055) in patients undergoing rescue angioplasty.105 A reduced combined endpoint of death or reinfarction was observed only in the stent era.

Wijeysundera et al105 performed a meta-analysis of 6 randomized trials in which the ST segments had not been well studied in 2 trials: ASSENT-382 described above and in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT TIMI 25) study.106 In the latter study, 20,506 patient were randomized to treatment with enoxaparin or unfractionated heparin. The composite endpoint of death or recurrent infarction was significantly reduced (9.9%) in the enoxaparin group compared with the heparin group (9.9%). In both trials, the patients receiving enoxaparin had better outcomes, but the enoxaparin was administered throughout the hospitalization, whereas heparin was given for 48 hours. Unlike current practice, the patients did not have routine early coronary angiography and angioplasty, thus benefiting the patient receiving enoxaparin. The major bleeding rate was significantly 0.8% higher in the patients receiving enoxaparin, but the stroke rate was the same.

The dose of enoxaparin prescribed is a 30-mg bolus given intravenously followed 15 minutes later by a subcutaneous injection of 1.0 mg/kg for 12 hours. For patients older than 75 years, the dose is adjusted as enoxaparin is primarily excreted by the kidneys and the danger of bleeding is higher. Therefore, no bolus is given and the maintenance dose is 0.75mg/kg.
significantly resolved by 90 minutes after thrombolysis. The mortality of the patients who had emergency angioplasty (in the later trials as late as 414 and 327 minutes after thrombolysis) was no different from those treated conservatively. However, there was a significant 27% relative (5% absolute) reduction in congestive heart failure and a 22% relative (4% absolute) reduction in reinfarction.

An earlier meta-analysis showed a significant incidence of major bleeding in the patients receiving rescue angioplasty (11.9%) compared with those treated conservatively (1.3%).

Routine Early Angioplasty after Thrombolysis

The value of early routine angioplasty within 6 hours of thrombolysis was evaluated in 1,059 high-risk patients who presented to Canadian hospitals without angioplasty facilities. The patients randomized to early angioplasty had their procedure at a median of 2.8 hours and the delayed routine patients at 32.8 hours. Stents were used in 98% of angioplasties. The combined endpoint of death, reinfarction, heart failure, and shock was significantly reduced in the early group compared with the delay-in-angioplasty group (11.0% versus 17.2%, \( P = .004 \)).

A meta-analysis of trials in the “stent” era showed nearly 50% reduction in mortality with routine early angioplasty compared with delayed or ischemia-guided therapy (7.5% versus 13.2%).

Primary Angioplasty Replacing Thrombolysis

Less than 30% of hospitals in the United States have facilities to perform percutaneous angioplasty. However, more than 90% of patients presenting with acute ST-segment MI are admitted to or can be transported within 90 minutes to a hospital performing emergency angioplasty. In a recent report from rural Illinois where 188 consecutive patients were eligible for emergent reperfusion therapy, 82% were transferred by ground transportation or helicopter to regional medical centers, and 8% received thrombolysis because of an anticipated delay in transportation on account of inclement weather.

Keely et al reviewed 23 trials with a total of 7,739 patients who were randomized to on-site thrombolysis or primary angioplasty. In the patients receiving thrombolysis, 24% received streptokinase, and 76% received a fibrin-specific agent. Coronary stents were used in 8 of the trials. The short-term death rate of the patients who had primary angioplasty was 7% compared with 9% in patients who were thrombolysed; non-fatal reinfarction was 3% and 7%; and stroke was 1% and 2%, respectively. The composite endpoint of death, reinfarction, and stroke was also significantly lower in the angioplasty group at 8% compared with 14% in the patients who were thrombolysed (Figure 19-4).

Complications

Intracranial Hemorrhage

An intracerebral bleed is the most feared complication following administration of thrombolytic agents. Results are generally devastating, with the event usually occurring within 24 hours of thrombolysis and carrying a high mortality of approximately 50%. However, it should be realized that the incidence of stroke in the prethrombolytic era was 1.7% to 2.4%. A meta-analysis of the major thrombolytic trials has shown that administration of thrombolytic agents is associated with an 0.4% absolute increase in the incidence of stroke (1.2% for patients receiving thrombolysis versus 0.8% in controls). This increase is attributed mostly to the 0.4% to 0.5% incidence of intracerebral bleeding that occurs on the first day. The 0.3% incidence of stroke is significantly lower in patients < 55 years, compared with 0.7% in patients aged 75 years or older (Table 19-5).
The incidence of intracerebral hemorrhage in a group of nonrandomized patients admitted to 61 hospitals in Holland over 18 months was 1.0% (95% confidence interval, 0.62%-1.3%). Analysis of events from a Myocardial Infarction Triage and Intervention (MITI) Study, where patients in the Seattle area with MI were monitored, revealed an equal incidence of stroke in patients receiving thrombolyis (1.6%) as in patients who did not (2.2%). The incidence of hemorrhagic stroke was 1.1% among the patients who received thrombolyis compared with 0.4% among those who did not.

The incidence of intracranial hemorrhage was as high as 1.3% in the TIMI-II trial, in which patients were treated with 150 mg of tPA. This was decreased to 0.4% when the dose of tPA was decreased to 100 mg; therefore, the larger dose of tPA is no longer used.

Although systemic hypertension is generally regarded as a significant risk factor in the development of an intracranial bleed following administration of thrombolytic agents, this has not been confirmed from the trials or general surveys. A multivariate logistic regression analysis found that only prior treatment with other anticoagulants, body weight < 70 kg, and age of more than 65 years were associated with a significantly greater incidence of intracerebral bleeding.

It was originally deemed that patients who had a cerebrovascular episode more than 6 months prior to the MI would be at low risk for an intracerebral bleed. When such patients were randomized to receive tPA in the TIMI study, the incidence of cerebral hemorrhage remained very high, at 3.4% compared with 0.5% in the later part of the trial when such patients were excluded.

There appears to be a small difference in hemorrhagic stroke according to the thrombolytic agent used. A significant difference in intracerebral bleeding was found in the ISIS-3 trial between patients who received tPA (0.7%) and those who received streptokinase (0.3%). This difference has been attributed to a higher dose of duteplase compared with a lower dose of tPA used today. In the GISSI-2 trial, the incidence of hemorrhagic stroke was 0.3% in the tPA group and 0.25% in patients receiving streptokinase. However, in the GUSTO trial, the incidence of hemorrhagic stroke was 0.7%, and significantly greater than 0.5% in patients receiving streptokinase. In patients older than 75 years, the incidence of hemorrhagic stroke was 2.08% in those treated with tPA, significantly greater than the 1.23% in the patients receiving streptokinase. Therefore, it may be more judicious to use streptokinase in very elderly patients presenting with AMI.

### Noncerebral Hemorrhage

Major noncerebral bleeds that require blood transfusion occurred more frequently in patients who received thrombolyis, with an excess of 7.3 per 1000 patients (1.1% in patients receiving thrombolyis and 0.4% in the patients in the control group).

### Treatment of Bleeding with Thrombolysis

Massive bleeding accompanied by hemodynamic compromise, particularly if the bleeding site is not compressible, should be treated with coagulation factors and volume replacement. If the patient is receiving heparin, it should be discontinued and protamine should be administered. In the absence of heparin therapy, a prolonged partial thromboplastin time will identify patients with a persistent fibrinolytic state. Such a patient should immediately receive 10 U of cryoprecipitate. The fibrinogen level should be monitored only after the cryoprecipitate has been given; if that level is < 100 mg/100 mL, the patient should receive an additional 10 U of cryoprecipitate. If bleeding persists after fibrinogen has been restored, 2 U of fresh frozen plasma should be given. If the bleeding continues to be uncontrolled, it is recommended that bleeding time be monitored. If this is longer than 9 minutes, the patient should receive 10 U of platelets; if the bleeding time is less than 9 minutes, it is suggested that the patient receive an antifibrinolytic agent such as aminocaproic acid.

### Myocardial Rupture

Myocardial rupture is a consequence of transmural myocardial necrosis and occurs in approximately 4% of patients admitted with AMI. It has been reasoned that early administration of thrombolytic therapy will reduce cardiac rupture by preventing transmural necrosis, whereas late thrombolysis, which promotes hemorrhage into a transmural MI, will increase the incidence of myocardial rupture. In a meta-analysis of placebo-controlled trials in which thrombolyis was administered to 1,638

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Control (%)</th>
<th>Thrombolytic (%)</th>
<th>Excess per 1000 (SD*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55</td>
<td>0.4</td>
<td>0.3</td>
<td>–1.7 (1.1)</td>
</tr>
<tr>
<td>55–64</td>
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<td>1.1</td>
<td>5.1 (1.5)</td>
</tr>
<tr>
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<td>4.8 (1.9)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>1.2</td>
<td>2.0</td>
<td>7.6 (3.7)</td>
</tr>
</tbody>
</table>

*Standard deviation.
patients, Honan et al. found that 58 patients had developed myocardial rupture. Regression-line analysis revealed that the incidence of myocardial rupture increased with the time interval between the onset of symptoms and the administration of the thrombolytic agent and that the odds ratio are > 1.0 of developing cardiac rupture when the thrombolytic agents are administered 11 hours after the onset of symptoms. However, in the prospective-designed LATE study, the incidence of myocardial rupture was greater with thrombolysis between 6 and 12 hours compared with 12 and 24 hours after the onset of symptoms. Therefore, it appears that the time course of rupture may be accelerated by thrombolysis but that the overall incidence may not be increased.

**Indications and Contraindications to Thrombolysis**

The indications for thrombolysis in patients with AMI are listed in Table 19-6 and the contraindications in Table 19-7. A more detailed discussion of the following items is provided in the earlier part of the text: time after MI, site of MI, non-Q-wave MI, cardiogenic shock, elderly patients, and hypertension. The distinction between absolute and relative contraindications to thrombolysis becomes less important when a cardiac catheterization laboratory is available for the performance of immediate coronary angioplasty.

**Thrombolysis for Conditions Other Than Acute Myocardial Infarction**

**Obstructive Mechanical Prosthetic Valve**

The incidence of thrombosis of mechanical mitral prostheses is greater than that observed with prostheses in the aortic position, with an annual incidence of < 0.5%. The operative mortality has been reported to be 11% to 12%, but it was significantly higher (17.5%) in patients with class IV New York Heart Association symptoms. Roudaut and colleagues describe successful thrombolysis in 73% of 75 thrombotic events, with a 92% success rate in patients with functional class I and II and 63% in patients with functional class III and IV symptoms. Embolic events occurred in 12 of the 64 patients; 4 of these were major. Thrombosis recurred in 11 patients in approximately 1 year. In a meta-analysis, thrombolysis was reported to be effective in 84% of cases, and streptokinase appeared to be more effective than urokinase.

Others have reported a very low rate of embolic events following thrombolysis in the presence of mobile thrombospases.

---

### Table 19-6. Criteria for Thrombolysis in Acute Myocardial Infarction

- Chest pain consistent with acute myocardial infarction lasting 30 min
- Electrocardiographic changes
- ST-segment elevation in at least two contiguous limb leads of 0.1 mV
  - $$V_1 - V_3$$ of 0.2 mV
  - $$V_4 - V_6$$ of 0.1 mV
- ST-segment depression in $$V_1 - 3$$ with tall R in $$V_2$$ with diagnosis of posterior infarction
- New or presumed new left bundle branch block
- Time from onset of symptoms:
  - < 6 h: most beneficial
  - 6–12 h: intermediate benefit
  - > 12 h: least benefit; consider if chest pain present or staggered pain course in high-risk patients

### Table 19-7. Contraindications to Thrombolytic Therapy

- **Absolute contraindications:**
  - Prior intracranial bleed
  - Thromboembolic stroke within 2 months
  - Neurosurgery within 1 month
  - Active internal bleeding (excluding menstruation)
  - Dissecting aortic aneurysm
- **Relative contraindications:**
  - Persistent hypertension ≥ 180/110 mm Hg despite therapy
  - Recent puncture of noncompressible vessel
  - Gastrointestinal and genitourinary bleeding within 1 month
  - Bleeding diathesis
  - Anticoagulant therapy
  - Significant liver and renal disease
  - Pericarditis
  - Proliferative diabetic retinopathy
  - Pregnancy
  - Recent surgery or biopsy of internal organ within 2 weeks
bi. However, most believe that a mobile thrombus is a relative contraindication to thrombolysis. Small clots (up to 5 to 10 mm) in patients can be treated with intravenous heparin or fibrinolysis. The risk of embolism is reported as a function of clot size.122

Successful thrombolysis is frequently achieved with 1 to 3 courses of a thrombolytic agent on a daily basis, using streptokinase 60,000 to 100,000 U/h over 16 to 24 hours or tPA with a 10-mg bolus followed by 90-mg infusion over 3 hours.123,124 It is advised that patients continue taking warfarin during thrombolysis and receive heparin until such time as the international normalized ratio is therapeutic. If the patient requires emergent surgery, it is advantageous to use tPA rather than streptokinase, as the latter is associated with a systemic thrombolytic state and depletion of thrombin.

It has been recommended that patients who have obstructed prostheses with minimal clot seen on transesophageal echocardiography should receive thrombolysis, which has an expected success rate of 92%.123,124 Surgery is also recommend for patients with large substantial clots or those who have class IV symptoms with obstructive prostheses. In the 2006 ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease, fibrinolytic therapy is recommended for patients with contraindication to surgery or in whom surgery risk is considered too high.125

### Pulmonary Embolism

In the Urokinase Pulmonary Embolism Trial (UPET) conducted in the early 1970s, in which urokinase followed by heparin was compared with heparin alone in a total of 160 patients, there was a trend toward reduction in mortality and recurrent emboli in patients assigned to receive thrombolysis.126 There was a significantly more rapid and complete dissolution of thrombi but also more bleeding complications in the patients receiving thrombolysis.

Unfortunately, the subsequent trials have utilized even fewer patients than in UPET. The Plasminogen Activator Italian Multicenter Study-2 (PAIMS-2) showed that thrombolysis produced a more efficient dissolution of thrombus and more rapid reduction in pulmonary arterial pressure following 2 hours of tPA infusion compared with heparin.127 When tPA was compared with urokinase in the European Cooperative Study Group, it was observed that there was a more significant and rapid reduction in pulmonary vascular resistance at 2 hours, but the outcomes were similar at 6 hours.128

In the series of trials carried out by Goldhaber et al.,129 it was shown that after tPA infusion there was significantly greater clot lysis after 2 hours when compared with urokinase administered over 24 hours; at 24 hours, however, there was no difference in clot lysis between these 2 groups.130 Similar efficacy resulted when a condensed dose of urokinase was administered.131 This group also demonstrated that there was significantly greater improvement in right ventricular systolic function as measured by echocardiography at 24 hours when tPA was administered compared with heparin.132,133 It has been shown that tPA administered via a pulmonary catheter or a peripheral vein resulted in similar rate of thrombolysis; thus thrombolytic agents did not have to be administered via a pulmonary catheter.134

The use of heparin and a thrombolytic agent were compared in a report from a multiple-center registry of 719 consecutive patients with major pulmonary embolism and specifically excluded patients who were hemodynamically unstable.135 The mortality rate was 4.7% for 169 patients receiving thrombolytic treatment, whereas it was 11.1% for 555 patients receiving heparin. Although the groups were not similar, multivariate logistic regression analysis demonstrated that thrombolytic treatment was an independent predictor of survival. The patients receiving thrombolysis had a significantly higher rate of major hemorrhage: 21.9% versus 7.8% of patients receiving heparin. Only 1.2% of the patients receiving thrombolysis developed intracranial hemorrhage.135

A meta-analysis of 9 trials in which 461 patients were randomized to receive either a thrombolytic agent followed by heparin or heparin alone, showed no statistical difference in mortality.136 Patients in shock were excluded. Major hemorrhage occurred statistically more frequently in patients receiving thrombolytic therapy (13.7%) than in patients receiving heparin alone (7.7%). However, a subsequent meta-analysis that included 748 randomized patients reported a nonsignificant increase in major bleeding.137

Konstantinides138 reported on one of the larger single pulmonary embolism trials with 256 patients with pulmonary hypertension or right ventricular dysfunction but not shock. Although there was no difference in mortality in the patients receiving tPA compared with those receiving heparin, the thrombolysed patients were less likely to deteriorate and require catecholamine infusion, intubation, or resuscitation (10.2%) versus the heparin group (24.6%).

It has now become accepted practice to treat massive pulmonary embolism associated with hemodynamic instability with thrombolysis. The presence of right ventricular dysfunction seen on echocardiography is also considered an indication for thrombolysis.138

Regimens approved by the US Food and Drug Administration (FDA) for the treatment of pulmonary embolism are as follows: streptokinase 250,000 U loading dose over 30 minutes followed by 100,000 U/h for 24 hours and tPA 100 mg over 2 hours. A recent study suggested that lower tPA doses can be given which preserve efficacy with less
bleeding. It is recommended that heparin not be given simultaneously with a thrombolytic agent.

Ischemic Stroke

The use of thrombolytic agents in the treatment of ischemic stroke no longer remains controversial (see Chapter 33, Drug Therapy of Cerebrovascular Disease). Earlier studies using streptokinase were prematurely stopped because of excessive intracranial hemorrhage or because treatment was of no benefit when tPA was used. These trials treated patients up to 6 hours after the onset of stroke. In the subsequent National Institute of Neurological Disorders and Stroke (NINDS) study, 624 patients were randomized to receive tPA or the placebo within 3 hours after the onset of stroke after a computed tomographic scan had excluded intracranial hemorrhage. In patients who received thrombolysis, 38% had minimal or no disability at 3 months compared with 21% of patients in the placebo arm. A subsequent study confirmed the efficacy and safety of tPA when used within 3 hours. The more recent ECASS 3 (European Cooperative Acute Stroke Study) trial evaluated 820 patients younger than 80 years within 3 to 4½ hours of stroke onset. The outcome at 3 months, assessed on the Rankin scale, was significantly improved in those patients receiving tPA compared with the placebo (52% versus 45%). In both of these studies, there was a significantly greater incidence of intracerebral hemorrhage in the patients receiving thrombolysis (6.4% and 7.9%) compared with the placebo (0.6% and 3.5%), but a similar mortality was reported. A meta-analysis published prior to ECASS 3 showed there was no benefit in thrombolysis after 4½ hours.

Thrombolysis with intravenous tPA is now accepted treatment when administered within 3 hours of the onset of nonhemorrhagic ischemic stroke, with some consideration for its administration in the time window up to 4½ hours after onset of symptoms. The only thrombolytic approved for this use in the United States is tPA. The dose for intravenous administration is 0.9 mg/kg with a maximum of 90 mg. The addition of heparin or low-molecular-weight heparin has not been shown to be beneficial and is currently not recommended. Aspirin may be given in an initial dose of 325 mg after 24 to 48 hours to prevent recurrence of thrombosis.

Intra-arterial pro-urokinase has been used within 6 hours of the onset of middle cerebral artery occlusion with resultant arterial recanalization in 66% of patients compared to 18% of controls and is associated with an improved neurological deficit. This agent is not approved for this use, nor is it available in the United States. Success with intra-arterial tPA has been reported.

Deep Venous Thrombosis

Standard treatment of deep venous thrombosis with heparin reduces the extension and embolization of thrombus but does not increase the rate of clot lysis. Therefore, permanent damage to the venous valvular system may ensue with a resultant postthrombotic syndrome of pain, edema, stasis, and dermatitis.

Faster resolution of deep venous thrombosis has been reported with the use of streptokinase, urokinase, and tPA, with approximately 45% complete resolution using a thrombolytic agent compared to 4% with heparin. Complete lysis of thrombus may require several days of treatment and is less successful for older thrombi, particularly those beyond 7 days. However, using selective catheter infusion of a thrombolytic agent may improve the rate of thrombolysis. Systemically administered thrombolytic agents have resulted in higher recanalization and a lower incidence of postthrombotic syndrome when compared to heparin. Because of a 6% rate of major bleeding complications, its use is advised only in patients with limb-threatening situations. A recent review recommended catheter-directed thrombolysis for patients with extensive acute (less than 14 days) proximal deep vein thrombosis, eg, iliofemoral vein syndrome.

Subclavian and axillary venous thromboses have been successfully treated with direct infusion of thrombolytic agents into the distal vein, and thrombectomy has generally been avoided. Those patients with primary thrombosis of the subclavian or axillary veins may require additional surgery to correct thoracic outlet syndrome.

The doses of thrombolytics used are as follows: streptokinase 2500 U bolus, followed by 100,000 U/h for up to 3 days; streptokinase 3 million U over 4 hours; tPA 0.05 mg/kg/h for 8 to 24 hours (for local or regional infusion of tPA 20 mg/day).

Thrombotic Arterial Occlusion

Patients with acute arterial occlusion of the lower limbs and pelvis are potential candidates for intra-arterial infusion of thrombolytic agents. With acute ischemia that threatens the viability of the limb, surgery should be the primary consideration, and thrombolysis should be considered only if surgery is not feasible or the limb is not threatened. Thrombolytic therapy should be infused by an intra-arterially directed catheter into the occluded artery. This has been successfully performed using streptokinase, urokinase, and tPA and has resulted in fewer lower limb amputations and a significant increase in clot lysis and recanalization. Thrombolytic artery occlusion therapy has also been used as a treatment for mesenteric thrombosis.
A consensus statement indicated that catheter-directed thrombolysis was more likely to be superior to surgery if the guidewire could pass through the thrombus, the occlusion were < 14 days old, the occlusion was thrombotic rather than embolic, and significant comorbid cardiopulmonary disease coexisted.\textsuperscript{161} Arterial emboli are better removed by balloon catheter techniques or surgery, since thrombolysis in such instances has not been as successful.

A meta-analysis of 5 prospective randomized trials comparing the outcome with thrombolysis and surgery demonstrated a similar mortality and amputation rate, but thrombolysis resulted in more distal embolization and hemorrhage.\textsuperscript{162}

In reviewing the data from numerous studies, there was no convincing evidence of superiority in efficacy or safety of any agent for catheter-directed thrombolysis.

The dose of catheter-directed thrombolytic agent used tPA 0.5 to 0.1 mg/kg/h for up to 12 hours.

**Conclusion**

Thrombolysis has been shown to be an effective mode of treatment for AMI associated with ST-segment elevation. It should be accompanied with the appropriate adjunctive therapy, followed with routine early cardiac catheterization, and if necessary, angioplasty. However, thrombolysis is being increasingly replaced by primary angioplasty, which has been shown to be generally more effective and less hazardous. Recent studies have reported equivalent outcomes in patients receiving prehospital thrombolysis within 2 or 3 hours of symptom onset. TNK tPA has become the thrombolytic agent of choice because of the ease of administration with a single bolus and less chance of error in dosage.

*Note: References for this chapter can be found here: www.cvpct3.com*
A direct relationship between elevated serum cholesterol levels, especially elevated low-density-lipoprotein (LDL) cholesterol levels, and the incidence of coronary artery disease (CAD) has been well established. The lowering of LDL cholesterol levels by means of diet and/or drug therapy has also been shown to reduce the progression of coronary artery lesions (Figure 20-1) and the incidence of clinical coronary artery events. As predicted from the Framingham Study, a 10% decrease in cholesterol levels is associated with a 20% decrease in the incidence of combined morbidity and mortality related to CAD. Elevations in triglycerides and reductions in high-density-lipoprotein (HDL) cholesterol levels may also contribute to an increased CAD risk.

Advances in the understanding of lipid metabolism and the development of new drugs and dietary strategies for the treatment of lipid and lipoprotein disorders have made effective therapy of hyperlipidemia, and thus CAD risk intervention, an understandable and attainable goal.

Gould et al performed a meta-analysis of 35 randomized trials and assessed the relation of cholesterol lowering to benefit or harm as well as the effects of specific drug regimens on clinical outcomes such as CAD mortality, noncoronary mortality, and total mortality. The authors concluded that for every 10 mg/dL of cholesterol lowering, coronary disease mortality was reduced significantly by 13% and total mortality by 10%. Cholesterol lowering per se had no effect on noncoronary mortality. Their analysis also indicated that fibric acid derivatives increased noncoronary mortality by 30% and total mortality by 17%. Hormones such as estrogen and d-thyroxine, which patients were given in the past, may have increased coronary disease mortality in men by about 27%, noncoronary mortality by 55%, and total mortality by 33%. Other interventions—such as niacin, resins, statins, diet, and partial ileal bypass—had no specific adverse effects.

Figure 20-1. Arteriographic CAD regression trials. The percentage of subjects classified as regression are to the left, and those classified as progression are to the right. The control groups are listed on top of the figure, and the treatment groups are on the bottom.

In the following introductory section, a framework for understanding the treatment of lipid disorders is presented. Recommendations are provided—based on the third expert panel report of the National Cholesterol Education Program (NCEP)—regarding screening and dietary and drug interventions in human populations with hyperlipidemia at risk for premature CAD.

**Rationale for the Treatment of Hyperlipidemia in Prevention of CAD**

The basis for the treatment of hyperlipidemia is the theory that abnormalities in lipid and lipoprotein levels are risk factors for CAD and that the lowering of blood lipids can decrease the risk of disease and its complications. Levels of plasma cholesterol and LDL cholesterol have consistently been shown to be directly correlated with the risk of CAD.

The results of the clinical trials with cholesterol and LDL cholesterol-lowering interventions support the premise that most cholesterol-lowering therapies aimed at reducing cholesterol by at least 20% to 25% produce clinically significant reductions in cardiovascular events in patients having pre-existing vascular disease across a broad range of cholesterol values within 5 years of starting treatment. The greatest impact of cholesterol lowering still occurs in individuals with the highest baseline cholesterol levels. The absolute magnitude of these benefits would be even greater in those individuals manifesting other risk factors for CAD, such as cigarette smoking and hypertension. These risk relationships are the basis for recommending lower cholesterol cut points and goals for those who are at high risk for developing clinical CAD.

The Heart Protection Study randomized 20,536 men and women (5,806 of whom were aged 70 to 80 years) with prior myocardial infarction (MI) (8,510 participants); other CAD (4,876 participants); and no CAD (7,150 participants) and a serum total cholesterol level of 135 mg/dL or higher to simvastatin 40 mg daily or to the placebo. Of the 7,150 participants without CAD, 25% of the participants had diabetes mellitus, and 3% had only treated hypertension without atherosclerotic vascular disease or diabetes mellitus. At 5-year follow-up, simvastatin significantly reduced all-cause mortality by 13%, any cardiovascular death by 17%, major coronary events by 27%, any stroke by 25%, coronary or non-coronary revascularization by 24%, and any major cardiovascular event by 24% compared to the placebo. These significant decreases in mortality and in cardiovascular events occurred regardless of initial levels of serum lipids, age, or gender. First major cardiovascular event was significantly lowered by simvastatin by 24% in participants younger than 65 years, by 23% in participants aged 65 to 69 years, and by 18% in participants aged 70 to 80 years at study entry. Five years of simvastatin treatment prevented MI, stroke, and revascularization in 70 to 100 persons per 1,000 treated persons.

In the Heart Protection Study, 3,500 participants had initial serum LDL cholesterol levels less than 100 mg/dL. Lowering of serum LDL cholesterol from 97 mg/dL to 65 mg/dL by simvastatin in these participants who would not be treated according to NCEP III guidelines caused a similar reduction in risk, as did treating patients with higher serum LDL cholesterol levels. The Heart Protection Study Investigators recommended treating persons at high risk for cardiovascular events with statins, regardless of the initial levels of serum lipids, age, or gender.

Thus, taking into consideration the recommendations of the NCEP and data from recently published trials, 2 general groups of patients that warrant aggressive therapy for hypercholesterolemia can be identified: (1) those without evidence of CAD who are at high risk for developing CAD (primary prevention, target LDL < 130 mg/dL) and (2) those with known CAD or other atherosclerotic processes and high cholesterol (secondary prevention, target LDL < 100 mg/dL). Patients with lesser degrees of risk are treated to less aggressive LDL targets (< 160 mg/dL). These guidelines have also identified a fourth group whose risk factors mark them as having a “coronary risk equivalent.” Such patients are treated in accordance with the aggressive goals recommended for known CAD (now all atherosclerotic disease). The most important category is diabetes mellitus, but—due to the important influence of age on coronary risk—many older individuals with other risk factors also meet current criteria for treatment to the target of < 100 mg/dL LDL.

Recommendations for the treatment of elevated triglycerides are less definitive. Several prospective studies have shown a correlation between levels of plasma triglycerides and CAD. Data from the Framingham Study, however, have indicated that when other risk factors—such as obesity, elevated serum cholesterol (or hypercholesterolemia), hypertension, and diabetes mellitus—are accounted for, triglycerides are not a potent independent risk factor for CAD. However, there is a select group of patients with isolated hypertriglyceridemia who are at increased risk of CAD and who can be identified by a strong family history of premature CAD. It should be kept in mind that, to some extent, the epidemiologic studies evaluating the independent risk associated with hypertriglyceridemia have been exercises of little relevance to clinical decision making. Clearly, one adjusts for some of the risk factors that are causes of hypertriglyceridemia (obesity, diabetes mellitus, lack of exercise, minimal dietary fiber, family history, etc.), risks associated with the correlates of hypertriglyceridemia...
(other manifestations of the insulin-resistance syndrome, such as hypertension) and the risks associated with the consequences of hypertriglyceridemia (low HDL, small dense LDL), then little measurable risk will remain. However, hypertriglyceridemia is a valuable marker of the insulin resistance syndrome, and therapy addressed at the bases of that syndrome will benefit all the causes and correlates of hypertriglyceridemia. In addition, the level of plasma triglycerides is a primary determinant of the level of HDL, the most potent predictor of the risk of atherosclerotic disease; the 2 measurements exhibit a strong inverse correlation.

In general, the direction of causation is clearly that of the level of triglycerides determining the level of HDL, and most therapies that raise the level of HDL are, in fact, directed at modifying triglyceride metabolism. Therefore, whether triglycerides or HDL are the more important element in the physiologic mediation of atherosclerotic risk cannot be determined from either epidemiologic studies or intervention trials. HDL is the more potent statistical predictor, but this is likely due to “ascertainment bias.” Triglyceride levels are quite variable, while HDL levels are fairly stable, leading to greater predictive value for the HDL measurement. In part, this is likely due only to its being a more accurately ascertained surrogate for the level of plasma triglycerides. There is now evidence that by lowering triglyceride levels or raising HDL levels (or both), the risk of CAD will be diminished. The Veterans Affairs Low HDL Intervention Trial (VA-HIT), showed a significant reduction in coronary events in otherwise high-risk patients with normal LDL levels associated with the use of an agent (gemfibrozil) that markedly lowered triglycerides and modestly raised HDL but had no effect on the level of LDL. However, similar benefit was not observed in another trial that used a related drug (Bezafibrate Infarction Prevention Study [BIP]).

While CAD is the most important clinical manifestation of atherosclerosis, it bears emphasis that lipid-lowering therapy has been shown to decrease the incidence of all atherosclerotic diseases. Comprehensive meta-analyses of the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor trials have specifically confirmed the value of these agents in preventing stroke in hyperlipidemic subjects.

**Risk Assessment**

For many years, clinicians depended on total cholesterol and triglyceride measurements for patient management. More sophisticated lipoprotein measurements were available only in research facilities. Methodologic advances have made lipoprotein subclass and apolipoprotein determinations available from many clinical laboratories. As a result, LDL cholesterol has been shown to be a more accurate predictor of CAD risk than total cholesterol. Likewise, low levels of HDL cholesterol have been demonstrated to be more powerful predictors of CAD than elevated total cholesterol. Levels of plasma lipoprotein(a), apolipoproteins A-I (Apo A-I) and B (Apo B), and the distribution of HDL subfractions (HDL2 and HDL3) are also accurate univariate predictors of CAD risk. However, in most cases, these measurements contribute little to the assessment of coronary risk provided by LDL, HDL, and triglyceride. Mean serum cholesterol and calculated LDL cholesterol values for various population groups have been reported and document a progressive decline in plasma cholesterol in the United States; this is consistent with the decreased mortality from atherosclerotic disease that has been observed simultaneously. A number of nonlipid measurements (homocysteine and a variety of inflammatory markers, including C-reactive protein), can also contribute to the assessment of coronary risk. Only C-reactive protein, as measured by the high-sensitivity assay, appears to provide significant prediction independent of the traditional lipid risk factors.

**Who Should Be Screened for Hyperlipidemia?**

The Third Report of the NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults continues to suggest that total cholesterol be measured in all adults 20 years of age and older at least once every 5 years. A controversy was raised when the American College of Physicians recommended only general cholesterol screening for middle-aged men—an approach that was vigorously challenged and did not receive acceptance. An NCEP panel recommended that cholesterol screening should not be done routinely in children unless there was a history of familial hyperlipidemia or a family history of premature CAD. Cholesterol values in the general pediatric population may not always predict the future development of hypercholesterolemia in adults.

**Who Should Be Treated for Hypercholesterolemia?**

Ideally, a fasting lipid profile (total cholesterol, HDL cholesterol, total triglycerides, calculated LDL) should be obtained in all cases. If this is not practicable, then screening cholesterol and HDL values should be obtained (Table 20–1). A total cholesterol above 200 mg/dL or an HDL cholesterol below 40 mg/dL mandates obtaining a fasting lipid profile. The presence of a high cholesterol should always be confirmed with a second lipid profile to make a more precise estimate of CAD risk. The standard deviation of repeated measurements in an individual over time...
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has been reported as 0.39 mm/L (15 mg/dL) for total cholesterol and 0.39 mm/L (15 mg/dL) for LDL cholesterol. Patients should be maintained on the same diet during these initial determinations before therapy is instituted. Secondary causes of hypercholesterolemia (hypothyroidism, nephrotic syndrome, diabetes mellitus) should also be considered.48

The NCEP recommends an approach in adults based on LDL cholesterol, which is shown in Tables 20–2 and 20–3. In most cases, management should begin with dietary intervention. When the response to diet is inadequate or when the target LDL is unlikely to be achieved by diet alone, the addition of pharmacologic therapy is recommended. Specific drug therapies are discussed in subsequent sections of this chapter.

The updated NCEP III guidelines state that in very high-risk persons, a serum LDL cholesterol level of < 70 mg/dl is a reasonable clinical strategy.72 When a high-risk person has hypertriglyceridemia or low HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol-lowering drug. For moderately high-risk persons (2 or more risk factors and a 10-year risk of 10% to 20% for CAD), the serum LDL cholesterol should be reduced to < 100 mg/dl. When LDL cholesterol-lowering drug therapy is used to treat high-risk persons or moderately high-risk persons, the serum LDL cholesterol should be reduced at least 30% to 40%. The authors concur with these updated guidelines. The serum LDL cholesterol should be reduced to < 160 mg/dl in persons at low risk for CAD. The authors would not treat older persons with life-threatening illness causing limited life expectancy or advanced dementia with lipid-lowering therapy.

Who Should Be Treated for Hypertriglyceridemia?

Interest in the link between serum triglyceride levels and CAD has grown in recent years.73-76 Triglyceride levels correlate positively with levels of LDL cholesterol77 and inversely with HDL.58 Clinical trials with the triglyceride-lowering drugs, nicotinic acid,8 and gemfibrozil9,52 have shown a benefit on the frequency of coronary artery events compared with the placebo therapy. However, therapy in these trials was not targeted to patients with primary hypertriglyceridemia. The currently recommended approach to the problem of hypertriglyceridemia is presented in the report of the NCEP.48

Normal triglycerides are defined as < 150 mg/dL, borderline high triglycerides as 150 to 199 mg/dL, high

Table 20-1. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
<th>Total Cholesterol</th>
<th>HDL Cholesterol</th>
</tr>
</thead>
<tbody>
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<td>&lt; 100</td>
<td>&lt; 200</td>
<td>&lt; 40</td>
</tr>
<tr>
<td>100–129</td>
<td>200–239</td>
<td>≥ 60</td>
</tr>
<tr>
<td>103–159</td>
<td></td>
<td></td>
</tr>
<tr>
<td>160–189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>Desirable</td>
<td>Low</td>
</tr>
<tr>
<td>Near or above optimal</td>
<td>Borderline high</td>
<td></td>
</tr>
<tr>
<td>Borderline high</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 20-2. LDL Goals, Cutpoints for Therapeutic Lifestyle Changes (TLC), and Drug Therapy in Different Risk Categories

<table>
<thead>
<tr>
<th>Therapy Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>Initiate Lifestyle Changes</th>
<th>Initiate Drug Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalents (10 yr risk &gt; 20%)</td>
<td>&lt; 100</td>
<td>≥ 100</td>
<td>≥ 130</td>
</tr>
<tr>
<td>2+ Risk factors (10 yr risk ≤20%)</td>
<td>&lt; 130</td>
<td>≥ 130</td>
<td>10 yr risk 10%–20% ≥ 130</td>
</tr>
<tr>
<td>0–1 Risk factor</td>
<td>&lt; 160</td>
<td>≤ 160</td>
<td>≥ 190 (160–189: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

triglycerides as 200 to 499 mg/dL, and very high triglycerides as > 500 mg/dL. Most hypertriglyceridemia up to 5.65 mm/L (500 mg/dL) is primarily due to insulin resistance related to the “metabolic syndrome.” Criteria for the diagnosis of this syndrome are shown in Table 20-4. Common contributors to this syndrome include obesity (body mass index [BMI] > 30 kg/m²); overweight (BMI > 25 kg/m²); physical inactivity; excessive alcohol consumption; and high consumption of low-fiber carbohydrate sources (> 60% of total energy). Other contributors to hypertriglyceridemia may include diabetes mellitus; hypothyroidism; marked obesity; chronic renal disease (failure or nephrotic syndrome); and certain drugs (glucocorticoids, estrogens, retinoids, and higher doses of either beta-adrenergic blocking agents or thiazide diuretics). Weight loss, exercise, dietary change (decreased saturated fat, increased omega-3 unsaturated oils, increased dietary fiber), reduction/elimination of triglyceride-raising drugs, and/or treatment of the primary disease process (eg, improved glycemic control of diabetes mellitus) may be sufficient to reduce triglycerides.

Patients with familial combined hyperlipoproteinemia often have associated hypertriglyceridemia. Patients with this condition are at risk for premature CAD. These patients should have dietary treatment first and, if necessary, drugs. Patients with borderline hypertriglyceridemia with clinical manifestations of CAD can be treated as if they had combined hyperlipoproteinemia, with lifestyle, LDL-lowering, and triglyceride-lowering therapies.

Table 20-3. Major Risk Factors (Exclusive of LDL Cholesterol) that Modify LDL Goals

- Cigarette smoking
- Hypertension (BP ≥ 140/90 mm Hg or on antihypertensive medication)
- Low HDL cholesterol (< 40 mg/dL)
- Family history of premature CAD
- CAD in male first degree relative < 55 years
- CAD in female first degree relative < 65 years
- Age (men ≥45 years; women ≥ 55 years)
- Diabetes (fasting glucose ≥ 127 mg/dL) in and of itself mandates an LDL goal of < 100 mg/dL

HDL cholesterol ≥ 60 mg/dL counts as a “negative” risk factor; its presence removes 1 risk factor from the total count.


Table 20-4. Clinical Identification of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity* (waist circumference†)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt; 102 cm (&gt; 40 in.)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt; 88 cm (&gt; 35 in.)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt; 150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&gt; 130/ &gt; 85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>&gt; 110 mg/dL</td>
</tr>
</tbody>
</table>

* Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated BMI. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.
† Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, eg, 94-102 cm (37-40 in). Such patients may have a strong genetic contribution to insulin resistance; they should benefit from changes in life habits, like men with categorical increases in waist circumference.


Approach to Low Serum HDL Cholesterol

A low serum HDL cholesterol level is a strong lipoprotein predictor of CAD. In one prospective study, after adjustment for other risk factors in predicting the risk of MI, a change in 1 unit in the ratio of total to HDL cholesterol was associated with a 53% change in risk. However, it is still unclear how low HDL levels are linked to CAD. A recent trial of combined LDL-lowering and HDL-raising therapy showed benefit well beyond that anticipated from LDL lowering alone. HDL metabolism is complex, and the utility of interventions to raise HDL will likely depend on the specific HDL-raising pathway that is targeted. The major causes of reduced serum HDL cholesterol are listed in Table 20-5. Clearly, attempts should be
made to raise low HDL cholesterol by hygienic means. When a low HDL is associated with an increase in plasma triglycerides, as is typically the case, the latter deserves consideration for therapeutic modification. However, when the HDL is reduced without hypertriglyceridemia or other associated risk factors, the utility of raising low HDL levels by drugs for primary prevention has not been adequately addressed in clinical trials.

Special Problems

Diabetes Mellitus

The frequency of lipid abnormalities and the increased risk of CAD in diabetes mellitus have long been recognized. Prospective intervention studies in diabetic patients have demonstrated that the improvement of LDL with fenofibrate is associated with a reduced risk of morbidity and mortality from atherosclerosis. In addition post hoc analyses of all the major statin trials and of the VA-HIT gemfibrozil trial have documented benefits that, on a percentage basis, are at least equal to those achieved in nondiabetic high-risk patients. Of note, despite the large difference in incidence rates at younger ages because of the greater life expectancy of women, the contribution of atherosclerotic disease to total mortality is only modestly less in women than in men. The role of postmenopausal estrogen replacement therapy remains controversial, despite the advantages suggested by the earlier observational literature and the apparently beneficial effects on the lipid profile.

Gender

Most clinical trials examining the effect of lipid-lowering therapy on the incidence of CAD have examined middle-aged males, owing to ease of recruitment in secondary prevention studies and increased statistical power in primary prevention studies. The rates of CAD are 4 times higher in middle-aged men than in women and 2 times higher in elderly men. However, epidemiologic evidence supports a dyslipidemia-associated increase in risk similar to that in men and a similar approach to lifestyle, dietary, and/or drug therapy. Such an approach is supported by the findings in those clinical trials that have included significant numbers of women. Of note, despite the large difference in incidence rates at younger ages because of the greater life expectancy of women, the contribution of atherosclerotic disease to total mortality is only modestly less in women than in men. The role of postmenopausal estrogen replacement therapy remains controversial, despite the advantages suggested by the earlier observational literature and the apparently beneficial effects on the lipid profile.

Age

Children and Adolescents

The NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents recommends the selective
screening (in the context of regular health care of children and adolescents) who have a family history of premature cardiovascular disease or at least 1 parent with high cholesterol.\textsuperscript{102} In children and adolescents from families with hypercholesterolemia or premature CAD, the NCEP established the following classifications for total cholesterol and LDL cholesterol values. For total cholesterol, desirable levels are $< 4.40$ mmol/L ($< 170$ mg/dL); borderline levels 4.40 to 5.09 mm/L (170 to 199 mg/dL); and high levels $> 5.17$ mm/L ($> 200$ mg/dL) (Figure 20-2).\textsuperscript{62} For LDL cholesterol, desirable levels are $< 2.84$ mm/L ($< 110$ mg/dL); borderline levels are 2.84 to 3.34 mm/L (110 to 129 mg/dL); and high levels are $> 3.36$ mm/L ($> 130$ mg dL).\textsuperscript{102}

For young individuals being screened because they have a parent with high cholesterol, the initial test may be measurement of total cholesterol. If the child’s or adolescent’s total cholesterol is high, a lipoprotein profile should be done.\textsuperscript{102} If the total cholesterol level is borderline, a second measurement of total cholesterol should be taken, and if the average is borderline or high, a lipoprotein profile should be performed (Figure 20-2). For young individuals being tested due to a documented history of premature atherosclerotic disease, a lipoprotein profile should, of course, be performed.\textsuperscript{102}

Once the lipoprotein analysis has been obtained, it should be repeated to determine the average LDL cholesterol level. The NCEP, as with adults, recommends a management approach to children and adolescents that is primarily based on LDL cholesterol (Figure 20-3).

Dietary therapy is the primary approach to treating children and adolescents with elevated blood cholesterol (Figure 20-4).\textsuperscript{102} Drug therapy is recommended in children aged 10 or older if the LDL cholesterol remains above 4.91 mm/L (190 mg/dL) or if the LDL cholesterol remains $> 4.14$ mm/L ($> 160$ mg/dL) and there are other cardiovascular risk factors present in the child or adolescent that cannot be controlled.\textsuperscript{102} At the time these guidelines were issued, until longer-term safety data with other lipid-lowering drugs become available, the NCEP was comfortable recommending only bile acid sequestrants as drug therapy.\textsuperscript{102} However, in boys and postmenarchal girls aged 10 to 17 with heterozygous familial hypercholesterolemia, simvastatin, atorvastatin, fluvastatin, lovastatin, and pravastatin are approved for reducing total cholesterol, LDL cholesterol, and Apo B after failing an
adequate trial of diet therapy. Clearly, in those rare children with homozygous familial hypercholesterolemia or with premature atherosclerotic disease due to severe heterozygous familial hypercholesterolemia, all therapies may be considered.

The Elderly

Increasing age in itself is a potent risk factor for CAD. As a consequence, a progressively declining fraction of the risk for CAD can be attributed to dyslipidemia. Nevertheless, while individuals older than 70 years have not been carefully examined, there has been no evidence of a significant age-related decline in the effectiveness of lipid-lowering therapy in preventing cardiovascular endpoints in the available clinical studies that included older individuals. Since the absolute risk of CAD increases with age and the benefits of lipid-lowering therapy are already evident after a year of therapy, a strong rationale emerges for the continued aggressive use of lipid-lowering therapy in the elderly.

To cite an illustrative example: the Framingham algorithm incorporated into the third edition of the NCEP guidelines mandates a target LDL of < 100 mg/dL for individuals whose risk is considered equivalent to that of known CAD. Such individuals who are male will have 15 or more “points” after applying the algorithm to their risk factor profile (23 for females). However, the algorithm assigns 13 points to men (and 16 to women) simply for an age between 75 and 79.

Systemic Hypertension

A report from the Working Group on Management of Patients with Hypertension and High Blood Cholesterol emphasizes the synergistic effects of hypertension and hypercholesterolemia on the risk of developing cardiovascular disease. Hypertension is more than randomly associated with dyslipidemia, since both conditions are commonly manifestations of the insulin resistance syndrome. In this regard, hypertension serves both as a cause of atherosclerotic disease and a marker of insulin resistance. In part because of this association, the risk associated with hypertension is not completely mitigated by good blood pressure control, and the NCEP guidelines continue to count hypertension as a risk factor even in patients under good pharmacologic control. Nonpharmacologic therapy—in the form of proper diet, exercise, and smoking cessation—is the foundation for the management of both hypertension and high cholesterol. Clinicians should use these nondrug measures as definitive or adjunctive therapy. The achievement of control using these strategies would lead to the elimination of hypertension as a factor to be considered in risk analyses. Pharmacologic agents can also be very beneficial in managing the risks. In selecting medications, it is important to consider benefits, costs, and potential untoward effects. A drug formulation is available that combines atorvastatin with amlodipine to treat both hypercholesterolemia and hypertension.

Myocardial Infarction

The post–MI setting is the paradigm of known atherosclerotic disease. Virtually all such patients require aggressive lipid lowering with the maintenance of LDL cholesterol < 100 mg/dL. All patients with known CAD should have a fasting lipoprotein analysis. If this is not accomplished promptly (within a few hours of presentation), the measured cholesterol levels will be artifactually depressed by the acute-phase response. Under these circumstances, the initial dosage of lipid-lowering therapy may have to be empiric, with the dosage adjusted subsequently based on the levels at least 3 months after the acute event, at which point the effects of the acute-phase response will have substantially resolved. The value of the immediate institution of high-dose LDL-lowering therapy in the setting of acute MI is an area of controversy. An observational study adjusted for possible confounders found a significantly lower incidence of short-term (30-day and 6-month) mortality in individuals discharged on lipid-lowering therapy. A randomized trial of high-dose (80 mg) atorvastatin after presentation with acute non-Q-wave MI or unstable angina pectoris found a significant decrease in rehospitalizations for ischemia within 16 weeks and a decrease in complicating stroke without any difference in death, recurrent MI, or heart failure.

Aggressive lipid-lowering therapy results in a marked reduction of cardiovascular thrombotic events with only minimal change in the size of the coronary artery plaque, but exactly how this happens is still uncertain. Once a plaque develops, it may remain stable for long periods of time. What triggers acute ischemic syndromes such as MI or unstable angina is the development of lesion instability. An unstable lesion has an increased tendency to rupture or crack, leading to exposure of the highly thrombogenic interior, with superimposed thrombosis and thereafter acute ischemic syndromes. Several studies have suggested that the lipid content of a plaque correlates with the risk of a subsequent rupture. Most commonly, the crack occurs at the junction of the plaque and the normal intima. Progressive accumulation of lipids appears to promote macrophage accumulation, which destabilizes the plaque, leading to thinning and destruction of the fibrous cap and resulting in rupture at points of high pressure. Thus, it has been suggested that limiting the lipid pool of the atherosclerotic plaque may prevent plaque thinning and facilitate the conversion of an unstable, vulnerable plaque to a stable one. Changes in plaque composition that predict vulnerability are not detectable by coronary angiography but have been shown to...
be detectable by specialized cardiac magnetic resonance imaging techniques. It is well established that atherosclerosis and hypercholesterolemia are associated with endothelial cell dysfunction, which may play a part in the pathogenesis of acute ischemic syndromes via an increased tendency to vasospasm and decreased secretion of prostaglandins, which suppress platelet aggregation. An important mediator of normal endothelial function is nitric oxide, which is released continuously, maintaining vascular tone and preventing platelet and leukocyte adhesion. Hypercholesterolemia and coronary atherosclerosis have been shown to impair nitric oxide release, whereas aggressive lipid lowering can improve nitric oxide–mediated responses. This likely represents an additional mechanism by which cholesterol reduction reduces the risk of MI.

**Coronary Artery Bypass Grafts**

In an important observational study, investigators at the Montreal Heart Institute performed angiography 1 and 10 years after surgery to determine the patency of vein grafts in 82 patients who had undergone saphenous vein bypass surgery. The 10-year examination confirmed that atherosclerotic changes are common in saphenous vein bypass grafts. At that time only 50 (37.5%) of 132 grafts that were patent at the 1-year examination showed no change at the 10-year examination, whereas evidence of atherosclerosis was found in 43 (33%) and complete occlusion in 30 (29.5%). Progressive atherosclerosis was identified as the single most important cause of occlusion in these grafts. When the investigators analyzed the relationship between cardiovascular risk factors and the development of atherosclerosis, they found no significant difference for smoking, hypertension, or diabetes mellitus between the group that developed disease and the group that did not. However, in a multivariate analysis, it was revealed that low HDL cholesterol, high LDL cholesterol, and high Apo B were the most significant predictors of atherosclerotic disease in grafts. Almost 80% of those who did not develop disease had normal lipid levels and normal LDL and Apo B levels, in contrast to 8% of patients who developed disease.

There is now evidence that aggressive dietary and LDL-lowering drug therapy with niacin/colestipol and with the hydroxymethylglutaryl (HMG)-CoA reductase inhibitors lovastatin and atorvastatin can slow down, arrest, and even reverse atherosclerotic disease in patients with saphenous vein coronary bypass grafts. Detailed lipoprotein analysis of the patients in the study using lovastatin indicated that the beneficial effects were achieved, as expected, by LDL lowering and not via effects on triglyceride-rich lipoproteins and HDL. However, a similar trial that used a triglyceride-lowering agent (gemfibrozil) in patients who have had coronary artery bypass grafts with low HDL also showed a beneficial effect on atherosclerosis progression. Of note, internal thoracic artery and other arterial grafts have a significantly lower rate of atherosclerosis than saphenous vein grafts and are now performed whenever it is feasible.

**Coronary Angioplasty**

Restenosis after successful isolated coronary angioplasty has been observed in 25% to 40% of patients undergoing this procedure. This incidence has been significantly reduced by the routine use of coronary stenting, but the problem of restenosis has not been eliminated. Attempts have been made to decrease the incidence of restenosis using a wide array of new drug-eluting stents (see Chapter 29, Drug-Eluting Stents). Restenosis after angioplasty appears to result from the proliferation of intimal smooth-muscle cells. Results of experiments in cholesterol-fed animals after balloon injury of the arterial wall have suggested that restenosis occurs primarily from the migration and proliferation of smooth muscle cells in response to platelet-derived growth factor released from platelets adherent to the site of deendothelialization. Antiplatelet drugs and calcium-channel blocking drugs have had little or no benefit in reducing the rate of postangioplasty restenosis. A study with fluvastatin has shown benefit, and some positive results have been achieved with probucol and a related antioxidant compound, drugs not currently approved in the United States. Local irradiation and specific drug-eluting stents have been the most promising of the currently studied modalities.

**Heart Transplantation**

Elevated plasma lipids as well as an increased risk of having accelerated CAD are commonly found in recipients of cardiac transplants. Although many of the drugs used to treat and/or prevent rejection (high-dose steroids, cyclosporine) can raise LDL cholesterol, hypercholesterolemia has not been found to be a primary risk factor for developing graft atherosclerosis. Pathologically, the CAD is often different from that seen in nontransplant- ed patients and is characterized as a diffuse, necrotizing vasculitis or, more commonly, intimal hyperplasia of the entire coronary arterial system. It has been proposed that the development of CAD in transplant recipients may be a manifestation of chronic tissue rejection. Monitoring of lipids after cardiac transplantation is still worthwhile, and intake of dietary fats and cholesterol should be modified. Use of lipid-lowering drug therapy does carry with it an increased risk of potential complications. However, prospective studies with both pravastatin and simvastatin have shown a prominent benefi t from lipid-lowering drug therapy in this population.
Cerebrovascular Disease

The results of recent trials indicate that lipid-lowering treatment can reduce the risk of stroke in patients with existing heart disease (see Chapter 33, Drug Therapy of Cerebrovascular Disease). The mechanism for risk reduction includes plaque stabilization and the retardation of plaque progression.145 Numerous studies have shown that statins reduce cerebrovascular events in patients with and without cerebrovascular disease, including men, women, diabetics, the elderly, younger persons, patients with cardiovascular disease, and patients with hypertension.22-29,31-34,36-40,146-148 Lowering serum LDL cholesterol to < 90 mg/dL was associated with a 7% incidence of new stroke, whereas decreasing serum LDL cholesterol to 90 to 99 mg/dL was associated with a 16% incidence of new stroke.146 The lower the serum LDL cholesterol in elderly persons treated with statins, the greater was the reduction in new stroke. In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) Study, 4,731 patients with a stroke or transient ischemic attack within 1 to 6 months prior to study entry were randomized to atorvastatin 80 mg daily or the placebo.148 At the 4.9-year median follow-up, the incidence of fatal or nonfatal stroke was significantly reduced 16% in patients receiving atorvastatin (absolute reduction 2.2%). Major cardiovascular events were significantly reduced 20% by atorvastatin (absolute reduction 3.5%).

Cognitive Function

Some observational studies have suggested that there is a higher prevalence and incidence of cognitive decline in hypercholesterolemia,149,150 and that statins may slow cognitive decline.149,150 However, large-scale, prospective, randomized, double-blind, placebo-controlled studies such as the Heart Protection Study29 and the PROSPER (The Prospective Study of Pravastatin in the Elderly at Risk) study30 have shown no effect of statins on cognitive function. It has been thought that pharmacologic interventions that reduce the risk of stroke would reduce the risk of vascular dementia, but this still needs to be shown in clinical trials.

Nephrotic Syndrome

The nephrotic syndrome is associated with increased levels of cholesterol and triglycerides.151 The elevated serum concentrations of LDL cholesterol, other lipids, and Apo B in patients with uncomplicated nephrotic syndrome are due to reversible increases in lipoprotein production.152 These lipid disorders are difficult to treat, and they predispose patients to early-onset CAD. It has been suggested that the treatment guidelines adopted by the NCEP be extended to patients with unremitting nephrotic syndrome.153 Statins have been shown to reduce plasma concentrations of very low density lipoprotein (VLDL)- and LDL cholesterol in patients with nephrotic syndrome with kinetic evidence of enhanced LDL receptor activity.154 In addition, statins may reduce renal protein excretion in hypertensive patients who are already receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. However, recently reported intervention trials have failed to show a benefit in cardiovascular disease in patients with advanced renal failure.

Calcific Aortic Stenosis

Hypercholesterolemia is associated with calcific aortic stenosis and may be implicated in its pathogenesis and progression.155-157 In a study of 180 participants, mean age 82 years, with mild valvular aortic stenosis, 62 participants (34%) were treated with statins.158 At the 33-month follow-up, use of statins was associated with a significant decrease in the progression of aortic stenosis. Statins may reduce the progression of rheumatic aortic valve stenosis.158

In a study of 174 participants with a mean age of 68 years, with mild to moderate aortic stenosis, 57 participants (33%) were treated with statins.159 At the 21-month follow-up, participants treated with statins had reduced progression of aortic stenosis. In a community-based study of 156 participants with a mean age of 77 years, with aortic stenosis, 38 participants (24%) were treated with statins.160 At the 3.7-year follow-up, participants treated with statins had slower progression of aortic stenosis.

These observational data were confirmed by 1 prospective trial using rosuvastatin.161 However, 2 prospective trials (1 using atorvastatin and 1 using simvastatin plus ezetimibe) did not confirm the results of previous studies.162-163a It is unlikely that statins will affect a heavily calcified valve with severe aortic stenosis.164 However, patients with aortic stenosis often have associated cardiovascular disease such as CAD, other atherosclerotic vascular disease, or diabetes mellitus that will benefit from treatment with statins.

Conclusion

Hyperlipidemia, specifically elevations in plasma cholesterol and LDL cholesterol, is associated with an increased risk of morbidity and mortality from CAD. Elevations in plasma triglycerides and lower HDL cholesterol val-
ues may also contribute to increased risk. It is now clear that dietary and/or drug therapy of hypercholesterolemia can modify this risk favorably. Guidelines for selecting subjects for drug treatment have been established. In the subsequent sections, pharmacologic interventions designed to treat hyperlipidemia and the associated cardiovascular disease risk are presented and discussed. The guidelines regarding lipid-lowering therapy will continue to be refined as more information becomes available from clinical trials in a wide range of patient populations.

**Bile Acid Sequestrants**

The bile acid–binding resins cholestyramine and coleste-pol have long been among the drugs of first choice for hypercholesterolemia in patients without concurrent hypertriglyceridemia. Despite the mounting data on the safety, efficacy, and tolerability of HMG-CoA reductase inhibitors, this remains true for children, adolescents, and women who may become pregnant. Colesevelam, a newer bile acid sequestrant (BAS) with increased bile acid–binding specificity—and consequently a decrease in bulk, in gastrointestinal (GI) adverse effects, and the potential for vitamin and drug malabsorption—has reawakened interest in this class.

Cholestyramine was originally used for treatment of pruritus caused by elevated concentrations of bile acids secondary to cholestasis. However, attention has focused on the ability of the BAS class of medications to lower the concentration of LDL cholesterol in plasma. The resins have been extensively tested in large-scale, long-term follow-up clinical trials to explore their efficacy for such an application. These drugs are not absorbed in the GI tract and therefore have a limited range of systemic adverse effects. For this reason, they are particularly useful for the treatment of pregnant women with hypercholesterolemia and are drugs generally recommended in children with heterozygous familial hypercholesterolemia. The disadvantage of the early sequestrants cholestyramine and colestipol lie in their mode of administration and the frequency of GI adverse effects.

**Chemistry**

Cholestyramine (Questran powder) is the chloride salt of a basic anion-exchange resin. The ion-exchange sites are provided by the presence of trimethylbenzylammonium groups in a large copolymer of styrene and divinyl benzene. The resin is hydrophilic yet insoluble in water. It is given orally after being suspended in water or juice. It is not absorbed in the GI tract and not altered by digestive enzymes, permitting it to remain unchanged while traversing the intestines.

Colestipol (Colestid), supplied as the powder coleste-pol hydrochloride, is a basic anion-exchange copolymer made up of diethylenetriamine and one chloro-2,3-epoxypropane. It has approximately 1 out of its 5 amine nitrogens protonated (chloride form). Like cholestyramine, colestipol is not altered by digestive enzymes, nor is it absorbed in the digestive tract. It is supplied in powder form and is taken orally after being suspended in liquid.

Colesevelam is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide; it has been engineered to bind bile acids specifically. It is a nonabsorbed hydrophilic polymer that is unmodified by digestive enzymes. It is supplied in tablet form and taken orally.

**Pharmacology**

Bile acids are synthesized in the liver from cholesterol, their sole precursor. They are then secreted into the GI tract, where they interact with fat-soluble molecules, thereby aiding in the digestion and subsequent absorption of these substances. Bile acids are absorbed along with the fat-soluble molecules and are subsequently recycled by the liver via the portal circulation for resecretion into the GI tract. The bile acids remain in the enterohepatic circulation and never enter the systemic circulation.

Cholestyramine, colestipol, and colesevelam bind bile acids in the intestine. The complex thus formed is then excreted in the feces. By binding the bile acids, the resins deny the bile acids entry into the bloodstream and thereby remove a large portion of the acids from the enterohepatic circulation. The decrease in hepatic concentrations of bile acids allows a disinhibition of cholesterol 7a-hydroxylase, the rate-limiting enzyme in bile acid synthesis. Also seen is an increase in activity of phosphatidic acid phosphatase, an enzyme responsible for the conversion of alpha-glycerol phosphate to triglyceride. The increased activity of this enzyme causes a shift away from phospholipid production and ultimately an increase in the triglyceride content and size of VLDL particles. There is also evidence to suggest that the BAS class of medications cause an increase in the activity of HMG-CoA reductase, the rate-limiting enzyme in the hepatic cholesterol synthesis pathway. Although cholesterol synthesis is increased when the BAS class of medications are used, there is no rise in plasma cholesterol, presumably because of the immediate shunting of the newly formed cholesterol into the bile acid–synthesis pathway. The apparent shortage of cholesterol causes the hepatocyte cell surface receptors for LDL particles to be altered either quantitatively, by increasing in number, or qualitatively, by increasing their affinity for the LDL particle.
By sequestering the cholesterol-rich LDL particles, the liver decreases the plasma concentration of cholesterol.

**Pharmacokinetics**

Cholestyramine, colestipol, and colesevelam bind bile acids in the intestines, forming a chemical complex that is excreted in the feces. There is no chemical modification of the resins while in the GI tract; however, the chloride ions of the resins may be replaced by other anions with higher affinity for the resin. Colestipol and colesevelam are hydrophilic but virtually insoluble in water (99.75%). The high-molecular-weight polymers of cholestyramine, colestipol, and colesevelam are not absorbed in the GI tract. Less than 0.05% of 14C-labeled colestipol or 14C-labeled colesevelam is excreted in the urine.

Since the resins are not absorbed into the systemic circulation, any interactions that occur between the resins and other molecules occur in the intestines, usually with substances ingested at or near the time of resin ingestion. In the case of cholestyramine and colestipol, interaction between resins and fat-soluble substances, such as the fat-soluble vitamins, causes a decrease in absorption of these substances. Malabsorption of vitamin K, for instance, has been associated with a hypoprothrombinemia. It is therefore recommended that vitamins K and D be supplemented in patients on long-term resin therapy. Likewise, medications taken with or near the time of resin ingestion may be bound by the resin and not be absorbed. Drugs at risk include phenylbutazone, warfarin, chlorothiazide (acidic), propranolol (basic), penicillin G, tetracycline, phenobarbital, thyroid and thyroxine preparations, and digitalis preparations. In the case of colesevelam, such interactions essentially do not occur, though modest and variable effects on verapamil absorption have been described.175

The dose-response curves for the bile acid resins are nonlinear, with increases in the antihypercholesterolemic effect being minimal for doses > 30 g per day. Furthermore, there tend to be adherence problems when large doses of resin are used, making doses > 15 g twice daily inefficacious.176 In the case of colesevelam, which has a lower dosing range, nonlinearity was evident in the dose (3.75 g), which had about twice (19%) the cholesterol-lowering efficacy of the 3g dose (9%).177

Since the BAS class of medications comprises polymeric cations bound to chloride anions, continued ingestion of the resins imposes a chloride load on the body. This chloride load may cause a decrease in the urine pH and also an increase in the urinary excretion of chloride, which can reach 60% of the ingested resin load. Furthermore, there may be an increase in the excretion of calcium ions, which is dependent on the extent of chloride ion excretion. Because of this increase in calcium ion excretion, care should be taken, especially in treating a person at risk for osteoporosis, to limit the extent of calcium excretion by controlling the dietary chloride load.178

**Clinical Experience**

Numerous studies have shown the BAS class of medications cholestyramine, colestipol, and colesevelam to be efficacious in lowering LDL and total cholesterol levels in the plasma.179,180 Studies have further correlated the decreased levels of LDL cholesterol with the slowing of progression of coronary atherosclerosis and a lowered incidence of coronary events.186-189,191-196 Similarly, the use of the BAS class of medications retards the progression of femoral atherosclerosis.187,188 Furthermore, studies of the lipoprotein content in resin-treated individuals have detected a qualitative effect that may contribute to the antiatherosclerotic effects of the drug.189,190 Sequestrants are limited to use in those patients having hypercholesterolemia that is not associated with severe hypertriglyceridemia. Therefore, unless bile acid resins are combined with other antihyperlipidemic drugs, their use is typically limited to treatment of individuals with isolated hypercholesterolemia. In addition, the BAS colesevelam has been shown to improve glycemic control in patients with type 2 diabetes mellitus.191

**Effects on LDL Cholesterol**

The Lipids Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)167 represents the most extensive study of the BAS class of medications and their effects on lowering the incidence of symptomatic CAD. The study involved 3,806 subjects with type II hyperlipoproteinemia with plasma cholesterol values > 6.85 mm/L (> 265 mg/dL). The subjects were placed into either a placebo group on a low-cholesterol diet or a treatment group consisting of cholestyramine therapy (24 g per day) plus diet. Results showed that diet accounted for a 5% decrease in total cholesterol in both groups. The cholestyramine-treated group experienced a decrease in mean total cholesterol and LDL cholesterol of 13.4% and 20.3%, respectively. These decreases were 9% and 13% lower than those in the placebo group for total and LDL cholesterol, respectively (placebo total cholesterol decreased 8.5%, and LDL cholesterol decreased 12.6%). The study then looked for correlations between lower cholesterol and the incidence of CAD. To do this, the researchers defined 2 primary endpoints that would be used as markers for CAD: death from CAD and nonfatal MI. The study found an overall 19% reduction in the incidence of the primary endpoints for the treated group over the placebo group. This included a 24% lower incidence of death from CAD and a 19% reduction in nonfatal MI.

**Effects on Intermediate-Density Cholesterol Particles**

Evaluation of a subset of the National Heart, Lung, and Blood Institute (NHLBI) study group examined the effect
of cholestyramine on intermediate-density cholesterol (IDL) particles.\textsuperscript{180} The study found that the drug-induced changes of IDL mass seen 2 years into treatment were the best predictors of progression of CAD 5 years into treatment. Based on these findings, it was hypothesized that the major antiatherosclerotic effect of cholestyramine may not be its LDL-lowering and HDL-raising effect but rather an IDL-lowering effect caused by the binding of the IDL particles to the upwardly regulated LDL receptors on the hepatocytes. This hypothesis is based on the fact that IDL particles are able to bind to the LDL receptor.\textsuperscript{181}

**Effects on VLDL Cholesterol and Triglycerides**

As previously mentioned, cholestyramine has the tendency to increase synthesis of triglycerides, which may contribute to the observed increases in VLDL particle concentration. In a study comparing normotriglyceridemic, hypertriglyceridemic, and obese patients, the observed increase in VLDL triglyceride seen with resin treatment was shown to be due to increased synthesis of the lipoprotein and not decreased catabolism.\textsuperscript{192} For the above reason, bile acid–binding resins should be used only in patients with triglyceride levels < 3.39 mm/L (< 300 mg/dL); it is therefore important to determine not only a patient’s LDL level but also the triglyceride level to distinguish hypercholesterolemia due to elevations in both LDL and VLDL.\textsuperscript{193}

**Effects on HDL Cholesterol**

In a study of 1,907 patients enrolled in the LRC-CPPT, the HDL levels were found to be inversely proportional to the extent of CAD (as defined by the number of patients reaching the primary endpoint).\textsuperscript{194} Each 0.30-mm/L (1-mg/dL) increase of HDL above the mean at baseline was associated with a 5.5% decrease in the chance of a definite CAD-associated death or a nonfatal MI. Furthermore, each 0.03-mm/L (1-mg/dL) increase of HDL from baseline during the course of the study was associated with a 4.4% risk reduction for the primary endpoints. There was a similar finding in the placebo group when diet appeared to induce an increase in HDL. Cholestyramine had its greatest antihypercholesterolemic effect in those patients with the highest HDL concentrations. It is important to keep in mind that the LRC-CPPT study was not designed to answer questions about HDL levels; therefore, the above suppositions are not conclusive.

**Clinical Use of Resins**

Bile acid resins are indicated as adjunct therapy to diet for reduction of serum cholesterol in patients with primary hypercholesterolemia. Dietary therapy should precede resin usage and should address both the patient’s specific type of hyperlipoproteinemia and his or her body weight, since obesity has been shown to be a contributing factor in hyperlipoproteinemia. Since resin use can cause a 5% to 20% increase in VLDL levels, it should be restricted to hypercholesterolemic patients with only slightly increased triglyceride levels. The increase in VLDL seen with resin use usually starts during the first few weeks of therapy and disappears 4 weeks after the initial rise. It is thought that excessive increases in the VLDL particles may dampen the LDL lowering effect of the drug by competitively binding the upwardly regulated LDL receptors on the hepatocyte. The resins should, therefore, not be used in patients whose triglyceride levels exceed 3.5 mmol/L unless accompanied by a second drug that has antihypertriglyceride effects; some suggest not using resins if the triglyceride level exceeds 2.5 mmol/L. A general rule of thumb is that if the triglyceride level exceeds 7 mmol/L, the LDL concentration is seldom raised; therefore, treatment with a bile acid resin would not be effective.

Both cholestyramine and colestipol are available as powders that must be mixed with water or fruit juice before ingestion; they are taken in 2 to 3 divided doses with or just after meals. The BAS class of medications can decrease absorption of some antihypertensive agents, including thiazide diuretics and propranolol. As a general recommendation, all other drugs should be administered either 1 hour before or 4 hours after the BAS. The cholesterol-lowering effect of 4 g of cholestyramine appears to be equivalent to that of 5 g of colestipol. The response to therapy is variable in each individual, but a 15% to 30% reduction in LDL cholesterol may be seen with colestipol given at 20 to 30 g per day or cholestyramine at 16 to 24 g per day. The fall in LDL concentration becomes detectable 4 to 7 days after the start of treatment and approaches 90% of maximal effect in 2 weeks. Initial dosing should be 4 to 5 g of cholestyramine or colestipol, respectively, 2 times daily. The drugs are also useful if they are administered once daily.\textsuperscript{195} In patients who do not respond adequately to initial therapy, the dosing can be increased to the maximum mentioned above.

Dosing above the maximum dose does not increase the antihypercholesterolemic effect of the drug considerably but does increase adverse effects and therefore decreases adherence. Since both resins are virtually identical in action, the choice of one over the other is based on patient preference, specifically taste and the ability to tolerate ingestion of bulky material.

To avoid some of the difficulties with use of the powders, colestipol is available in tablets (1 g) that are swallowed whole.\textsuperscript{196} In addition, colestipol is available in a flavored powdered form. Cholestyramine is also available in a low-calorie, lower-volume formulation that contains 1.4 cal per packet.\textsuperscript{197}

If resin treatment is discontinued, cholesterol levels return to pretreatment levels within a month. In patients with heterozygous hypercholesterolemia who have not...
achieved desirable cholesterol levels on resin plus diet, the combination therapy of colestipol hydrochloride and nicotinic acid has been shown to provide further lowering of serum cholesterol, triglycerides, and LDL and cause an increase in serum HDL concentration. Other drug combinations have been studied; of particular promise is the combination therapy of a BAS and HMG-CoA reductase inhibitor.

Oral colesevelam can be administered alone or in combination with an HMG-CoA reductase inhibitor as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol. In addition, the drug is approved for improving glycemic control in patients with type 2 diabetes mellitus in combination with insulin, sulfonlureas, and metformin. The recommended dose is three 625 mg tablets taken twice daily with meals or 6 tablets once a day with a liquid meal. The dose can be increased to 7 tablets a day.

Adverse Effects of Resins

Since cholestyramine and colestipol are not absorbed in the body, the range of adverse effects is limited. A majority of patients’ complaints stem from the resins’ effect on the gastrointestinal (GI) tract and from subjective complaints concerning the taste, texture, and bulkiness of the resins. The most common adverse effect is constipation, which is reported in approximately 10% of patients on colestipol and 28% of patients on cholestyramine but is less common with colesevelam. This adverse effect is seen most commonly in patients taking large doses of the resin and most often in patients older than 65 years. Although most cases of constipation are mild and self-limiting, progression to fecal impaction can occur. A range of 1 in 30 to 1 in 100 patients on colestipol and approximately 12% on cholestyramine experience abdominal distention and/or belching, flatulence, nausea, vomiting, and diarrhea. Peptic ulcer disease, GI irritation and bleeding, cholecystitis, and cholelithiasis have been reported in 1 of 100 patients taking colestipol but have not been shown to be purely drug-related.

Fewer than 1 of 1000 patients on colestipol experience hypersensitivity reactions such as urticaria or dermatitis. Asthma and wheezing were not seen with colestipol treatment but were reported with cholestyramine treatment in a small number of patients. In a small percentage of patients, muscle pain, dizziness, vertigo, anxiety, and drowsiness have been reported with both drugs. With cholestyramine treatment, hematuria, dysuria, and uveitis have also been reported. Resin therapy has been associated with transient and modest elevations of serum glutamic oxaloacetic transaminase and alkaline phosphatase. Some patients have shown an increase in iron-binding capacity and serum phosphorus along with an increase in chloride ions and a decrease in sodium ions, potassium ions, uric acid, and carotene.

Case reports have described hyperchloremic acidosis in a child taking cholestyramine suffering from ischemic hepatitis and renal insufficiency, in a child with liver agenesis and renal failure, and in a patient with diarrhea due to ileal resection. For these reasons, those patients at risk for hyperchloremia should have serum chloride levels checked during the course of resin treatment.

In the LRC-CPT study, the incidence of malignancy in the cholestyramine-treated group was equal to that in the control group; however, the incidence of GI malignancy in the treated group was higher than in the control group with more fatal cases in the treated group (8 deaths in the treated group versus one in the control group). In animal studies, cholestyramine was shown to increase the mammary tumorigenic capabilities of 7,12-dimethylbenzanthracene (DMBA) in Wistar rats. In the rats treated with cholestyramine plus DMBA, there was a fivefold increase in the incidence of mammary cancer over control. Owing to the resin’s ability to disrupt the normal absorption of fat-soluble vitamins in the gut, there have been a number of reports concerning the occurrence of hypoprothrombinemic hemorrhage secondary to vitamin K malabsorption. In both of the cases cited above, the patients responded to adjunctive vitamin K therapy. An early study showed that colestipol can bind T₄ in the gut and in vitro. This binding can theoretically upset the normal reabsorption of T₄ from the gut and thereby disrupt normal T₄ recycling, causing hypothyroidism. However, a subsequent study showed that for euthyroid patients, thyroid function tests remained normal throughout resin treatment.

It is advisable for patients on thyroid replacement therapy to avoid taking the replacement drug at the same time as the resin so as to avoid any malabsorption problems.

Colesevelam appears to have a better adverse-effect profile than cholestyramine and colestipol and fewer associated drug interactions. Compared to the placebo, a significantly greater incidence of dyspepsia, constipation, and myalgia has been reported in clinical trials with cholestyramine and colestipol.

Conclusion

The BAS class of medications has been extensively studied and has been proved effective in reducing cholesterol levels in patients with primary hypercholesterolemia caused by increases in LDL cholesterol (type IIa). Studies have shown that resins have the ability to slow the progression of atherosclerosis when used alone and in combination and to limit the clinical consequences of the disease. Because of their effectiveness and safety, the BAS class of medications will continue to be a drug of first resource.
for certain patients who have hypercholesterolemia unresponsive to diet therapy. The newer agent, colesevelam, may possess the beneficial properties of the BAS class of medications, causing less constipation and vitamin/drug malabsorption. Further use of BAS class of medications will focus on combination therapy with other antihyperlipoproteinemic drugs, such as nicotinic acid or HMG-CoA reductase inhibitors. The use of these combination therapies will increase the range of the antihyperlipoproteinemic effect of the agents and allow for a decrease in dosage of the drugs used, thereby decreasing the incidence of adverse effects.

Fibric Acid Derivatives

Fibric acid derivatives (FADs) are a class of drugs that have been shown to inhibit the production of VLDL, while enhancing VLDL clearance, principally owing to decreased hepatic synthesis of the endogenous lipoprotein lipase inhibitor apolipoprotein C-III (Apo C-III) and, to some extent, via stimulation of lipoprotein lipase gene expression. The drugs can reduce plasma triglycerides and concurrently raise HDL cholesterol levels, primarily due to the effects of lower plasma triglycerides but, in part, also due to a modest direct effect on the production of the principal HDL apolipoproteins (Apo), Apo A-I and Apo A-II. Their effects on LDL cholesterol are less marked and more variable. FADs also modify intracellular lipid metabolism by increasing the transport of fatty acids into mitochondria and improving peroxisomal and mitochondrial fatty acid catabolism. All effects of the currently available FADs are felt to be due to ligation and activation of the ligand-activated transcription factor peroxisome proliferator activated receptor (PPAR)-alpha. PPARs (there are three: PPAR-alpha, PPAR-gamma, and PPAR-delta) heterodimerize with the retinoid X receptor (RXR) and bind to characteristic DNA sequence elements.

In screening tests in rats carried out in 1962 and 1963, a series of arloxyisobutyric acids reduced plasma concentrations of total lipid and cholesterol. The compound that combined maximal effectiveness with relatively little toxicity was clofibrate. However, when the drug was used in the large World Health Organization trial to determine its effect on primary prevention of CHD, problems with the agent were identified. Although a decline in the rate of nonfatal MI was observed, an increase in the rates of noncardiac death and overall mortality was also reported.

There was also an observed increase in the frequency of GI diseases with the drug, specifically cholelithiasis. A twofold increase in the rate of cholelithiasis was also reported with clofibrate as compared with the placebo in the Coronary Drug Project. During the 1960s and 1970s, many analogues of clofibrate were developed and tested for their hypolipidemic potential (Figure 20-5). Of these, gemfibrozil and fenofibrate are currently marketed in the United States. The results of the Helsinki Heart Study demonstrated the safety and efficacy of gemfibrozil as a lipid-modifying agent and its potential role for reducing the risk of CAD in patients with specific lipid and lipoprotein disorders. Other FADs—bezafibrate, ciprofibrate, etofibrate, and etophylline clofibrate—are available in Europe and many have been investigated in the United States.

This section reviews the clinical pharmacology of gemfibrozil and the other FADs, discusses the therapeutic experiences with these agents, and provides recommendations for their clinical use.

Pharmacokinetics

Gemfibrozil is well absorbed from the GI tract, with peak plasma levels seen 1 to 2 hours after administration. The plasma half-life is 1.5 hours after a single dose and 1.3 hours after multiple-dose therapy. The plasma drug concentration is proportional to dose and steady state is reached after 1 to 2 weeks of twice-daily dosing.
metabolites (in total, there are 4 major metabolites). No reports as yet have described distribution of the drug into human breast milk or across the placenta. Two-thirds (66%) of the twice-daily dose is eliminated in the urine within 48 hours; 6% is eliminated in the feces within 5 days of dosing; and less than 5% of the drug is eliminated unchanged in the urine. Regardless of the dosing schedule, there is no drug accumulation with normal or impaired renal function.

In vitro, gemfibrozil is 98% bound to albumin at therapeutic levels. There have been reports that when gemfibrozil is combined with warfarin in vitro, a doubling of the unbound warfarin fraction ensues. Similarly, clofibrate has been found to potentiate the anticoagulant activity of warfarin.

The other FADs behave in much the same way as gemfibrozil. Fenofibrate has been studied most extensively. It is well absorbed after oral administration and is hydrolyzed to fenofibrin acid, subsequently undergoing carbonyl reduction, which results in reduced fenofibrin acid. Fenofibrate and reduced fenofibrin acid are both active pharmacologically. Sixty-five percent of fenofibrate is excreted into the urine, principally as fenofibryl glucuronide (<20% is excreted through the bile). Drug elimination is completed within 24 to 48 hours, and the half-life of the drug is approximately 4.9 hours. Steady-state equilibrium is established within 2 to 3 days. Unlike gemfibrozil, the newer FADs—particularly ciprofibrate, fenofibrate, and bezafibrate—can accumulate in patients with renal and hepatic failure; therefore dose adjustments may be necessary. No pharmacokinetic interaction exists between fenofibrate and BAS.

Mechanism of Action of Gemfibrozil and Other FADs

The PPAR-alpha transcription factor has a central role in coordinating fatty acid metabolism in the liver, kidney, heart, and muscle. Much of current knowledge of the role of this transcription factor has emerged from studies on the effects of the fibrate drugs on individual lipoprotein components and cholesterol-triglyceride metabolic pathways.

One direct action of FADs appears to be an increase in the level of plasma lipoprotein lipase (LPL). LPL is deficient in patients with type I hyperlipoproteinemia, types I and II diabetes mellitus, hypothyroidism, heart failure, and nephrotic syndrome. LPL is increased by insulin treatment of diabetes mellitus, aerobic exercise, and FADs. LPL is the rate-limiting enzyme governing the removal of triglycerides from lipoproteins in the plasma. It functions at the luminal surface of the vascular endothelium and depends on the presence of AC-II (Apo C-II) on chylomicrons, VLDL, and HDL to activate its hydrolytic capacity. The level of LPL has been found to be increased after the addition of gemfibrozil. Enhancement of LPL is also found with fenofibrate therapy. Similarly, bezafibrate has been found to increase LPL activity. When coupled with the decrease in apo C-III, the catabolism of VLDL is dramatically increased. An increase in lipoproteins containing both apo B and apo C-III has been shown to be an important discriminator of atherosclerotic risk in a number of clinical trials. A decrease in these lipoproteins may be part of the antiatherosclerotic benefit of the FAD.

VLDL is produced in the liver and circulates in the plasma, where LPL hydrolyzes it to a VLDL remnant by removing triglyceride. The VLDL remnant is then either taken up by an apoE receptor-mediated process in the liver or converted to LDL. FADs have been shown to decrease the production of VLDL and to increase its fractional catabolic rate (FCR).

Gemfibrozil has been studied predominantly in subjects with hypertriglyceridemia. The newer FADs have been studied both in subjects with hypertriglyceridemia and those with hypercholesterolemia. Although the FADs have similar triglyceride-lowering abilities, fenofibrate, bezafibrate, and ciprofibrate appear to have a greater cholesterol-lowering effect than do gemfibrozil and clofibrate, which may relate to their having additional HMG-CoA reductase-inhibiting activity.

In the hypertriglyceridemic state, there are alterations in the usual homogeneity of lipoprotein subfractions. For instance, much of the LDL of hypertriglyceridemic patients contains a smaller amount of cholesterol ester and a greater amount of triglyceride than is usual. Presumably, this aberration results from an exchange of triglyceride for cholesterol between VLDL and LDL. The triglyceride-enriched LDL is then hydrolyzed by hepatic triglyceride lipase, leading to a further reduction in size and increase in density of the LDL molecule. Thus, in the hypertriglyceridemic state, there are LDL fragments of normal composition coexisting with triglyceride-enriched and triglyceride depleted forms. The clinical consequences of this heterogenous LDL population are not yet apparent.

In the hypertriglyceridemic state, the production and fractional clearance of LDL are also increased. Thus, patients with isolated hypertriglyceridemia may have low to normal LDL levels. Correction of the hypertriglyceridemic state with gemfibrozil restores the normal LDL population as well as reduces the production and catabolism of LDL. The result is often a slight increase in LDL levels. Similarly, when treating with fenofibrate or bezafibrate, treatment increases levels of LDL when there are normal or low LDL levels. Grundy and Vega offer the explanation that during fibrate therapy, the increased lipolysis of VLDL triglyceride promotes increased hepat-
ic uptake of VLDL remnants, leaving fewer receptors for clearance of LDL and thus increased plasma LDL.225

It has been suggested that the short-term result of FAD therapy is an increased production of LDL cholesterol secondary to increased VLDL catabolism and a resultant downregulation of hepatic LDL receptors.223 As the VLDL levels decrease, the LDL cholesterol content increases, establishing a more normal LDL particle. Regardless of the mechanism for changes in LDL levels, the importance of inhibiting production of VLDL as well as enhancing catabolism has been well documented.226 Studies show that in the primary hypertriglyceridemic state, gemfibrozil increases LDL less than clofibrate, a drug that enhances VLDL catabolism without altering production.226 Fenofibrate treatment of hypertriglyceridemic patients improves the conversion of VLDL to LDL and causes LDL levels to increase by 25% as VLDL levels decrease by 77%.227 However, the drug also increases the clearance rate of apo B and causes a decrease in apo B levels of approximately 35%.228 Thus these changes would be expected to be, on balance, antitherapeutic. Similar observations have been made with bezafibrate treatment of hypertriglyceridemia.228

The composition of HDL is also altered in hypertriglyceridemia. Normally, the cholesterol ester–rich subfraction (HDL2a) predominates in the circulation. HDL2a is transformed to HDL2b when it acquires triglyceride. HDL3 is formed from the removal of triglyceride from HDL2b by hepatic triglyceride lipase and LPL. HDL3 then acquires new cholesterol ester via lecithin cholesterol acetyl transferase (LCAT) and forms HDL2a.229 Hypertriglyceridemia markedly reduces HDL2a concentration and increases HDL2b concentrations. Essentially, hypertriglyceridemia decreases the cholesterol content of HDL. FAD therapy reverses this process, leading to increased cholesterol content of HDL.222 Gemfibrozil has also been found to stimulate the synthesis of apo AI, the major apoprotein on HDL, without altering its catabolism. Similarly, fenofibrate and bezafibrate increase apo AI levels during treatment of hypertriglyceridemia. However, the levels of apo AI rarely increase to the extent that HDL rises.220

Finally, the hypertriglyceridemic state is thought to be associated with an increase in cholesterol synthesis.221 One explanation for this is that hypertriglyceridemic LDL is altered and may present less cholesterol to the cells, thus leading to less effective downregulation of LDL receptors and less inhibition of HMG-CoA reductase. Consequently, cholesterol synthesis is increased. There is some evidence that FADs inhibit cholesterol synthesis.222 From comparison studies conducted by Hunninghake and Peters, it would appear that the newer FADs—fenofibrate, bezafibrate, and ciprofibrate—are more effective than gemfibrozil and clofibrate in reducing cholesterol levels.222 The results of animal studies appear to confirm that these new agents inhibit HMG-CoA reductase.227 Although the older agents may have some minimal activity in inhibiting HMG-CoA reductase, the results of animal studies have shown much greater activity with the newer agents such as bezafibrate versus clofibrate.222 In vivo, fenofibrate has been shown to decrease HMG-CoA reductase activity on human mononuclear cells in type IIa and IIb patients.224 Similarly, bezafibrate has been found to inhibit HMG-CoA reductase activity from mononuclear cells of both normal and hypercholesterolemic patients.225 Other data suggest an increased peripheral mobilization of cholesterol from tissues with FADs and feedback inhibition of hepatic cholesterol synthesis.225

FADs are also known to increase the secretion of cholesterol into bile and to decrease the synthesis of bile acids.246 This effect is modulated by LDL receptor activity, with FADs increasing hepatic uptake of cholesterol, and subsequent secretion into the bile. Grundy et al first noticed this increased lithogenicity of bile accompanying clofibrate therapy in 1972.242 Since then, other investigators have reported decreased fecal bile acid secretion and increased fecal excretion of neutral steroid with gemfibrozil therapy.247 The net effect of decreased bile acid concentration and increased cholesterol concentration is a cholesterol supersaturation of bile, providing the potential nidus for gallstone formation. Studies with the newer FADs, especially fenofibrate, have shown variable results in terms of total bile acid synthesis and subsequent bile acid saturation.248 European and American studies, so far, have shown no increase in gallstone formation in patients on fenofibrate therapy.248 Thus, the newer FADs may have less potential for gallstone formation.

Patients with elevated cholesterol levels are believed to have increased platelet-mediated coagulation secondary to enhanced platelet reactivity and thromboxane A2 production.250 A suggested pathogenesis is the ability of elevated LDL and cholesterol to alter the lipid membranes of platelets. Hypertriglyceridemia has also been associated with platelet hyperaggregability; however, the postulated defect in this condition is abnormal fibrinolysis.231 Carvalho et al have demonstrated that patients with type II hyperlipoproteinemia have a platelet abnormality causing increased aggregation in response to mediators such as adenosine diphosphate and epinephrine.250 After the onset of aggregation, these platelets release factors that continue to accelerate the coagulation process, leading to increased fibrin formation. Data available thus far suggest that FADs might help correct the defective coagulation and fibrinolytic problems induced by hyperlipidemia.251 Torstila et al studied the effects of gemfibrozil on type II patients and found that plasma prekallikrein and kininogen levels increased by 10.5% and 18.5%, respectively.232 Laustiola et al observed that in patients with hypercholesterolemia who exercised, gemfibrozil caused a decrease in
platelet reactivity and aggregability. Sirtori et al also studied gemfibrozil’s effect on platelet function and found no statistically significant effect on aggregation or thromboxane A2 levels. However, clofibrate and other FADs have been shown to decrease platelet aggregation in type II patients.

Fenofibrate and bezafibrate have been found to reduce platelet aggregation. In a study of 62 patients with atherosclerotic vasculopathy and hyperfibrinogenemia, treatment with bezafibrate resulted in dose-dependent increases in fibrinolytic activity, with decreased fibrinogen, blood filterability, and platelet aggregation as compared with the placebo. It was recently demonstrated in young dyslipidemic male postinfarction patients in a placebo-controlled study, the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT), that bezafibrate therapy improved dyslipidemia, lowered plasma fibrinogen, and reduced the progression of focal coronary artery narrowing on coronary angiography. In addition, recurrent coronary events were reduced in the bezafibrate-treated group. With regard to the myocardial microcirculation, Lesch et al found that when 35 patients were treated with fenofibrate, there was a significant decrease in platelet viscosity and erythrocyte aggregation. Moreover, in 8 of 12 patients in this study selected for thallium myocardial scintigraphy, 2 showed global and 6 showed regional improvement in myocardial blood flow after 8 weeks. Thus, a reduction in fibrinogen concentration may lead to an improved coronary microcirculation.

Additionally, fenofibrate has been shown to decrease platelet-derived growth factor (PDGF) in vitro, which inhibits smooth muscle proliferation in rabbit aorta. Thus, the FADs may directly inhibit atherosclerotic plaque formation.

An additional property unique to fenofibrate is the ability to decrease uric acid by 10% to 28% in 90% to 95% of all treated patients with an increase in renal uric acid secretion. The exact mechanism and clinical significance of this observation is unclear.

Clinical Experience

The effects of FADs are largely dependent on the pre-treatment lipoprotein classification of the patient. In short, most patients respond to therapy with a decrease in triglyceride levels and an increase in HDL levels. Hypertriglyceridemic patients without hypercholesterolemia often have a slight increase in cholesterol and LDL levels. However, patients with hypercholesterolemia often have a decrease in their cholesterol and LDL levels. The predominant difference between gemfibrozil and the newer FADs is that the latter appear to lower LDL to a greater degree than does gemfibrozil. As mentioned earlier, 1 explanation for this is that these new derivatives may also inhibit HMG-CoA reductase to some extent.

The clinical data for FADs are best summarized according to their effect on hypertriglyceridemic patients, subjects with combined hypertriglyceridemia and hypercholesterolemia, and subjects with only hypercholesterolemia. Patients with type I chylomicronemia would benefit little from FADs because these individuals lack LPL, the enzyme responsible for the increased clearance mediated by the FADs.

The Helsinki Heart Study, a 5-year double-blind intervention trial, used gemfibrozil on 2,051 middle-aged men, 8.8% of whom had isolated hypertriglyceridemia (type IV hyperlipidemia). In this subgroup, there was a 5% increase in LDL with gemfibrozil compared with a 7% increase with the placebo. There was a 10% increase in HDL and a significant decrease in total cholesterol. Type IV patients experienced the greatest drop in triglycerides compared with type IIa or IIb subjects. There was a 2% incidence in cardiovascular endpoints in this treated group compared with 3.3% in the placebo group. A relationship between the decreased triglyceride levels and the decreased cardiovascular morbidity was not observed. Instead, it was proposed that the elevated HDL, perhaps resulting from triglyceride lowering, conferred protection. A recent analysis of this study population 18 years later showed continued benefit, especially in those patients with metabolic syndrome.

The BECAIT trial was a small (81 patients) 5-year angiographic trial of bezafibrate. Given the small numbers, there was a small but statistically significant and unanticipated reduction in coronary events. The Bezafibrate Infarction Prevention Study (BIP) was a much larger undertaking: 3,090 patients divided between the placebo and active drug who were followed for a mean of 6.2 years to assess an effect on clinical coronary endpoints. A modest decrease in ischemic endpoints did not reach statistical significance, and there was no effect on mortality. A post hoc subgroup analysis speculated that the very modest benefit detected in the group as a whole may have been due to its apparent concentration in the small number of individuals with plasma triglycerides over 200 mg/dL. In contrast, the Lipid Coronary Angiographic Trial (LOCAT), which used gemfibrozil in 372 men with prior coronary artery bypass graft surgery, did show a significant benefit in decreasing angiographic progression and new lesion development in both native vessels and saphenous vein grafts. The VA-HIT study, which used gemfibrozil to detect an effect on clinical endpoints in over 2,500 men with normal (< 140 mg/dL) LDL and low HDL (< 40 mg/dL), also showed a significant benefit with this agent, including a favorable effect on stroke incidence. While specific differences with bezafibrate are possible, this difference may reflect the fact that VA-HIT patients had higher triglyceride levels (triglyceride levels up to 300 mg/dL were permitted) and were at higher risk than BIP patients, corresponding to the increased benefit.
in hypertriglyceridemic patients that was suggested in the post hoc analysis of BIP.265

The results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial in 9,745 patients did not show a significant reduction in fatal and nonfatal MIs with fenofibrate 200 mg, but a secondary endpoint that included fatal cardiovascular disease events (including stroke and coronary revascularizations) was reduced significantly. The study results were affected by a higher statin drop-in-rate in the control group during the treatment period, which resulted in minimal differences in lipids between the treatment groups. Diabetic patients seemed to have the greatest benefit with fenofibrate therapy, including protection against diabetic retinopathy.267

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, patients were randomly assigned to receive either simvastatin plus fenofibrate or simvastatin alone. The combination did not result in a significant improvement in the primary outcomes compared to simvastatin alone.267a,b An increased risk was seen in women with the combination. In those participants with triglycerides >204 mg/dl and HDL cholesterol levels <34 mg/dl, there was a trend towards benefit with fenofibrate plus simvastatin.267

**Clinical Use**

It is well established that FADs are first-line therapy to reduce the risk of pancreatitis in patients with very high levels of plasma triglycerides. Results from the Helsinki Heart Study have also suggested that the hypertriglyceridemic patient with low HDL values can derive a cardioprotective effect from gemfibrozil.215 Isolated low HDL levels are not as responsive to fibrate therapy.268 Niacin therapy, when tolerated, may be preferable in these patients. Nevertheless, the benefit in decreased coronary endpoints demonstrated in such patients in the VA-HIT study is supportive of the use of gemfibrozil to reduce coronary risk in patients with isolated low HDL, despite the rather modest increase in HDL that was achieved.52

FADs, particularly the newer generation, decrease total cholesterol and LDL levels. However, in the absence of elevated triglycerides, they should not be first-line therapy for hypercholesterolemic patients. Type IIb patients are the subset most commonly seen in clinical practice who would benefit from FAD therapy. HMG-CoA reductase inhibitors combined with FADs are excellent therapy for severe type IIb disease; however, the development of symptoms of myositis must be monitored. Bile acid resins plus gemfibrozil are also a reasonable combination for type IIb disease; however, HDL levels may drop slightly.

Gemfibrozil is approved for clinical use in the United States for the treatment of patients with very high serum triglycerides who are at risk of developing pancreatitis and for reducing the risk of clinical CAD in patients with type IIB hypercholesterolemia who are not symptomatic and who have low HDL cholesterol and elevated LDL cholesterol and triglyceride levels. The recommended dose for gemfibrozil is 600 mg before the morning meal and 600 mg before the evening meal.217 Some patients may respond to 800 mg per day, but in most instances the therapeutic benefit is augmented with an increase to 1200 mg daily. Some patients derive benefit from increasing the dosage of gemfibrozil to 1600 mg daily.269

Gemfibrozil tablets are approved for clinical use as adjunctive therapy to diet for the reduction of LDL cholesterol, total cholesterol, triglycerides, and apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (types IIA and IIB). The drug is also indicated as adjunctive therapy to diet for the treatment of patients with hypertriglyceridemia (types IV and V hyperlipidemia). For treatment of primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of non-micronized fenofibrate is 160 mg once daily. For patients with hypertriglyceridemia, the initial dose is 54 to 160 mg once daily. Dosage should be individualized according to the patient’s response and should be adjusted as necessary following repeat lipid determinations at 4- to 8-week intervals. The maximum dose is 160 mg daily. Micronized formulations are also available in different dosage forms.

Fenofibric acid is an active metabolite of fenofibrate and is approved for clinical use to reduce triglycerides and to increase HDL cholesterol in patients with mixed dyslipidemia on optimal doses of statins who have risk factors for CAD. It was the first fibrate to be approved specifically for combined use with a statin.270 It is available in a delayed-release oral capsule in doses of 45 and 135 mg. The usual daily dose is 135 mg once daily with a statin. In patients with renal impairment, the initial dose is 45 mg once daily.271

Bezafibrate and ciprofibrate are not approved for clinical use in the United States. Clofibrate is available for clinical use in the United States. The recommended daily dose of 2000 mg is usually divided into 2 to 3 daily doses.

**Adverse Effects and Drug Interactions**

Clofibrate, 1 of the earliest FADs, became unpopular because of its causative association with cholelithiasis and cholecystitis in the Coronary Drug Project.214 The World Health Organization trial then reported a 29% increase in overall mortality in clofibrate-treated compared to placebo-treated subjects.213 The mortality was principally due to postcholecystectomy complications, pancreatitis, and assorted malignancies. The Helsinki Heart Study reported a decrease in cardiovascular mortality but not overall mortality in gemfibrozil-treated subjects.216 The reason for the similarity of overall mortality rates with the placebo and gemfibrozil remains a mystery at this time.
Obviously, these findings have led to careful scrutiny of currently used and tested FADs. The significant adverse effects noted in the Helsinki Heart Study included atrial fibrillation, acute appendicitis, dyspepsia, abdominal pain, and nonspecific rash. The review of the European clinical trials of fenofibrate with 6.5 million patient-years shows a 2% to 15% adverse reaction rate, the most common adverse reactions being GI disturbances, dizziness, headache, muscle pains, and rash. However, the only adverse effect significant in frequency was skin rash. In a US multicenter study of fenofibrate in 227 patients, there was a 6% increase in adverse effects from the drug, similar to the observations of the European studies. Three of four of the patients who withdrew from the US fenofibrate study had skin rashes; the fourth had fatigue and impotence. Overall, the adverse experiences with bezafibrate have been similar to fenofibrate, with GI and neurologic disturbances, muscle aches, and rashes most commonly seen.

In the Helsinki Heart Study, there was a 55% excessive incidence of gallstones and a 64% excessive incidence of cholecystectomy in the drug-treated compared with placebo-treated group. Although European studies of fenofibrate may show some increased lithogenicity of the bile, there has been no increase in the incidence of gallstone formation, either during the trials or during postmarketing surveillance.

The manufacturers of gemfibrozil and fenofibrate have reported mild depressions of hemoglobin, white blood cell count, and hematocrit with the drugs. The Helsinki Heart Study did not find significant alterations in these parameters.

The combination of fibrates and HMG-CoA reductase inhibitors has been repeatedly shown to predispose to rhabdomyolysis and, in some cases, renal failure. The Helsinki Heart Study did not report any cases of myopathy in patients treated with only gemfibrozil.

Fenofibrate therapy is associated with increases in liver function tests, leading to discontinuation of treatment in 1.6% of patients in double-blind trials. Like treatment with other fibrates, fenofibrate treatment may cause myopathy, especially in patients with impaired renal function, which interferes with the drug’s excretion. Uric acid is noted to increase 10% to 28% on fenofibrate therapy, the clinical significance of which is unknown.

Gemfibrozil is a potent inhibitor of the cytochrome P4502C8 metabolic pathway which can potentiate many of the statin drugs and oral hypoglycemic agents, an effect not seen with fenofibrate.

Conclusion

Gemfibrozil, fenofibrate, and fenofibric acid can inhibit VLDL production and enhance VLDL clearance owing to stimulation of lipoprotein lipase activity. The drugs lower plasma triglyceride levels while raising HDL cholesterol levels. They have variable effects on LDL levels, although the newer FADs may have greater cholesterol-lowering potential than gemfibrozil. The drugs are particularly useful in patients with very high triglycerides who are at risk of pancreatitis, and gemfibrozil specifically has been shown to reduce the risk of CAD complications in men with type IIb hyperlipoproteinemia. How well these drugs protect against the complications of coronary vascular disease is still not known, and morbidity and mortality studies with the newer FADs still need to be done.

The FADs are well tolerated; however, there is a small risk of cholelithiasis with these drugs. Combination therapy with HMG-CoA reductase inhibitors may be associated with an increased incidence of myositis and rhabdomyolysis.

HMG-CoA Reductase Inhibitors

In 1987, the US Food and Drug Administration (FDA) approved the marketing of lovastatin, a competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme step in cholesterol synthesis in the body. The pharmacology and clinical efficacy of this cholesterol-lowering drug and other drugs in this class that were also approved for marketing are reviewed in this section.

Lovastatin

Chemistry

Lovastatin (Mevinolin) is a fermentation product of the fungus Aspergillus terreus. It is similar in structure to the earlier compound mevastatin, a less potent inhibitor of HMG-CoA reductase, whose clinical development was limited by its possible cardiogenicity in animals. The chemical structures of lovastatin and some other HMG-CoA reductase inhibitors are shown in Figure 20-6.

Pharmacology

Lovastatin, as a competitive inhibitor of HMG-CoA reductase, interferes with the formation of mevalonate, a precursor of cholesterol. Mevalonate also is a precursor of ubiquinone and dolichol, nonsterol substances essential for cell growth. It was initially thought that the HMG-CoA reductase inhibitors might inhibit formation of these substances, but this is not the case. Nonsterol synthesis does not appear to be inhibited by HMG-CoA reductase inhibitors.

Pharmacokinetics

Lovastatin is an inactive lactone (prodrug) that is hydrolyzed in the liver to an active β-hydroxyacid form. The prodrug was developed rather than the active hydroxy-
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acid form because the prodrug undergoes more efficient shunting to the liver on first pass. The potential result of this enhanced liver uptake is lower peripheral drug concentrations and fewer systemic adverse effects.280 This principal metabolite is the inhibitor of the enzyme HMG-CoA reductase. The dissociation constant of the enzyme inhibitor complex (Ki) is approximately 1029 mol/L.281

An oral dose of lovastatin is absorbed from the GI tract, with greater absorption at meals. The drug undergoes extensive first-pass metabolism in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. It is estimated that only 5% of an oral dose reaches the general circulation as an active enzyme inhibitor. The drug is excreted via the bile (83%) and the urine (10%).291,292

Lovastatin and its β-hydroxyacid metabolite are highly bound to human plasma proteins.292 Lovastatin crosses the blood-brain and placental barriers. The major active metabolites present in human plasma are the β-hydroxyacid of lovastatin, its 61-hydroxy derivative, and 2 unidentified metabolites. Peak plasma levels of both active and total inhibitors are attained 2 to 4 hours after lovastatin ingestion. The half-life of the β-hydroxyacid is approximately 1 to 2 hours. This rapid metabolism would seem to necessitate multiple doses per day. Clinical trials, however, have indicated that once- or twice-daily dosing is optimum. With a once-daily dosing regimen, within the therapeutic range of 20 to 80 mg per day, steady-state plasma concentration of total inhibitors after 2 to 3 days was about 1.5 times that of a single dose.292 Single daily doses administered in the evening are more effective than the same dose given in the morning, perhaps because cholesterol is mainly synthesized at night (between 12 and 6 AM).293 A substantial clinical effect of lovastatin is noted within 2 weeks and a maximal effect at 4 to 6 weeks; the effect dissipates completely 4 to 6 weeks after the drug is stopped. A tachyphylaxis effect has been suggested with prolonged use of statins.294

Clinical Experience
Several investigators have demonstrated that lovastatin lowers the cholesterol levels of normal and hypercholesterolemic animals.277,285,286 These studies demonstrate that the increased LDL receptor activity and decreased LDL synthesis are responsible for the hypocholesterolemic effect of the drug. Several studies in humans have confirmed this observation.285–288 This increase in LDL receptor activity occurs in response to a decrement in cholesterol synthesis by HMG-CoA reductase inhibition. LDL may be reduced by either its increased clearance from the plasma or its decreased production.

Clinical Endpoints
In a report from the Familial Atherosclerosis Treatment Study (FATS),289 the combination of lovastatin 40 mg and colestipol 30 g daily was more effective than colestipol and diet alone in reducing LDL and raising HDL in patients with CAD and elevated apo B levels. There were also fewer cardiovascular events, less progression of coronary lesions, and more regression.

In the Monitored Atherosclerotic Regression Study (MARS),290 patients whose cholesterol was 190 to 295 mg/dL and who were receiving lovastatin 80 mg per day and a cholesterol-lowering diet showed a slower rate of progression and an increase in the regression in coronary artery lesions, especially in more severe lesions, compared with the placebo plus diet. These anatomic changes on coronary angiography with lovastatin were associated with a significant reduction in total cholesterol, LDL cholesterol, and apo B levels, with a modest increase in HDL cholesterol. In this study, lovastatin was also shown to reduce the progression of early, preintrusive
atherosclerosis of the carotid artery as evaluated by B-mode ultrasonography.

In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), 331 patients with diffuse but not necessarily severe coronary atherosclerosis on coronary angiography and cholesterol between 220 and 300 mg/dL were randomized to receive either diet plus lovastatin (20, 40, and 80 mg), titrated to achieve an LDL cholesterol below 130 mg/dL, or diet plus the placebo. Lovastatin treatment was shown to slow the progression of coronary atherosclerosis, especially of the milder lesions, and inhibited the development of new lesions. In a substudy analysis of female participants in CCAIT, lovastatin was shown to be effective in slowing the progression and neo- genesis of coronary atherosclerotic lesions.

The effects of lovastatin on atherosclerotic lesions in the carotid arteries was assessed in The Asymptomatic Carotid Artery Progression Study (ACAPS). In this study, 919 asymptomatic men and women with early carotid atherosclerosis as defined by B-mode ultrasonography and LDL cholesterol levels between 130 and 159 mg/dL were randomized to receive 20 to 40 mg of lovastatin or the placebo. In addition, all patients received 80 mg of aspirin daily, and one-half were treated with 1 mg of warfarin daily.

Lovastatin reduced LDL cholesterol levels and, after 3 years of follow-up, slowed the progression of mean intimal-medial thickness of the common carotid arteries and decreased mortality and major cardiovascular events.

As in the findings in ACAPS, FATS, MARS, and CCAIT, reductions in cardiac event rates were also observed with lovastatin compared with the placebo. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a double-blind placebo-controlled primary prevention study using lovastatin that targeted 5,608 men and women with average LDL levels (mean 60th percentile) and low HDL level (mean 25th percentile for men, 16th for women). Its primary endpoint was the development of a first major acute coronary event (MI, unstable angina, or sudden cardiac death). The drug was well tolerated, with no clinical difference in liver enzyme abnormalities, myositis, etc. After a mean 5.2 years of follow-up, lovastatin reduced the incidence of the primary endpoint by 37% (P < .001), with a similar benefit on a variety of other atherosclerotic endpoints (coronary revascularizations, etc.), presumably via the noted 25% reduction in LDL and 6% increase in HDL. Mortality was limited in this relatively low-risk population, and the apparent benefit of treatment did not reach statistical significance. Most of these individuals would not have met criteria for therapy under the NCEP guidelines then in force. However, post hoc subgroup analysis revealed that the benefit was substantially confined to the two-thirds of subjects with HDL levels below 40 mg/dL. Lovastatin is approved as an adjunct to diet for the reduction of elevated total and LDL cholesterol in patients with primary hypercholesterolemia (type IIa and IIb) when the response to a diet restricted in saturated fat and cholesterol has not been adequate. In individuals without symptomatic cardiovascular disease, average to moderately elevated total cholesterol, and LDL cholesterol and below-average HDL cholesterol, lovastatin is indicated to reduce the risk of MI, unstable angina, and coronary revascularization procedures. The drug is also indicated for slowing the progression of atherosclerosis in patients with CAD.

Lovastatin doses as low as 5 mg twice daily produce significant reductions in serum cholesterol. Patients should be placed on a standard cholesterol-lowering diet prior to drug treatment. The recommended starting dose is 20 mg once daily given with the evening meal. The recommended dosing range is 20 to 80 mg daily in single or divided doses. Adjustments should be made at intervals of 4 weeks or more. A dose of 40 mg daily can be initiated in patients with cholesterol levels >7.76 mm/L (>300 mg/dL).

Twice-daily dosing appears to be the most effective treatment regimen, with daily evening doses being slightly less effective and daily morning doses least effective. Maximal and stable cholesterol reduction typically is achieved within 4 to 6 weeks of treatment initiation. A new extended-release formulation of lovastatin has been approved for once-daily clinical use.

Niacin, BAS, and fibrates, in combination with lovastatin, may provide additional efficacy. A combination extended-release niacin lovastatin formulation has been approved for clinical use in a capsule-shaped tablet containing 500, 750, or 1000 mg of niacin and 20 mg of lovastatin or 1000 mg of niacin and 40 mg of lovastatin.

Adverse Effects

Several hypercholesterolemic agents are available, each having a significant adverse-effect profile. Lovastatin and other HMG-CoA reductase inhibitors have an acceptable rate of adverse effects, but must be used with some caution.

In the published trials, approximately 2% of patients were withdrawn from treatment because of adverse reac-
tions. GI adverse effects (diarrhea, abdominal pain, constipation, flatulence) are the most commonly reported adverse effects. Marked, persistent, but asymptomatic increases (to greater than 3 times the upper limit of normal) in serum transaminases have been reported in 2% of patients receiving the drug for 1 year. The increases are predominantly in serum glutamate pyruvate transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT) rather than alkaline phosphatase, suggesting a hepatocellular, not cholestatic, effect. These abnormalities rapidly return to normal after the discontinuation of the drug, and no permanent liver damage has been reported with the drug. Symptomatic hepatitis in patients treated with the drug, and no permanent liver damage has been reported with the drug. Symptomatic hepatitis in patients without underlying disease or other known hepatotoxic medications has been observed. It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevations of dose, and semiannually thereafter.

In a recent meta-analysis, statin therapy was shown to be associated with an increased prevalence of diabetes mellitus, however, clinical practice should not change. The adverse effect of greatest concern with lovastatin is a myopathy, which appears to develop in 3 clinical patterns. The first, a moderate elevation in plasma creatinine kinase levels, is asymptomatic. Second, patients may develop muscle pain, primarily in the proximal muscle groups. CPK elevations may or may not be present. Finally, patients may develop a severe myopathy marked by extreme elevations in CPK, muscle pain with weakness, myoglobinuria and, rarely, acute renal failure. This finding most often occurs in the setting of concurrent immunosuppressive therapy (cyclosporine), particularly when gemfibrozil, erythromycin, or niacin is added. Similarly, the use of itraconazole, an antifungal drug, has been shown to drastically increase plasma concentrations of lovastatin and lovastatin acid. Inhibition of CYP3A4-mediated hepatic metabolism probably explains the increased toxicity of lovastatin caused not only by itraconazole but also by cyclosporine, erythromycin, and other inhibitors of CYP3A4. Cases of myopathy have been identified as early as a few weeks and as late as 2 or more years after the initiation of therapy. CPK elevations appear to correlate little with the severity of the symptoms, but if CPK levels rise or muscle pain develops, it is recommended that lovastatin be reduced. If levels rise drastically (> 10 times the upper limits of normal) with muscle pain, therapy should be discontinued.

In a study of 11 cardiac transplant patients, all were treated withlovastatin and cyclosporine, and monitored closely for 1 year; they were not treated with other hepatotoxic medications or lipid-lowering agents. None developed any evidence of hepatic, muscle, or renal toxicity, and the authors concluded that in the absence of other effective therapy, cardiac transplantation should not be a contraindication to the use of lovastatin. Combinations of lovastatin with hepatotoxic agents, in the absence of cyclosporine, have also been reported to be associated with myositis. The FDA has documented multiple cases of myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy and has discouraged the use of this regimen. Although the reason that myopathy has been associated with lovastatin is not well understood, it has been postulated that drugs that impair hepatic function may alter the first-pass extraction of lovastatin and produce elevated levels, which, in turn, may be responsible for the myotoxicity. Lovastatin may disrupt the proper assembly of membrane glycoproteins, the oxidation-reduction reactions of the mitochondrial respiratory chain, or the regulation of DNA replication. Tobraet does report, however, 4 cases of myositis with lovastatin monotherapy, but 3 of these patients had biliary stasis, leading to decreased clearance of the drug.

Several reports of bleeding or increase in prothrombin time or both have been observed in patients on concomitant warfarin anticoagulation. Although these accounts have not been attributed to lovastatin, it is recommended that prothrombin time be carefully regulated in these patients, as in all patients receiving oral anticoagulation.

In addition to reports of rashes during the clinical trials, there have been several accounts of serious hypersensitivity reactions during prescription use: anaphylaxis, arthralgia, a lupus-like syndrome, angioedema, urticaria, hemolytic anemia, leukopenia, and thrombocytopenia have all been reported. Twenty-five cases were considered serious, but all of these patients recovered with discontinuation of lovastatin therapy. Since these adverse effects were never reported during the clinical trials, it is likely that the incidence is significantly less than 1 per 1,000. Sleep disturbances, characterized by insomnia or shortening of the sleep period, have also been described.

Lovastatin (40 mg daily) and pravastatin (40 mg daily) were compared in a double-blind study of effects on quality of life and drug tolerability in men aged 20 to 65 years with primary hypercholesterolemia who received treatment for 12 weeks. No significant differences between the 2 groups were observed in tolerability, health-related quality-of-life measures, or changes in lipid profile.

**Simvastatin**

Simvastatin (Svinvinolin) is a prodrug that is enzymatically hydrolyzed in vivo to its active form. In clinical trials since 1985 and approved in 1992, simvastatin is synthesized chemically from lovastatin and differs from lovastatin by only 1 methyl group. Like lovastatin, it has a very high affinity for HMG-CoA reductase; but on a milligram-per-milligram basis, simvastatin is twice as potent. Peak plasma concentrations of active inhibitor
occur within 1.3 and 2.4 hours.\textsuperscript{319} One 12-week multicenter double-blind study comparing simvastatin to probucol found that a daily dose of simvastatin of 20 and 40 mg lowered LDL cholesterol by 34% and 40%, respectively. Simvastatin also reduced total cholesterol, triglycerides, and apo B. HDL was increased.\textsuperscript{320} As with lovastatin, interactions with warfarin and digoxin have been noted. Another multicenter study comparison with cholestyramine demonstrated that a low dose of simvastatin (10 mg) was sufficient to reduce total cholesterol by 21% and LDL by 30%, while HDL increased by 17%.\textsuperscript{321} In comparisons of simvastatin to FADs and BAS, simvastatin produced greater reductions in total and LDL cholesterol, whereas the latter had a greater effect on the serum triglycerides.\textsuperscript{322,323} In a small study of patients with familial hypercholesterolemia, it was shown that 40 mg of simvastatin in combination with 12 g of cholestyramine reduced total cholesterol by 43% and LDL cholesterol by 53%.\textsuperscript{324}

The effects of simvastatin are achieved using a single evening dose.\textsuperscript{325} Despite its potency, simvastatin has never been shown to disrupt adrenocortical function.\textsuperscript{326} Side effects are predominantly headaches and dyspepsia, but asymptomatic myositis has also been noted.\textsuperscript{320} It is interesting that some patients who experienced enzyme elevations with lovastatin and lovastatin rechallenge tolerated simvastatin well.\textsuperscript{327}

Simvastatin has been shown to be useful in all the hypercholesterolemic conditions where HMG-CoA reductase inhibitors are used.\textsuperscript{327} The drug is about twice as potent as lovastatin. Simvastatin (10 mg daily) or 20 mg of pravastatin or lovastatin usually produce about 25% to 30% reductions in LDL cholesterol compared with about 20% to 25% reductions with 20 mg of fluvastatin. Lovastatin (80 mg), pravastatin (40 mg), or simvastatin (40 mg) generally decrease LDL cholesterol by about 30% to 40%; maximum doses of fluvastatin (40 mg) decrease LDL cholesterol by about 25%.\textsuperscript{328} The maximum approved daily dose of simvastatin is 80 mg, found to be more effective than 20 mg on outcomes.\textsuperscript{328a}

As a treatment for nephrotic hyperlipidemia, simvastatin was noted to be more effective and better tolerated than cholestyramine.\textsuperscript{329} Simvastatin has also been evaluated for its effect on the cholesterol saturation index of gallbladder bile, a potential adverse effect of several hypcholesterolemic agents. A mean decline of 23% was noted in the 10 hypercholesterolemic patients studied, raising the possibility that an HMG-CoA reductase inhibitor may play a future role in the treatment of gallstones.\textsuperscript{330}

Effect on Clinical Endpoints

Like lovastatin and pravastatin, simvastatin was shown to slow the progression of coronary atherosclerosis assessed by coronary angiography.\textsuperscript{331,332} In the Multicentre Anti-Atheroma Study (MAAS), simvastatin, 20 mg daily, was compared with the placebo in 381 patients with CAD receiving a similar lipid-lowering diet. Patients on simvastatin had a 23% reduction in total cholesterol, a 31% reduction in LDL cholesterol, and a 9% increase in HDL cholesterol compared with the placebo over 4 years. Patients on simvastatin had less progression and more regression of existing lesions and a lower rate of new lesion development.\textsuperscript{332}

In a landmark secondary prevention study, The Scandinavian Simvastatin Survival Study (4S), simvastatin was shown to reduce mortality and morbidity in patients with known CAD and hypercholesterolemia.\textsuperscript{22,333} In this study, 4,444 patients with prior angina or MI and elevated total serum cholesterol levels (220 to 320 mg/dL or 5.5 to 8.0 mmol/L) were randomized in double-blind fashion to receive either simvastatin, 20 to 40 mg, or the placebo and were followed for a median of 5.4 years (Figure 20-7). All patients were on a cholesterol-lowering diet. Compared with the placebo, simvastatin reduced total cholesterol 25% and LDL cholesterol 35% and increased HDL cholesterol 8%. Compared with the placebo, there were highly statistically significant reductions of all fatal coronary events by 42% with simvastatin; all fatal cardiovascular events were reduced by 35% (Figure 20-8), and all-cause mortality was reduced by 30%. Patients older than 60 years had a 27% reduction in mortality, essentially identi-
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The Heart Protection Study (HPS) enrolled 20,536 patients aged 40 to 80 years with CHD, noncoronary arterial disease, diabetes mellitus, and treated hypertension. Patients were randomized to simvastatin (40 mg daily), a vitamin cocktail (1600 mg E, 250 mg C, 20 mg beta carotene), or the placebo. Patients were followed for 5 years. There was no effect from the vitamin therapy. Simvastatin caused a one-third reduction in the risk of MI, stroke, coronary and noncoronary revascularization regardless of baseline cholesterol levels.

Based on experimental studies, the suggestion has been made that simvastatin may reduce cardiovascular events beyond the effect on lipid lowering. The possibility of such effects is a continuing area of controversy. Simvastatin and other HMG-CoA reductase inhibitors have been shown to reduce factor VIIc activity and inhibit platelet activation, while reducing the propensity of LDL to oxidation. In addition, the drug has been shown to depress blood clotting by inhibiting activation of prothrombin, thrombin factor V, and factor XIII. A beneficial effect to statins has been associated with a lower risk of deep venous thrombosis. Simvastatin was also shown to have a favorable action in causing regression of cardiac hypertrophy in an animal model of hypertrophic cardiomyopathy.

Clinical Use

Similar to other marketed HMG-CoA reductase inhibitors, simvastatin is approved for use in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson types IIa and IIb). In addition, based on the results of the 4S study, the drug has also been approved in patients with CAD as long-term treatment for hypercholesterolemia and to reduce the risk of total mortality by reducing coronary death, the risk of nonfatal MI, the risk for undergoing myocardial revascularization, and the risk of stroke or transient ischemic attack. In addition, the drug is approved for use in patients with hypertriglyceridemia (Frederickson type IV), primary dyslipoproteinemia (Fredrickson type III), and adult patients with homozygous familial hypercholesterolemia. Simvastatin is administered orally as a single dose in the evening. The recommended starting dose is 20 mg daily, which is then titrated according to the individual patient's response at 4-week intervals to a maximum 80 mg daily dose. Simvastatin can be combined with FADs, niacin, and the BAS class of medications—including colesevelam—to achieve maximal cholesterol lowering. A combination formulation of simvastatin and ezetimibe, a cholesterol absorption inhibitor, is now in clinical use, as well as the combination of niacin extended-release and simvastatin.

In patients with severe renal insufficiency or those receiving cyclosporine, the recommended starting dose is 5 mg daily, and close monitoring is required. Drug-drug interactions with amiodarone and verapamil require dosing adjustments. The dose of simvastatin should not exceed 20 mg/d. In patients taking fibrates, niacin, or cyclosporin, the simvastatin dose should not exceed 10 mg/d. The low risk of liver enzyme abnormalities and their lack of clinical severity has led to less stringent requirements for liver function testing. Testing is now recommended prior to initiating or increasing the dose of therapy and twice during the subsequent year, with routine laboratory monitoring ceasing a year after the last dosage increment if liver function tests remain normal.

Adverse Effects

The adverse-effects profile of simvastatin is similar to that of lovastatin and other HMG-CoA reductase inhibitors. The rare occurrence of a lupus-like syndrome has recently been reported with both lovastatin and simvastatin.

Pravastatin

Pravastatin (Pravachol CS 514, SQ 3100, epstatin) is the 6 alpha-hydroxy acid form of compactin. It is the...
first HMG-CoA reductase inhibitor to be administered in the active form and not as a prodrug. In vitro studies by Tsujita et al demonstrated that pravastatin has a greater specificity for hepatic cells than lovastatin. In vivo animal studies comparing pravastatin to lovastatin and simvastatin, however, found that the concentration of pravastatin in the liver was only half that of the latter two, whereas the concentrations in peripheral tissues were 3 to 6 times greater.

Pravastatin was also found to be a specific inhibitor of hepatic HMG-CoA reductase in humans. Other enzymes involved in cholesterol metabolism (alpha-hydroxylase, which governs bile acid synthesis and acyl-coenzyme A: cholesterol O-acetyltransferase [ACAT], which regulates cholesterol esterification) were not affected by treatment. Inhibition of hepatic HMG-CoA reductase activity by pravastatin results in an increased expression of hepatic LDL receptors, which explains the lowered plasma levels of LDL cholesterol.

Multiple studies have already been conducted on humans to establish efficacy and dosage. Despite its short plasma half-life of approximately 2 hours, a single daily dose of pravastatin has been shown to be as effective as twice-daily doses. As with all HMG-CoA reductase inhibitors, the sustained duration of benefit relates to the relatively long half-life of plasma LDL and is independent of the systemic half-life of the drug, most of which is removed in the first pass through the liver in any event. As with other drugs in this class, administration of the drug in the evening rather than the morning appears to bring about greater cholesterol-lowering activity. Mabuchi et al treated patients with homozygous FH with pravastatin, 10 mg and 20 mg. They found a 26% and 33% decrease in LDL, respectively. HDL was significantly increased. Nakaya et al also found that 5 mg, 20 mg, and 40 mg doses lowered the total serum cholesterol by 11.1%, 18.8%, and 25.3%, respectively, in hypercholesterolemic patients. The investigators reported some mild adverse effects but no myositis.

The efficacy and safety of pravastatin has been evaluated in various patient subgroups. A low dose (10 mg) of pravastatin daily was shown to be a safe and effective method of reducing total and LDL cholesterol in hypercholesterolemic, hypertensive elderly patients who were receiving concurrent antihypertensive drug therapy. The safety and efficacy of using lovastatin (20 mg and 40 mg) in the elderly was also confirmed in the Cholesterol Reduction in Seniors Program. The effect of pravastatin on morbidity and mortality in the elderly was evaluated in the NIH-funded Antihypertensive Lipid Lowering Heart Attack Trial (ALLHAT). In this controlled study, 10,355 subjects aged 55 years or older who met lipid criteria were followed for 8 years and were treated with pravastatin 40 mg. A small reduction in LDL cholesterol was seen related to drop-ins in the placebo group and drop-outs in the treatment groups. There was an insignificant reduction in cardiac outcomes with pravastatin and no effect on stroke.

Pravastatin (20 mg daily) has been shown to be well tolerated and effective in lowering total cholesterol and LDL cholesterol in patients with type I or II diabetes mellitus and hypercholesterolemia. Finally, pravastatin (20 mg daily) has been found to be an effective and safe lipid-lowering agent, as have other drugs in this class, in blacks with primary hypercholesterolemia and in the elderly.

Lovastatin, simvastatin, and pravastatin have been directly compared, and the published data suggest that, at equipotent dosages, the drugs are approximately equal in efficacy with respect to reducing LDL cholesterol.

Effects on Clinical Endpoints

The benefit of using pravastatin to reduce morbidity and mortality in patients with CAD was first established in the Pravastatin Multinational Study. In this 6-month trial, pravastatin treatment was demonstrated to reduce the incidence of serious cardiovascular events including MI and unstable angina.

Four vascular regression trials using pravastatin have been completed, with the results reported on 2 of the trials. PLAC-I (Pravastatin Limitation of Atherosclerosis in the Coronary Arteries) and REGRESS (Regression Growth Evaluation Statin Study) included patients with CAD to assess by serial angiography the effects of pravastatin on CAD. PLAC-II was designed to evaluate the ability of pravastatin to retard the ultrasonographic 3-year progression of extracranial carotid artery in patients with known CAD. The KAPS (Kuopio Atherosclerosis Study) was a 3-year ultrasonographic study that evaluated the effects of pravastatin on the progression of carotid and femoral atherosclerosis.

All the studies were placebo-controlled, and pravastatin doses of 20 to 40 mg were used as monotherapy. Patients receiving pravastatin in PLAC-I had a 40% to 50% reduction in the progression of coronary lesions, a 28% reduction in LDL cholesterol, and fewer nonfatal and fatal MIs compared with the placebo. In PLAC-II, pravastatin-treated patients showed a 35% reduction of atherosclerosis in the common carotid artery and a 80% reduction in fatal and nonfatal infarctions compared with the placebo. In KAPS, there was a significant reduction in the progression of carotid atherosclerosis compared with the placebo. In REGRESS, there was a significant reduction in the progression of coronary atherosclerosis with pravastatin and a reduced rate of adverse cardiovascular events compared with the placebo, including fewer MIs, sudden deaths, strokes, and invasive coronary procedures.

In these 4 studies, a total of 1891 patients had been evaluated, and although the major objective was to assess...
regression of atherosclerosis with aggressive lipid lowering with pravastatin, a meta-analysis was performed to assess the impact of treatment on clinical cardiovascular events compared with the placebo. The risk of fatal plus nonfatal MIs was reduced by 62%, the risk of stroke reduced by 62%, and total mortality by 46%.

In a prospective study of patients with known cardiovascular disease, pravastatin was shown to reduce the level of the inflammatory biomarker C-reactive protein in a largely LDL cholesterol–independent manner, suggesting that statins may have anti-inflammatory in addition to lipid-lowering effects that contribute to their clinical benefit in patients at risk for CAD.

Pravastatin was also shown to have a blood pressure–lowering effect in patients with moderate hypercholesterolemia and hypertension. In addition, the drug improves endothelial function after acute coronary syndromes and decreases thrombus formation.

Pravastatin has been used in 1 large primary prevention and several secondary prevention studies with reported benefit on clinical cardiovascular outcomes. In the West of Scotland Prevention Study (WOSCOPS), 6,595 middle-aged men with no history of MI and average plasma cholesterol values above 252 mg/dL were randomized to receive either the placebo or 40 mg of pravastatin and followed for an average of almost 5 years. Pravastatin decreased LDL cholesterol by 26% and increased HDL cholesterol by 5%. Pravastatin treatment also significantly reduced the incidence of MI and death from cardiovascular causes by 31% as well as decreasing a variety of other coronary endpoints without adversely affecting the risk of death from noncardiovascular causes. Total mortality was decreased by 22% (Figure 20-9). The benefit persisted with long-term follow up.

The Cholesterol and Recurrent Events Study (CARE) was designed to assess whether pravastatin treatment (40 mg daily) could reduce the sum of fatal CAD and nonfatal MIs in patients who have survived a MI yet have a total cholesterol below 240 mg/dL. The study looked at the effects of treatment on coronary endpoints without adversely affecting the risk of death from noncardiovascular causes. Median LDL levels, at 150 mg/dL, were slightly higher. The primary endpoint was decreased by 24%; there were similar significant effects on other coronary endpoints; and all-cause mortality was decreased by 22% as well. In addition, a beneficial effect was seen on the risk of nonhemorrhagic stroke from any cause.

An additional pravastatin study evaluating the use of HMG-CoA reductase inhibitors with or without vitamin E and marine polyunsaturated fats (fish oil) in 6,000 patients with a history of MI was stopped early due to the publication of the CARE and LIPID data.

The Long-term Intervention with Pravastatin in Ischemic Heart Disease trial (LIPID) was a relatively similar trial that evaluated the placebo versus pravastatin, 40 mg, in patients who had either an acute MI or an unstable angina episode and had cholesterol values of 155 to 271 mg/dL. The study looked at the effects of treatment on CAD mortality as the primary endpoint. Median LDL levels, at 150 mg/dL, were slightly higher. The primary endpoint was decreased by 24%; there were similar significant effects on other coronary endpoints; and all-cause mortality was decreased by 22% as well. In addition, a beneficial effect was seen on the risk of nonhemorrhagic stroke from any cause.

Clinical Use

Pravastatin has a similar approval for treatment of hypercholesterolemia as other HMG-CoA reductase inhibitors and, in addition, is approved for both the primary and secondary prevention of complications related to CAD. The drug is also approved for the secondary prevention of stroke and ischemic attacks as well as the progression of coronary atherosclerosis. The drug is approved for use in patients with primary hypertriglyceridemia (Fredrickson type IV), primary dyslipoproteinemia (Fredrickson type III), primary hypercholesterolemia (Fredrickson type...
IIa), and mixed dyslipidemia (Fredrickson type IIa). The recommended starting dose is 10 to 20 mg once daily at bedtime for primary hypercholesterolemia, with a usual dosing range of 10 to 40 mg daily. A 40 mg dose may be necessary to achieve the clinical benefits observed in the primary and secondary prevention trials done with the drug. The drug is also approved for pediatric use in children aged 8 to 18 years with familial hypercholesterolemia in doses of 20 and 40 mg daily. A pravastatin/ascorbic acid co-package has become available for the long-term management to reduce the risk of cardiovascular events in patients with clinically evident coronary disease.

Similar to other HMG-CoA reductase inhibitors, the drug may be combined with other classes of lipid-lowering drugs. When combined with cholestyramine or colestipol, pravastatin should be administered 1 hour before or 4 hours after the bile-acid resin is given. Such precautions appear not to be necessary with colesevelam.

**Adverse Effects**

The adverse effect profile is similar to other HMG-CoA reductase inhibitors in use. Since the drug does not cross the blood–brain barrier, it has been proposed to cause a lower incidence of sleep disturbances than either lovastatin or simvastatin. A rare peripheral–neuropathic complication with both lovastatin and pravastatin has been described.

As with simvastatin, the low risk of liver enzyme abnormalities and their lack of clinical severity has led to less stringent requirements for liver function testing. The recommendation for liver function testing at 6 weeks has been eliminated, as has the recommendation for semi-annual testing if liver function tests are normal at 12 weeks, twice a year, ceasing a year after the last dosage increment if liver function tests remain normal.

**Fluvastatin**

Fluvastatin was the first synthetic HMG-CoA reductase inhibitor, and it is structurally distinct from the fungal derivatives lovastatin, simvastatin, and pravastatin. It was approved for clinical use in the United States for the treatment of primary hypercholesterolemia (type IIa and IIb). The drug also received approval as the fourth statin and, like other HMG-CoA reductase drugs, undergoes extensive first-pass metabolism. Its adverse-effect profile is similar to those of other HMG-CoA reductase inhibitors, and it may cause less myopathy and risk of rhabdomyolysis when used alone or with gemfibrozil, nicotinic acid, cyclosporine, and erythromycin. The drug has been combined with other lipid-lowering therapies—including cholestyramine, bezafibrate, and nicotinic acid—to achieve greater lipid-lowering effects; it has been used safely in diabetic and hypertensive patients.

**Effects on Clinical Endpoints**

Although many patients with known CAD have received fluvastatin, there are as yet no published survival studies with the drug. One study assessed the efficacy of high-dose fluvastatin (80 mg daily) in preventing restenosis after balloon angioplasty; no significant benefit was detected. In another study, known as the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effects of fluvastatin versus the placebo on long-term progression of atherosclerosis were assessed in patients with known CAD using serial coronary angiography. Results from the LCAS demonstrated a benefit of fluvastatin treatment on the progression and regression of atherosclerosis. The results of the prospective Lescol Intervention Prevention Study (LIPS) demonstrated that statin therapy initiated soon after successful percutaneous coronary intervention improved clinical outcomes. These data support the use of early lipid-lowering therapy in post-percutaneous coronary intervention patients regardless of baseline cholesterol level.

Fluvastatin has been evaluated as an anti-ischemic drug in patients immediately following MI (Effects of Fluvastatin Administration Immediately after an Acute MI on Myocardial Ischemia—FLORIDA), with no benefit compared to the placebo after 1 year. The drug has been shown to lower total and LDL cholesterol as well as dense LDL, a more atherogenic subfraction of LDL.

**Clinical Use**

Fluvastatin (capsules and an extended-release tablet form of the drug) is indicated as an adjunct to diet to reduce elevated total cholesterol, LDL cholesterol, triglycerides, and apo B levels and to increase HDL cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson types IIa and IIb). Both formulations are also indicated to slow the progression of coronary atherosclerosis in patients with CAD as part of a treatment strategy to lower total and LDL cholesterol. The
drug is also approved for use in adolescent boys and girls with familial hypercholesterolemia.

The recommended starting dose in adults is 40 mg as 1 capsule or 80 mg as 1 extended-release tablet administered as a single dose in the evening or 80 mg in divided doses of the 40 mg capsules given twice daily. As in the case of other HMG-CoA reductase inhibitors, it takes at least 4 weeks to achieve the maximal effect. If fluvastatin is combined with cholestyramine, fluvastatin plasma levels drop considerably. Fluvastatin must be given at least 4 hours after a cholestyramine dose. The recommended starting dose for children is 20 mg.

**Atorvastatin**

Atorvastatin is a newer synthetic HMG-CoA reductase inhibitor with a long half-life (14 hours, 20 to 30 hours for activity due to the presence of active metabolites) that is similar in structure to fluvastatin. Atorvastatin is twice as potent on a milligram-to-milligram basis as simvastatin and much more potent than fluvastatin in reducing total cholesterol and LDL cholesterol. Early investigations proposed that atorvastatin was unique in its ability to reduce triglycerides. This has been less striking in subsequent studies; if such potency is present at all, the advantage is modest. In 1997, the drug was approved for clinical use in patients with types Ia and IIb hypercholesterolemia and homoyzogous familial hypercholesterolemia. Its adverse-effect profile appears to be similar to those of other HMG-CoA reductase inhibitors in doses up to 80 mg daily used once daily.

**Effects on Clinical Endpoints**

Aggressive therapy with atorvastatin 80 mg was shown to produce less progression of noninvasively quantitated carotid atherosclerosis than lower-dose therapy with simvastatin 40 mg. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial showed that the administration of atorvastatin 80 mg immediately after hospitalization for unstable angina or non-Q-wave MI reduced the incidence of recurrent ischemic events over the first 16 weeks. Patients who were treated with either simvastatin or pravastatin in the 3 major secondary prevention statin trials (4S, CARE, LIPID) or pravastatin or lovastatin in the 2 major primary prevention trials (WOSCOPS and AFCAPS/TexCAPS) did not show benefit at such an early time point. This may reflects differences in the biology of acute as opposed to chronic coronary syndromes, increased statistical power due to a high risk of short-term ischemic complications in unstable patients, or particular advantages of the high-dose atorvastatin regimen used. It is noteworthy that at high doses, atorvastatin loses some of its effectiveness in raising HDL, an effect not seen with equipotent doses of simvastatin.

The Atorvastatin versus Revascularization Treatment study (AVERT) examined 341 patients with stable CAD who were referred for percutaneous transluminal coronary angioplasty. Patients were randomly assigned to either atorvastatin 80 mg per day or to angioplasty followed by usual care, which did not exclude lipid-lowering therapy. Over 18 months of follow-up, the incidence of ischemic events was 36% lower in the atorvastatin group ($P = .048$, but not significant after statistical adjustment for interim analyses). The patients who received atorvastatin also had a longer time to the first ischemic event ($P = .03$). There was no “usual care” placebo group, and it is unclear to what extent the results in this study reflect the benefit of atorvastatin versus possible disadvantages of angioplasty in the study population.

In the Collaborative Atorvastatin Diabetes Study (CARDS), 2,838 patients (62% older than 60 years) with diabetes mellitus, no cardiovascular disease, and a serum LDL cholesterol < 160 mg/dL were randomized to atorvastatin 10 mg daily or the placebo. At 3.9-year median follow-up, compared with the placebo, atorvastatin significantly reduced time to first occurrence of acute CAD events, coronary revascularization, or stroke. In 4,162 patients hospitalized for an acute coronary syndrome (29% with unstable angina and 71% with an acute MI) in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, the median serum LDL cholesterol was 95 mg/dL in patients randomized to pravastatin 40 mg daily versus 62 mg/dL in patients randomized to atorvastatin 80 mg daily. At 2-year follow-up, the primary endpoint of death from any cause, MI, documented unstable angina requiring rehospitalization, coronary revascularization (performed at least 30 days after randomization), and stroke was 26.3% in the pravastatin group versus 22.4% in the atorvastatin group, a significant 16% reduction in favor of atorvastatin.

If one pools the data from 8,658 post-acute coronary syndrome patients from the PROVE IT-TIMI 22 trial and the Aggrastat to Zocor (A to Z) trial, serum LDL cholesterol levels at 8 months were a median of 64 mg/dL in the group treated with intensive statin therapy versus a median of 87 mg/dL in the group treated with moderate statin therapy. All-cause mortality was significantly reduced 23% from 4.9% to 3.6% in the group treated with intensive statin therapy compared to treatment with moderate statin therapy.

In the Treating to New Targets (TNT) study of 10,001 patients with stable CAD and a serum LDL cholesterol level < 130 mg/dL, the effect of atorvastatin 10 mg daily versus 80 mg daily was investigated in a randomized, double-blind trial. The mean serum LDL cholesterol levels were 77 mg/dL in patients treated with atorvastatin 80 mg daily versus 101 mg/dL in patients treated with
Atorvastatin 10 mg daily. At 4.9-year median follow-up, the primary endpoint of a first major cardiovascular event was significantly reduced 22% by atorvastatin 80 mg daily. In addition, strokes were reduced with the higher atorvastatin dose.

A prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins was performed. This meta-analysis showed that statin therapy can safely decrease the 5-year incidence of major coronary events, coronary revascularization, and stroke by about one-fifth per 38.7 mg/dL reduction in serum LDL cholesterol, irrespective of the initial lipid profile or other presenting characteristics (Figure 20-10). The absolute benefit related chiefly to a person's absolute risk of such events and to the absolute reduction in serum LDL cholesterol achieved. These findings reinforce the need to give prolonged statin therapy with substantial serum LDL cholesterol reduction in all patients at high risk of any type of major vascular event. This meta-analysis also showed that statins did not cause an increase in any site-specific cancer. The 5-year excessive risk with statin use of rhabdomyolysis was 0.01%.

In the Study Assessing Goals in the Elderly (SAGE), 893 ambulatory CAD patients aged 65 to 85 years with at least one episode of myocardial ischemia lasting at least 3 minutes during 48-hour ambulatory electrocardiographic screening were randomized to atorvastatin 80 mg daily or to pravastatin 40 mg daily and followed for 12 months. Total duration of myocardial ischemia detected by 48-hour ambulatory electrocardiograms at month 3 and at month 12 after randomization was significantly reduced by both atorvastatin and pravastatin with no significant difference between the 2 treatment groups. Compared with pravastatin, atorvastatin significantly reduced serum LDL cholesterol levels, insignificantly reduced major acute cardiovascular events by 22%, and significantly decreased all-cause mortality by 67%. Recently the drug was shown to be safe and effective in improving abnormal liver tests and cardiovascular morbidity in patients with probable nonalcoholic liver disease.

Clinical Use
Atorvastatin is approved for reducing elevated total cholesterol, LDL cholesterol, apo B, and triglyceride levels and to increase HDL cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia. In addition, the drug is approved for use in patients with primary dysbetalipoproteinemia and elevated triglyceride levels; for the prevention of cardiovascular disease in patients without clinically evident CAD but with multiple risk factors for CAD such as age, smoking history, hypertension, low HDL cholesterol, a family history of early CAD; to reduce the risk of MI, stroke, and the need for coronary

Figure 20-10. Relation between proportional reduction in incidence of major coronary events and major vascular events and mean absolute LDL cholesterol reduction at 1 year. Square represents a single trial plotted against mean absolute LDL-cholesterol reduction at 1 year, with vertical lines above and below corresponding to 1 SE of unweighted event rate reduction. Trials are plotted in order of magnitude of difference in LDL cholesterol at 1 year. For each outcome, regression line (which is forced to pass through the origin) represents weighted event rate reduction per mmol/L LDL cholesterol reduction.

revascularization procedures; and angina. In addition, the drug is approved for patients with type 2 diabetes mellitus and those without clinically evident CAD such as retinopathy, albuminuria, smoking, or hypertension to reduce the risk of MI and stroke.\textsuperscript{403,404} In patients with clinically evident CAD, atorvastatin is indicated to reduce the risk of non-fatal MI, fatal and non-fatal stroke, the need for revascularization procedure, the need to be hospitalized for congestive heart failure, and for reducing the risk of angina. The drug is also approved for use in boys and postmenarchal girls aged 10 to 17 with familial hypercholesterolemia.

The recommended starting dose of atorvastatin is 10 mg once daily. The dosage range is 10 to 80 mg once daily. The drug can be administered as a single dose at any time of the day, with or without food. The drug is also available in combination with amlodipine, the first combination product for 2 distinct indications.

**Rosuvastatin**

Rosuvastatin is a highly efficacious statin that is more potent in reducing LDL cholesterol and triglycerides and in raising HDL cholesterol than the other statins discussed.\textsuperscript{398-402} It appears to combine a number of the characteristics of the currently available statins. Like pravastatin, rosuvastatin is liver-selective, hydrophilic, and minimally metabolized via CYP3A4. Like atorvastatin, rosuvastatin has a prolonged half-life in systemic plasma of about 20 hours and is quite potent. The maximum tested dose of 80 mg reduced LDL 65%, significantly more than is possible using current monotherapy; however, the high dose was not well tolerated in some patients. Rosuvastatin also produced greater increases in HDL than is seen with high-dose atorvastatin. The 10 mg dose reduced LDL by approximately 50%.

**Effects on Clinical Endpoints**

In a prospective, open-label blinded endpoints trial of 507 patients with CAD in the Effect of Rosuvastatin on Intravascular Ultrasound–Derived Coronary Atheroma Burden (ASTEROID) trial, rosuvastatin 40 mg daily for 2 years reduced serum LDL cholesterol 53% from 130 to 61 mg/dL, increased serum HDL cholesterol 15% from 43 to 49 mg/dL, and reduced serum triglycerides 20% from 152 to 121 mg/dL.\textsuperscript{403,404} Intravascular ultrasound showed significant regression of atherosclerosis for all 3 prespecified intravascular ultrasound measures of disease burden at 2-year follow-up. The ASTEROID trial also showed at 2-year follow-up that rosuvastatin therapy to reduce the serum LDL cholesterol level to less than 70 mg/dL produced regression of CAD by reducing the percentage of diameter stenosis and improving minimum lumen diameter as measured by quantitative coronary angiography.\textsuperscript{415}

Another study with rosuvastatin showed reductions in the rate of progression of carotid-intima media thickening.\textsuperscript{406}

In the Justification for the Use of Statins in Prevention: an Intervention Trial evaluating Rosuvastatin (JUPITER), 17,082 apparently healthy participants with a LDL cholesterol of <130 mg/dL and high-sensitivity C-reactive protein levels ≥2.0 mg/L were randomized to rosuvastatin 20 mg daily or the placebo.\textsuperscript{41} At 1.9-year median follow-up, rosuvastatin significantly reduced serum LDL cholesterol levels by 50%, high-sensitivity C-reactive protein levels by 37%, and the primary endpoint of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes by 44%. Benefits with rosuvastatin were also seen in patients with chronic kidney disease,\textsuperscript{404} and the benefits were similar in men and women.\textsuperscript{406} In patients with systolic heart failure, the drug did not provide additional benefit on outcomes, but was safe to use.\textsuperscript{407} In addition, rosuvastatin showed no benefit in patients undergoing dialysis.\textsuperscript{408} However, a benefit of the drug in preventing venous thromboembolism was confirmed.\textsuperscript{409}

The drug is approved for use in patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total cholesterol, LDL cholesterol, Apo B, non-HDL cholesterol and triglyceride levels, and to increase HDL cholesterol. It is also approved for use in patients with hypertriglyceridemia and with homozygous familial hypercholesterolemia and for slowing the progression of atherosclerosis as part of a treatment strategy to lower total cholesterol and LDL cholesterol.

The drug is available in 5, 10, 20, and 40 mg tablets. The starting dose is 10 mg.

**Pitavastatin**

Pitavastatin is a potent statin that was approved for use in a 4 mg dosage by the FDA on August 3, 2009. Evaluable intravascular ultrasound evaluations were made at baseline and at 8-12 month follow-up in 252 patients with an acute coronary syndrome randomized to statin therapy with pitavastatin 4 mg daily or atorvastatin 20 mg daily in an open-label, prospective study with blind endpoint evaluation.\textsuperscript{410,411} Significant regression of coronary plaque volume occurred in both treatment groups with no significant difference between the 2 statins.

**Clinical Use**

Pitavastatin is available in 2 and 4 mg tablets for the treatment of hyperlipidemia. The initial dose is 2 mg daily.

**Other Statin Uses**

**Intermittent Claudication**

Three double-blind, randomized, placebo-controlled studies showed that statins prolonged exercise time in patients with intermittent claudication and peripheral
arterial disease (see Chapter 34, Drug Treatment of Peripheral Vascular Disorders). Sixty-nine patients with intermittent claudication due to peripheral arterial disease and hypercholesterolemia were randomized to simvastatin 40 mg daily or the placebo. Compared with the placebo, simvastatin significantly increased treadmill exercise time until the onset of intermittent claudication by 24% at 6 months after treatment and by 42% at 1 year after treatment.

In a study of 354 participants with intermittent claudication due to peripheral arterial disease and hypercholesterolemia randomized to atorvastatin 80 mg daily or the placebo, atorvastatin 80 mg daily significantly improved pain-free treadmill walking distance by 40% and community-based physical activity at 1-year follow-up compared with the placebo. In another study of 86 participants with intermittent claudication due to peripheral arterial disease and hypercholesterolemia, simvastatin 40 mg daily significantly improved pain-free walking distance and total walking distance on a treadmill, significantly improved the mean ankle-brachial index at rest and after exercise, and significantly improved symptoms of claudication at 6-month follow-up compared with the placebo.

Implantable Cardioverter-Defibrillators

The use of lipid-lowering drugs in 27 of 78 patients with CAD and life-threatening ventricular arrhythmias treated with an implantable cardioverter-defibrillator (ICD) was associated with a significant decrease in recurrence of life-threatening ventricular arrhythmias from 57% to 22%. The use of lipid-lowering drugs in 83 of 362 patients with CAD treated with an ICD for ventricular tachycardia/ventricular fibrillation significantly decreased the recurrence of ventricular tachycardia/ventricular fibrillation by 60%. The use of statins in 154 of 281 patients with CAD and ventricular arrhythmias treated with an ICD was associated with a significant decrease in recurrence of ventricular arrhythmias from 50% to 30%.

Statins significantly reduced death or ventricular tachycardia or ventricular fibrillation by 35% in patients with an ICD in the Multicenter Automatic Defibrillator Implantation trial (MADIT-II). The use of statins in 402 of 965 patients treated with an ICD was significantly associated with a 42% reduction in all-cause mortality. The use of statins in 121 of 209 patients with heart failure treated with combined cardiac resynchronization-ICD therapy was associated with a significant 54% reduction in appropriate ICD shocks and with a significant 95% reduction in mortality. Randomized clinical trials need to be performed to confirm the validity of these studies.

Innovative Uses

Statins have also been used as potential antiarrhythmic drugs and as possible therapies for treating autoimmune disease and sepsis. Recently it was shown that statins reduced the occurrence of venous thromboembolism in patients with cancer.

Conclusion

There has been an evolution of more rigorous and aggressive approaches to the primary and secondary prevention of CAD that have occurred in parallel with growing evidence for the safety and effectiveness of HMG-CoA reductase inhibitors in treating hypercholesterolemia and for reducing the incidence of cardiovascular morbidity and mortality in patients at greater risk. The HMG-CoA reductase inhibitors are the most effective agents for reducing both total and LDL cholesterol and can be used in conjunction with other lipid-lowering treatments for achieving maximal lipid-lowering effectiveness in patients. HMG-CoA reductase inhibitors, to a variable extent, also produce modest increases in HDL that may be clinically significant and, in higher doses, also lower triglycerides. In addition, these drugs have been shown to have protective actions beyond the
effects of cholesterol reduction (nitric oxide–mediated improvement of endothelial dysfunction, plaque stabilization, antioxidant effect, anti-inflammatory properties, and anticoagulant and antihypertensive effects). The drugs have been shown to reduce the risk of hip fracture and dementia in elderly patients and may counteract the adverse effects of hormone replacement in postmenopausal women with CAD. In practice, inadequate utilization and, in particular, titration of HMG-CoA reductase inhibitor therapy continues to be a problem, and information regarding the safety record of HMG-CoA reductase inhibitor therapy and the benefits of this treatment on clinical outcomes must be disseminated more widely, both to clinicians and patients.

Statins need to be prescribed at discharge after MI in order to achieve a maximal benefit. Statin pretreatment in patients with acute coronary syndromes is associated with improved clinical outcomes. However, discontinuation of statins after onset of symptoms negates the beneficial effect.

**Nicotinic Acid (Niacin)**

Nicotinic acid (pyridine-3 carboxylic acid, or niacin) is a water-soluble B-complex vitamin (Figure 20-11) that is used for the prophylaxis and treatment of pellagra. The substance functions in the body after conversion to either nicotinamide-adenine dinucleotide or nicotinamide-adenine dinucleotide phosphate. In 1955, Altschul and colleagues demonstrated that large doses of nicotinic acid lower the concentration of plasma cholesterol in humans. This property of nicotinic acid is not shared by nicotinamide and appears to have nothing to do with the role of these compounds as vitamins. Subsequently, nicotinic acid in high doses was shown to reduce triglycerides and have favorable effects in patients with various hyperlipoprotein-emias. From the results of controlled clinical trials with nicotinic acid, there is evidence that cardiovascular morbidity can be reduced with long-term therapy. In this section, the clinical pharmacology of nicotinic acid as a lipid-lowering agent is reviewed and recommendations for its clinical use are presented.

**Pharmacokinetics**

Nicotinic acid is readily absorbed from the intestinal tract after the oral administration of pharmacologic doses. The level of free nicotinic acid in plasma reaches a peak value between 30 and 60 min after a single dose of 1 g is ingested. Because nicotinic acid is rapidly eliminated, the doses necessary to achieve pharmacologic effects (2 to 8 g daily) are much greater than the amount needed for its physiologic functions as a vitamin. When large doses of the vitamin were given to rats by intraperitoneal injection, the half-life of the compound in blood was found to be approximately 1 hour. The half-life of nicotinic acid seems to be determined primarily by the rate of renal clearance of the unchanged compound when given in high doses. At lower doses, it is mainly excreted as its metabolites.

The metabolic fate of nicotinic acid is complex and varies with the dose. Under normal conditions, metabolites of nicotinic acid found in the urine are mainly the products of catabolism of the pyridine nucleotides, the stored forms of the vitamin. The primary route of metabolism is via methylation to N-methyl-nicotinamide, which is further oxidized to N-methyl-2- and -4-pyridone carboxamides. With pharmacologic doses, the excretion of nicotinuric acid, produced by the conjugation of nicotinic acid and glycine, is enhanced and seems to play a role as a detoxification product at these higher doses. Once the dose is large enough to overcome the production rate of nicotinuric acid, nicotinic acid is excreted largely unchanged.

**Pharmacology**

Nicotinic acid in large doses lowers total plasma cholesterol and has been found to have beneficial effects on the levels of the major serum lipoproteins, including Lp(a). Specifically, it decreases the levels of VLDL triglyceride (VLDL-Tg) and LDL cholesterol and causes an increase in the levels of HDL cholesterol. This lipid-altering activity is not shared by nicotinamide and seems to be unrelated to the role of nicotinic acid as a vitamin in the nicotinamide-adenine dinucleotide and its phosphate coenzyme systems. Pharmacologic doses of nicotinic acid result in a rapid decrease in plasma triglyceride (Tg) levels, in part by lowering VLDL-Tg concentrations by 20 to more than 80%. The magnitude of the reduction is
related to the initial VLDL levels. Within 1 week of initiation of therapy, concentrations of LDL cholesterol decrease. Typically, a 10% to 5% reduction in LDL cholesterol is observed within 3 to 5 weeks of attaining full dosage. The magnitude of the drop is also related to the dose of nicotinic acid. In addition to these lipid-lowering effects, nicotinic acid raises HDL cholesterol concentrations.\textsuperscript{454,455} Mobilization of cholesterol from peripheral tissues seems to occur after prolonged therapy, as evidenced by the regression of eruptive, tuboeruptive, tuberosous, and tendon xanthomas.\textsuperscript{454}

There are several mechanisms by which nicotinic acid alters serum lipoprotein levels. Nicotinic acid’s actions as an antilipolytic agent may be related to its effects on lowering VLDL-Tg concentration. Nicotinic acid has been found to decrease lipolysis in adipose tissue, resulting in decreased levels of plasma free fatty acids.\textsuperscript{456} After oral administration of 1 g of nicotinic acid, a significant depression of free fatty acids occurs as well as a reduction in plasma glycerol levels. During fasting, free fatty acids released from adipose tissue serve as the major precursors for the formation of VLDL-Tg, which is synthesized mainly in the liver and serves as the major carrier of endogenous triglyceride.\textsuperscript{454} The decrease in the release of free fatty acid from adipose tissue that is induced by nicotinic acid is thought to decrease uptake of free fatty acid by the liver and thereby reduce the hepatic synthesis of VLDL.\textsuperscript{454}

**Clinical Experience**

As outlined above, nicotinic acid has been shown to have beneficial effects on all plasma lipoprotein fractions, including lipoprotein(a), and was identified as one of the drug choices for the treatment of hypercholesterolemia by the Adult Treatment Panel of the NCEP.\textsuperscript{48} Studies of the clinical efficacy of nicotinic acid fall into 2 main groups: those that examine the use of nicotinic acid in patients with known CAD and those that test its efficacy, often in combination with other lipid-lowering agents, in altering plasma lipoprotein levels in patients with various types of hyperlipoproteinemias.

The Coronary Drug Project, a long-term nationwide, double-blind, placebo-controlled study, looked at a number of lipid-altering regimens, including nicotinic acid and clofibrate, in male survivors of MI.\textsuperscript{214}

Over the follow-up period, nicotinic acid effected mean decreases in total serum cholesterol of 9.9% and in total triglycerides of 26.1%.\textsuperscript{214} However, the incidence of all deaths in the follow-up period (8.5 years) was significantly lower than that in the placebo group (24.4% versus 25.4%). In contrast to the findings on total mortality, the incidence of definite, nonfatal MI over the total follow-up period was 27% lower in the treatment group than in the control group (10.1% versus 13.9%). Also, during this period, the treatment group showed a 24% lower incidence of fatal or nonfatal cerebrovascular events than the placebo group. There was also a lower incidence of bypass surgery in the group receiving nicotinic acid (0.9% versus 2.7%).

Investigators in the Coronary Drug Project conducted a follow-up study nearly 9 years after termination of the original trial.\textsuperscript{457} With a mean total follow-up of 15 years, total mortality in the nicotinic acid group was found to be 11% lower than in the placebo group (52% versus 58.2%). The men in the study had presumably stopped taking the drug after the original mean follow-up of 6.2 years. The decreased mortality is primarily due to a decrease in CAD mortality, with smaller decreases in death due to cerebrovascular causes, other cardiovascular events, cancer, and other noncardiovascular and noncancer causes.

Explanations for this observed late benefit of nicotinic acid on mortality include the early decreases in incidence of nonfatal reinfarction and the cholesterol-lowering effects of nicotinic acid on the coronary arteries.\textsuperscript{457} It seems that patients with the largest decreases in cholesterol at 1-year follow-up had lower subsequent mortality than did subjects with increases in cholesterol. Nearly 30% of the men in the nicotinic acid group adhered poorly to the treatment regimen (took less than 60% of the amount of drug called for by the protocol), yet there was a significant benefit in 15-year mortality. This suggests that less than optimal doses of nicotinic acid may nevertheless result in therapeutic benefits. Of course, statements regarding the efficacy of nicotinic acid as a primary prevention of CAD or whether the administration of nicotinic acid over longer periods of time would be beneficial or detrimental cannot be made based on the findings of this study.

In a Swedish study by Carlson et al.,\textsuperscript{458} the effects of combined treatment with nicotinic acid (up to 3 g daily) and clofibrate (2 g daily) were examined in 558 survivors of MI randomly assigned to 1 of 2 groups 4 months after their acute events. Both groups received advice regarding diet, and the treatment group received both drugs as above. Subjects in the treatment group exhibited mean reductions in total serum cholesterol and serum triglycerides of 15% to 20% and 30%, respectively. Control group subjects showed insignificant reductions in these levels. There were no significant differences between the 2 groups with regard to total and CAD-related deaths. However, over a 4-year period, the number of nonfatal reinfarctions in the treatment group was reduced by 50% compared with the control group. In comparison, the Coronary Drug Project reported a 27% reduction in nonfatal reinfarctions in the nicotinic acid group and insignificant reductions in the clofibrate group. Considering the more modest decreases in serum cholesterol and tri-
glycerides (6% and 10%, respectively) found in the Coronary Drug Project as compared with those observed in this study, it has been suggested that the rate of nonfatal reinfarction may be related to the degree of serum lipid lowering.\

The Cholesterol-Lowering Atherosclerosis Study (CLAS) employed a colestipol-nicotinic acid combination to test the hypothesis that aggressive lowering of LDL cholesterol and raising of HDL cholesterol reverses or retards the progression of atherosclerotic lesions. The subjects, chosen to minimize the effects of other major nonlipid risk factors for atherosclerosis, included 162 normotenive nonsmoking men aged 40 to 59 years with previous coronary bypass surgery and fasting levels of total cholesterol in the range of 4.78 to 9.05 mm/L (185 to 350 mg/dL).

The results of angiographic readings show that the treatment group’s score distribution was more significantly shifted toward lower scores than that of the control group, indicating less disease progression with coleste- pol-nicotinic acid treatment. In fact, 61% of the treatment group subjects improved or remained the same, and 16.2% showed regression of atherosclerotic lesions at 2 years. This differs from the results in the placebo control group of 39% and 2.4%, respectively. Regarding native vessels, treatment reduced the average number of lesions that progressed per subject and the percentage of subjects with new lesions. Similarly, with respect to bypass grafts, the percentage of subjects either with new lesions or showing any adverse change in preexisting lesions was significantly lower in the treatment group. Recently reported were the results of a 7-year follow-up of a subpopulation from CLAS. These findings suggest that, following coronary artery bypass surgery, patients should receive intensive interventions to improve blood lipid and lipoprotein levels.

The results of the Familial Atherosclerosis Treatment Study (FATS) demonstrated a favorable effect of nicotinic acid plus colestipol on the progression of coronary atherosclerotic disease. With the nicotinic acid-colestipol combination, 25% of patients showed progression of coronary lesions and 39% showed regression; only 2 cardiovascular events occurred. In contrast, 10 cardiovascular events occurred in the control group, 46% of patients showed regional progression, and 11% showed regression of coronary lesions. Patients with disease, a family history of premature cardiovascular events, and elevated levels of apo B (3.23 mm/L or 125 mg/dL) were counseled on diet and assigned to 1 of 3 treatment regimens: nicotinic acid 4 g per day plus colestipol 30 g per day; lovastatin 40 mg per day plus colestipol; or colestipol alone (control).

The combination regimens caused the greatest reductions in LDL and the greatest elevations in HDL. Bimonthly visits spanned 2.5 years between coronary angiograms. Favorable changes in clinical course and lesion severity appeared with the combination regimens.

The results of a blinded, placebo-controlled larger (160 patients) angiographic regression trial of combination therapy were recently reported. The effects of combination therapy with simvastatin and niacin or of an antioxidant vitamin cocktail (or both) were evaluated in a population with known CAD and normal LDL levels (mean 125 mg/dL). The vitamin supplement (vitamin E, vitamin C, beta-carotene, and selenium) was without effect on lipid levels but was documented to decrease the susceptibility of LDL to in-vitro oxidation. Simvastatin was titrated to obtain an LDL below 90 mg/dL and then slow-release niacin was added in the ultimate dose of 1 g twice a day. Patients whose HDL did not exhibit a desired increase (5 mg/dL at 3 months, 10 mg/dL by 12 months) were switched to crystalline niacin in higher doses. Simvastatin was back titrated if the LDL fell below 40 mg/dL. Combined antioxidant therapy significantly blunted the benefit of the drug regimen, both on plasma lipids and on angiographic progression. Proximal coronary stenosis increased by a mean 3.9% in the placebo group, 1.8% in the antioxidant group, and 0.7% in the combined therapy group, but it decreased by 0.4% in the group receiving drug therapy alone. In addition, there was a 90% decrease in the incidence of a first cardiovascular event (death, MI, stroke, or revascularization) in this group. The endpoint was reached in 24% of the placebo-treated patients, 21% of the patients given antioxidant alone, 14% of those given both, and 3% of those given simvastatin and niacin alone. These benefits were out of proportion to the LDL lowering achieved (42%), particularly given the limited period of follow-up (38 months). The results provide support for the potential value of HDL-raising therapy, in particular using niacin, in the management of coronary risk. The negative effect of combining vitamins with drug therapy cannot be considered established given the modest size and statistical power of this study. However, any benefits of vitamins alone on angiographic disease did not reach statistical significance and were not correlated with any effect on clinical endpoints. Recently, the drug was shown to have an advantage over ezetimibe on the progression of atherosclerosis.

Clinical Use

Nicotinic acid—through its beneficial effects on total cholesterol, LDL and HDL cholesterol, total triglycerides, VLDL triglycerides, Lp(a), Apo B, and Apo A1—is indicated in most forms of hyperlipoproteinemia and for patients with depressed HDL. This includes patients with types II, III, IV, and V hyperlipoproteinemia. It is particularly useful in patients who have elevated plasma
VLDL triglyceride levels as a part of their lipid profile. It is important to remember that a diet low in cholesterol and saturated fats is the foundation of therapy for hyperlipoproteinemia. The drug is indicated for use in combination with lovastatin and simvastatin, and combination formulations are available. In patients with a history of MI and hypercholesterolemia, niacin is indicated to reduce the risk of recurrent MI. In patients with a history of CAD and hypercholesterolemia, niacin in combination with BAS is indicated to slow progression or promote regression of atherosclerotic disease.

Niacin therapy should be initiated with a low-dosage regimen (100 mg daily), gradually increasing the dose every few days over a period of several weeks until the patient attains a dosage level of 3 g daily given in 3 divided doses. If, while increasing the dose, the patient develops any adverse effects, the dose should be cut back and then resumed at a more gradual pace. Taking the doses with meals decreases gastric irritation and cutaneous flushing. Further, cutaneous flushing can be reduced or avoided by taking 1 aspirin tablet daily (more frequent administration is unnecessary, as 1 tablet will inhibit cyclooxygenase for up to 2 weeks). It is interesting that tachyphylaxis to the flushing phenomenon often occurs within a few days, although the bothersome episodes may recur if the patient misses 2 or 3 doses.

Once the initial maintenance dose is reached, it is important to evaluate for therapeutic effects by measuring plasma lipoprotein values. If the therapeutic effects are unsatisfactory, the dose should be increased by a further 1.0 to 1.5 g per day, with periodic increases to a maximum of 7 to 8 g daily as needed. Usually, when doses of 4 g daily are achieved, another lipid-lowering drug is added. Regardless of the dose, it is important to make several laboratory evaluations for potential adverse effects at regular intervals. These include assessment of liver function (bilirubin, alkaline phosphatase, and transaminase levels), uric acid levels, and serum glucose levels. Nicotinic acid is contraindicated in patients with active peptic ulcer disease. The drug may also impair glucose tolerance and is contraindicated in patients with diabetes mellitus that is difficult to control. Nicotinic acid is also associated with reversible elevations of liver enzymes and uric acid and should not be used in patients with hepatic disease or a history of symptomatic gout.

Various sustained-release preparations of nicotinic acid are available without prescription. Timed-release forms of nicotinic acid were developed after it was noted that the incidence of cutaneous flushing was reduced when the drug was taken with meals, suggesting that this adverse effect is related to the rate of GI absorption. In fact, patients taking the timed-release preparation do have a lower incidence of flushing than patients on unmodified nicotinic acid and require less frequent administration. However, this is outweighed by the far greater incidence of GI and constitutional symptoms experienced by patients on the timed-release form, including nausea, vomiting, diarrhea, fatigue, and decreased male sexual function. In addition, the timed-release preparations appear to be associated with greater hepatotoxicity, even at low doses, including greater alkaline phosphatase and transaminase elevations. In the doses required for the treatment of hyperlipidemia, they clearly have an increased potential for chemical hepatitis that can be severe. A flush-free niacin was developed but did not receive clinical approval.

A proprietary “intermediate release” formulation of nicotinic acid (Niaspan) that requires a prescription is also suitable for once-daily administration. This preparation also appears to decrease adverse effects to some extent and is without an increased risk of hepatitis in its recommended dosing range (only up to 2 g daily). Other newer delayed-release preparations are still undergoing evaluation for safety and efficacy. A combination of a delayed-release nicotinic acid and lovastatin is now available for clinical use, as well as a combination of delayed-release niacin with simvastatin. A clinical experience was reported with the use of a new form of nicotinic acid that employs a wax-matrix vehicle for sustained-release drug delivery. Studies have been done with laropiprant, an antagonist of the PGD2 receptor in combination with niacin to avoid flushing, but this combination is not yet available.

Adverse Effects

Despite the efficacy of nicotinic acid in beneficially altering serum lipoprotein levels, its use is limited by a variety of troublesome and sometimes serious adverse effects. Some studies have experienced as much as a 50% dropout rate as a result of drug-related adverse effects.

The Coronary Drug Project, with 1,100 subjects on nicotinic acid therapy, reported the common occurrences of cutaneous flushing and pruritus. Other dermatologic adverse effects include dryness of skin, rash, and acanthosis nigricans, which are all reversible with cessation
of therapy. The mechanism of the flushing is presumed to be related to the effect of nicotinic acid on vasodilatory prostaglandins and is frequently attenuated by pretreatment with aspirin. This vasodilatory effect in combination with antihypertensive therapy may potentially result in postural hypotension. The Coronary Drug Project also described an increased incidence of atrial fibrillation; other transient cardiac arrhythmias were noted. In addition, elevations in uric acid levels associated with an increased incidence of acute gouty arthritis were observed.

GI symptoms including diarrhea, nausea, vomiting, and abdominal pain were also frequent complaints encountered in the Coronary Drug Project. Activation of peptic ulcer disease by nicotinic acid is a potential adverse effect, but it was not observed in this large-scale study.

Liver function tests are frequently abnormal during nicotinic acid therapy. Generally, there is elevation in alkaline phosphatase and hepatic transaminases. Some studies have also noted elevations in bilirubin, occasionally leading to jaundice. The elevations in transaminases are generally transient and reverse with decrease in dosage or cessation of therapy; these elevations can be minimized by increasing the dosage in gradual increments when therapy is being initiated.

Unlike the elevations in hepatic enzymes associated with HMG-CoA reductase inhibitors, the elevations that occur with the use of nicotinic acid may be symptomatic. Several cases of niacin hepatitis progressing to fulminant hepatic failure have been described, most frequently with the time-release formulation, with biochemical, clinical, and histologic evidence of hepatocellular injury. This seems to be a dose-related hepatotoxicity rather than a hypersensitivity, occurring in almost all cases at doses greater than 3 g daily. In most cases, cessation of therapy leads to eventual resolution of abnormalities. Hyperglycemia and impaired glucose tolerance may occur with nicotinic acid therapy and often necessitates adjustments in diet and hypoglycemic therapy in diabetic patients.

The results of a recent study demonstrated that niacin is an effective treatment for hyperlipidemia in patients with diabetes mellitus and that its adverse effects on glycemic control are modest.

The Coronary Drug Project noted a statistically significant increase in creatine phosphokinase levels with nicotinic acid therapy, and there have been reports of associated reversible myopathy. The combination of lovastatin and nicotinic acid has been causally implicated in at least 1 case of rhabdomyolysis.

Conclusion

Nicotinic acid is a second or third choice for isolated hypercholesterolemia because of the troublesome adverse effects associated with the drug. However, patients who are consistent with their regimen will usually see adverse effects diminish after several months. Niacin has a therapeutic advantage as monotherapy in patients with combined hyperlipidemia when reduction of elevated concentrations of total plasma cholesterol, LDL cholesterol, and triglycerides is needed along with an elevation of HDL. Niacin is uniquely potent in reducing lipoprotein(a) compared to all other currently available agents. The drug is, therefore, potentially useful for the management of all types of hyperlipoproteinemia except type I; however, untoward adverse reactions must be carefully monitored. The combination of nicotinic acid with a BAS resin, HMG-CoA reductase inhibitor, or gemfibrozil may allow for greater effectiveness in lowering the concentration of both LDL cholesterol and triglycerides along with an increase in HDL, with an associated increased benefit in angiographic and clinical parameters of CAD.

Cholesterol Absorption Inhibitor—Ezetimibe

Pharmacology

Ezetimibe is the first drug to be approved for clinical use in this novel class of lipid-lowering agents (the 2-azetidinones), known as selective cholesterol absorption inhibitors. Using a genetic approach, investigators have identified Niemann-Pick C1-like 1 (NPC1L1) as the critical mediator of cholesterol absorption and the direct target of the drug. Ezetimibe acts at the brush border of the small intestine and inhibits the uptake of dietary and biliary cholesterol into enterocytes and the delivery of cholesterol to the liver. This action causes a reduction of hepatic cholesterol stores and increase in clearance of cholesterol from the blood. The drug does not affect the absorption of fat-soluble vitamins.

Ezetimibe reduces total cholesterol, LDL cholesterol, and Apo B and increases HDL cholesterol in patients with hypercholesterolemia. Administration with statins is effective in improving total cholesterol, LDL cholesterol, Apo B and HDL cholesterol beyond the effects of either treatment alone. After oral administration, ezetimibe is absorbed and extensively conjugated in the small intestine and liver to a pharmacologically active phenolic glucuronide. The drug and its metabolite are highly bound to plasma proteins. Ezetimibe and its metabolite are eliminated slowly from the plasma, with a half-life of approximately 22 hours for both, with their excretion mostly in stool.

Clinical Experience

A randomized, double-blind, 12-week trial in 892 patients with primary hypercholesterolemia found that ezetimibe 10 mg once daily as monotherapy lowered LDL cholesterol by 17% and triglycerides by 6% and increased
HDL cholesterol by 1.3%, all statistically significant compared with the placebo. In a randomized, double-blind, 8-week trial, 769 patients at or above their target LDL cholesterol concentration on monotherapy with various statins received supplementary treatment with the placebo or ezetimibe 10 mg daily. Ezetimibe plus statin lowered mean LDL cholesterol from 138 to 104 mg/dL (25%), whereas the placebo plus statin lowered it from 139 to 134 mg/dL (4%). A 12-week study in 668 patients with primary hypercholesterolemia found that ezetimibe at 10 mg daily plus simvastatin at 10, 20, 40, or 80 mg daily started together decreased LDL by 44% (10 mg); 45% (20 mg); 53% (40 mg); and 57% (80 mg) compared with reductions of 27%, 36%, 36%, and 44% with simvastatin used alone.

In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-mediated thickness as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein. Another study found similar effects.

In a comparative effectiveness trial, it was shown that the use of extended-release niacin caused a significant regression of carotid intima-media thickness when combined with a statin; the trial also showed that niacin is superior to ezetimibe.

Based on these studies, it has been suggested that niacin be added to a statin for additional cholesterol lowering before using ezetimibe. However, morbidity and mortality studies are still missing with ezetimibe and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) is now in progress to address this issue.

**Clinical Use**

Ezetimibe, administered alone or with statins, is approved as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, and Apo B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia. The drug is also approved for clinical use in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments and for patients with homozygous sitosterolemia as adjunctive therapy to diet.

The recommended dose of ezetimibe is 10 mg once daily. The drug can be taken with or without food, and can be administered with statins at the same time. Ezetimibe should be taken 22 hours before or 74 hours after administration of a BAS. The co-administration of ezetimibe with fibrates is not recommended because the safety and effectiveness of this combination has not been established. Ezetimibe is also available for once daily dosing in combination with simvastatin in doses of 10/10, 10/20, 10/40, and 10/80 mg.

**Adverse Effects and Contraindications**

Ezetimibe is generally well tolerated in contrast to the BAS class of medications, which cause constipation and gas and interfere with the absorption of other drugs. In clinical trials, the overall incidence of adverse effects reported with ezetimibe was similar to that reported with the placebo, and the discontinuation rate due to adverse effects was similar.

The adverse experience rates were similar between ezetimibe with various statins and statins used alone. However, the frequency of increased transaminases was slightly higher in patients receiving ezetimibe administered with statins than with statins alone. With combination therapy, it is recommended that liver function tests be performed at the initiation of therapy and according to the recommendations of the particular statin being used. Ezetimibe is not recommended in patients with moderate or severe hepatic insufficiency and should not be used in pregnancy. There has been no excess in myopathy or rhabdomyolysis associated with ezetimibe monotherapy or combination with statins.

The drug has no significant effects on medications metabolized by cytochrome P450 and is neither an inhibitor nor an inducer of cytochrome P450. No pharmacokinetic interactions have been observed with warfarin or digoxin. No dose adjustments are necessary in the elderly or for patients with mild renal and hepatic insufficiency. Concomitant cholestyramine administration decreases the plasma levels of ezetimibe by 50%.

**Combination Lipid-Lowering Drug Therapy**

Rosuvastatin is a more potent statin in lowering serum LDL cholesterol than atorvastatin or simvastatin. If the serum LDL cholesterol cannot be reduced to goal level by a high dose of a potent statin, a BAS, nicotinic acid, or ezetimibe should be added to the therapeutic regimen. Ezetimibe is a cholesterol absorption inhibitor that inhibits dietary and biliary cholesterol absorption at the brush border of the small intestine. Unlike nicotinic acid, ezetimibe and BAS do not increase the incidence of myopathy when combined with a statin. Studies are in progress investigating whether ezetimibe will reduce cardiovascular events.

If a high-risk person has hypertriglyceridemia or a low serum HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol–lowering drug. When serum triglycerides are ≥ 200 mg/dl, non-HDL cholesterol is a secondary...
target of therapy, with a goal 30 mg/dl higher than the recommended serum LDL cholesterol goal. If a fibrate is administered together with a statin, fenofibrate rather than gemfibrozil should be used since fenofibrate does not interfere with catabolism of statins and does not substantially increase the risk for clinical myopathy as does gemfibrozil.

Fish Oil Supplements

Omega-3 (n-3) polyunsaturated fatty acids (PUFAs), mainly eicosapentaenoic acid (EPA) and docosahexaenoic (DHA), are essential human nutrients. An increased intake of EPA and DHA has been shown to modify membrane function, inhibit thrombus formation, decrease inflammation, lower plasma triglycerides, and alter myocardial electrophysiology. Two fish oil supplements are FDA-approved as adjunct to diet for reducing elevated triglycerides (≥ 500 mg/dL). Many other brands of fish oil capsules are sold over the counter as dietary supplements without any regulation of their content or purity.

Pharmacology

The mechanism of action of fish oil to reduce triglycerides is not completely understood. Potential mechanisms include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal beta oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. EPA and DHA are also poor substrates for the enzymes responsible for triglyceride synthesis.

Clinical Experience

Daily doses of 3 to 12 mg of n-3 PUFAs can decrease fasting triglycerides by 20% to 50%. The effects on LDL cholesterol and HDL cholesterol are minimal, although HDL cholesterol may increase with time and LDL cholesterol may increase as triglycerides decrease. There are no interactions with statins to cause rhabdomyolysis, unlike gemfibrozil.

There is a large clinical trial base evaluating the effects of n-3 PUFAs in patients with acute CAD, chronic CAD, and arrhythmias, with some suggestion of benefit on morbidity and mortality. Reviews published in 2008 and 2010 reported no conclusive evidence of the impact of n-3 supplementation on cardiovascular morbidity and mortality; however, the American Heart Association recommends 1 gm daily of n-3 PUFAs in patients with CAD, and for those without CAD, the consumption of a variety of fish at least twice a week.

Clinical Use

For hypertriglyceridemia, patients should be placed on an appropriate lipid-lowering diet and the usual dose of 1 g capsule twice a day.

Adverse Effects

Fish oil supplements are well tolerated. Adverse effects include eructation, dyspepsia, and an unpleasant after taste. Large doses can inhibit platelet aggregation.

Hormones

Both estrogen and thyroxine have the ability to reduce LDL cholesterol.

Estrogen

A number of reports have shown possible benefit from estrogen use in preventing CAD in postmenopausal women. In contrast, the Heart and Estrogen/Progesterin Replacement Study (HERS), a recent randomized clinical trial, demonstrated that estrogen and progestin therapy did not reduce the overall rate of coronary events in postmenopausal women with established CAD, despite reductions in total cholesterol and LDL cholesterol and increases in HDL cholesterol with estrogen.

Several studies, including HERS, have shown increases in plasma triglyceride concentration by estrogen, which can reduce the size of LDL particles. In postmenopausal patients with estrogen-induced hypertriglyceridemia, the resulting reduction in size of LDL particles makes them more susceptible to oxidation, which may counteract the antioxidant effect of estrogen. Future studies are needed to investigate the possible benefit of lowering plasma triglyceride concentrations during hormone replacement therapy versus the risk of cardiac events in postmenopausal women with established CAD.

A current question that has yet to be fully answered is whether estrogen is more effective for primary prevention or for treating atherosclerosis once it is already established. According to results in HERS, estrogen may not be effective for secondary prevention of cardiovascular disease. The Estrogen and Prevention of Atherosclerosis Trial (EPAT) is the first randomized clinical trial of estrogen intervention for atherosclerotic disease in postmenopausal women with elevated LDL cholesterol levels but no evidence of CAD. The newest data from the EPAT study show increased carotid wall thickness in the placebo group, as compared with slight decrease in the estrogen group, suggesting that estrogen may be more effective as primary prevention.
Health Initiative (WHI) did not demonstrate a benefit from estrogen use alone or estrogen plus progesterone despite favorable effect on LDL cholesterol and HDL cholesterol. One can conclude from these studies that estrogen and estrogen plus progesterone should not be used as a lipid-lowering therapies.

**Thyroxine Analogues**

A thyroxine analogue, CGS 26214, devoid of the cardiovascular effects seen with thyroxine, has been shown in animal models to lower LDL cholesterol and lipoprotein(a). In hypercholesterolemic rats, it produced a reduction in LDL of 31% at a dose of 1 μg/kg, which was equivalent to that obtained with 25 μg/kg of liothyronine. CGS-26214 also reduced LDL and lipoprotein(a) levels by 43% in normal chow-fed monkeys, which was consistent with effects observed in hypothyroid patients receiving thyroid hormones.

Another thyroxine analogue that lacks the undesirable cardiotoxic effects of thyroid hormone is CGS 23425. In hypercholesterolemic rats, it produced a 44% decrease in LDL cholesterol at a dose of 10 μg/kg. The reduction in plasma cholesterol is mediated by an increase in hepatic LDL receptor activity. In addition, CGS 23425 produces a dose-dependent increase in Apo A-I, an activator of LDL receptor activity. In addition, CGS 23425 produces a reduction of increased insoluble dietary fiber with increased vegetable protein, which may be the actual therapeutic agent.

Psyllium hydrophilic mucilloid, a well-known bulk laxative, is a potential cholesterol-lowering agent. Its effectiveness relates to its ability in delivering 5 times more soluble fiber than oat bran and its ease of administration as a dietary supplement to patients with hypercholesterolemia.

Psyllium is a soluble gel-forming fiber derived from the husks of blond psyllium seeds of the genus *Plantago*, plants grown in the Mediterranean region and in India. The processing of psyllium involves the initial separation of the seeds from the plant husks and then grinding the husks to make the final psyllium substance. The seed husk is then enriched with mucilloid, a hydrophilic substance that forms a gelatinous mass when mixed with water. The nonutilized seed extracts are marketed as health foods or as animal feed. The chemical composition of psyllium is based on its being broken into an 85% mucilage polysaccharide and a 15% nonpolysaccharide component. The polysaccharide fraction is the active one and is made of 63% D-xylose, 20% L-arabinose, 6% rhamnose, and 9% D-galacturonic acid, as derived by acid hydrolysis and methylation analysis. Structural features of this component are those of a highly branched acidic arabinoxylan: xylan backbone with sugar 1:4 and 1:3 linkages. The nonpolysaccharide component has nitrogen and other nonactive components.

Several investigators have studied the activity of psyllium as a cholesterol-reducing agent. It is the universal impression from clinical trials that psyllium is a hypocholesterolemic agent with and without a modified diet.
However, there is still debate as to the degree of cholesterol reduction with psyllium.

**Mechanism of Action**

The mechanism by which psyllium and other soluble fiber lower serum cholesterol is currently uncertain. Available information suggests that one or more of the following mechanisms may be operative. First, psyllium has been shown to prevent the normal reabsorption of bile acids in the gut. A similar mechanism of action is also seen with cholestyramine and other BAS drugs. Second, soluble fibers such as psyllium may interfere with micelle formation in the proximal small intestine, resulting in decreased absorption of cholesterol and fatty acids. Finally, short-chain fatty acids are produced by bacterial fermentation of soluble fiber in the colon. These fatty acids (predominantly propionate and acetate) are rapidly absorbed into the bloodstream and may inhibit hepatic cholesterol synthesis. Short-chain fatty acids may also decrease hepatic cholesterol concentrations and secretions by interfering with compensatory mechanisms.

**Adverse Reactions and Drug Interactions**

Psyllium and other soluble fibers are well tolerated by patients. In many of the clinical trials, treatment adherence was high. A possible reason for the acceptability of psyllium therapy is that patients will have well-formed stools and a low incidence of adverse effects.

Some patients placed on psyllium report abdominal distention, excessive gas, and flatulence, but these symptoms usually subside after a few weeks. Rarely, allergic reactions to psyllium have been described. Animal studies have revealed the absence of teratogenic effects of psyllium. Some studies have revealed an effect of psyllium on the binding of sodium warfarin. Any potential problem can be avoided by separating the intake of psyllium and drug by 1 to 2 hours. Finally, patients with congestive heart failure may be at risk from an excessive salt load with psyllium ingestion.

**Clinical Recommendations**

The current recommendation for fiber in the diet is 25 to 35 g per day for adults and 5 to 10 g per day for children. Fiber supplementation is widely accepted as part of achieving a healthful diet in adults and children. This is in conjunction with a low-fat, low-cholesterol diet, which is considered to be prudent by the American Heart Association. The phase I diet in the treatment of hypercholesterolemia consists of no more than 300 mg of dietary cholesterol per day, with a maximum 30% total energy as fat. This diet has been shown to decrease cholesterol by varying amounts. With the addition of fiber, the cholesterol-lowering effect of this diet can be improved significantly.

The efficacy of psyllium in lowering cholesterol is consistent with that of many other soluble fibers. Studies have found that, in contrast to oat bran, 15 g of pectin added to the diet lowered cholesterol by an additional 11%. The addition of 100 g of oat bran to the diet has been shown to lower cholesterol by 19% and LDL cholesterol by 11%. However, the effectiveness of oat bran alone as a long-term hypercholesterolemic intervention has come into question.

The efficiency of psyllium is revealed in its ability to achieve reductions in cholesterol in studies that have used only 10.2 g of the substance daily. It is concluded that psyllium is useful as an adjunct to dietary therapy in the treatment of patients with mild to moderate hypercholesterolemia. Clearly, cholestyramine and the HMG-CoA reductase inhibitors have greater efficacy than psyllium alone in reducing cholesterol. However, combining psyllium with the other drug treatments for lowering cholesterol appears to be quite useful.

**β-Sitosterol (Plant Sterols)**

β-Sitosterol is a plant sterol with a structure similar to that of cholesterol except for the substitution of an ethyl group at C-24 of its side chain. Despite this structural relation to cholesterol, it is poorly absorbed from the intestine. β-Sitosterol is known to compete with cholesterol for incorporation into mixed micelles, thereby reducing intestinal cholesterol absorption. β-Sitosterol is also thought to inhibit absorption of endogenous biliary cholesterol. The importance of dietary intake of plant sterols on cholesterol absorption and serum cholesterol has been demonstrated in human beings; dietary intake of plant sterols is negatively related to fractional cholesterol absorption and overall cholesterol synthesis.

Sitosterol may also inhibit 7a-hydroxylase. β-Sitosterol is used for treatment of hypercholesterolemia in Europe. It is quite effective in reducing cholesterol by 5% to 15%. It is a very safe substance, although a high dose is required (6 g), taken before meals and at bedtime. Another plant sterol, β-sitostanol, reduces serum cholesterol more effectively than sitosterol at a lower dose.

Miettinen and colleagues reported on the use of sitostanol ester, a derivative of the plant sterol sitosterol, which reduces the intestinal absorption of cholesterol and
serum cholesterol more than sitosterol.\textsuperscript{545} In this study, sitostanol ester was dissolved in margarine in a double-blind, randomized trial of men with moderate hypercholesterolemia. The formulation achieved a reduction in serum LDL cholesterol of 14\% with 2.6 g of sitostanol.

A more recent study showed significant reduction of serum total cholesterol and LDL cholesterol even at a dose of 1.6 g of stanol. While the dose of 2.4 g resulted in a slightly greater reduction of serum cholesterol than the dose of 1.6 g, the actual difference was not statistically significant.\textsuperscript{552}

Because the inhibition of dietary cholesterol could increase endogenous cholesterol synthesis, several studies investigated the combination of sitostanol with HMG-CoA reductase inhibitors.\textsuperscript{553} Combined administration of a sitostanol ester margarine with a statin increased the net reduction in LDL cholesterol from 38\% to 44\% in non-insulin-dependent diabetics\textsuperscript{554} and from 35\% to 46\% in postmenopausal women with coronary heart disease.\textsuperscript{553} A larger, more recent study confirmed the effective reduction of total cholesterol and LDL from the administration of a stanol with a stable dose of statin. The study showed a 10\% reduction in LDL cholesterol from the combined therapy of a plant stanol ester spread with either atorvastatin, pravastatin, simvastatin, or lovastatin.\textsuperscript{555}

In children with hypercholesterolemia, sitostanol is effective and could be considered a treatment of choice.\textsuperscript{556,557} Replacement of regular daily fat intake by a margarine with a soluble ester form of stanol reduced total cholesterol and LDL cholesterol levels by 11\% and 15\%, respectively, and increased HDL cholesterol by 4\% in children with heterozygous familial hypercholesterolemia.\textsuperscript{558} The study suggests that familial hypercholesterolemic children with high baseline lathosterol proportions in serum can be expected to be good responders to LDL cholesterol lowering by dietary sitostanol ester.\textsuperscript{558}

Another group of plant compounds, the saponins, also interfere with cholesterol absorption by causing cholesterol precipitation, interference with micelle formation, or bile acid absorption. A synthetic saponin, \(\beta\)-tigogenin cellobioside, was found to reduce plasma cholesterol and LDL cholesterol in men with hypercholesterolemia.\textsuperscript{559} \(\beta\)-Ketogenin cellobioside, a derivative, selectively inhibits cholesterol absorption and is being evaluated as a potential replacement for bile acid resins.\textsuperscript{559}

**Policosanol**

Policosanol is an orally active sugar cane mixture of octacosanol within other heavy alcohols; it has a confirmed lipid-lowering effect with a platelet antiaggregant action.\textsuperscript{560,561} It has been demonstrated to inhibit the progression of carotid and coronary atherosclerosis.\textsuperscript{562,563} In the cuffed carotid artery of rabbits, policosanol showed better protective effect than did lovastatin against neointima formation through a greater inhibition of smooth-muscle cell proliferation.\textsuperscript{564} In patients with hypercholesterolemia or combined hyperlipidemia, policosanol in usual and high doses does not demonstrate a reduction in lipid values beyond the placebo.\textsuperscript{565}

**New Medical Therapies Under Investigation for the Treatment of Hyperlipidemia and Atherosclerosis**

This section discusses some of the new and innovative drug therapies under investigation for the treatment of hyperlipidemia and the prevention of atherosclerosis (see Chapter 37, Cardiovascular Drugs in Development).

**Lifibrol**

Lifibrol is a novel lipid-lowering agent with an unknown mechanism of action. Lifibrol undergoes biotransformation to a glucuronide and exists in the circulation mainly as the glucuronide.\textsuperscript{566} Lifibrol can cause dramatic reductions in LDL cholesterol, total cholesterol, Apo B, and triglycerides in hypercholesterolemic patients.\textsuperscript{567} It does not act as an inhibitor of HMG-CoA reductase, but it does inhibit sterol synthesis to the same degree as the HMG-CoA reductase inhibitors without affecting the production of essential compounds in the mevalonate pathway.\textsuperscript{568} A study involving hypercholesterolemic patients treated with lifibrol (450 to 900 mg/d) showed decreases in LDL cholesterol (40\%), total cholesterol (35\%), and Apo B (30\%) after 4 weeks.\textsuperscript{566} These reductions were similar to the decreases achieved by high doses of HMG-CoA reductase inhibitors. The study also demonstrated a 20\% reduction in lipoprotein(a) and a 20\% decrease in serum triglycerides by 6 weeks. Serum uric acid levels were also decreased by 10\% to 15\%.

A study done in patients afflicted with severe familial hypercholesterolemia suggests that lifibrol decreases levels of cholesterol through the enhancement of the LDL-receptor pathway.\textsuperscript{566} In addition, this study showed that patients with a severe reduction or complete absence of LDL receptors did not experience reductions in either plasma LDL-Apo B or LDL cholesterol levels after 4 weeks of treatment with lifibrol. This study provides evidence that lifibrol's action is dependent on the expression of LDL receptor. A study of hypercholesterolemic patients measured the net cholesterol balance and the urinary excretion of mevalonic acid to determine whether lifibrol interfered with cholesterol synthesis.\textsuperscript{568} There were no significant changes to the net cholesterol balance and the urinary excretion of mevalonic acid in patients treated...
with lifibrol, in contrast to the decreases in net cholesterol balance and urinary excretion of mevalonic acid seen with simvastatin. These results led researchers to believe that lifibrol’s mechanism of LDL-receptor enhancement is not dependent on the inhibition of HMG-CoA reductase. Another key finding has been the demonstration that lifibrol seems to have a quicker onset of action than the HMG-CoA reductase inhibitors. Separate investigators have shown that lifibrol reaches a maximum effect on LDL cholesterol reduction at 4 weeks, rather than the 4 to 8 weeks seen with the HMG-CoA reductase inhibitors.568–571

Lifibrol also does not seem to act through the inhibition of cholesterol absorption. One study showed that lifibrol increases both the levels and the clearance of Apo A-1, a possible factor in the drug’s ability to lower LDL cholesterol.572 Despite the findings of some earlier studies, it has also been discovered that lifibrol may act as a weak competitive inhibitor of HMG-CoA synthase.573 In vitro studies were performed comparing the effects of lifibrol on the enzymatic activities of HMG-CoA synthase and HMG-CoA reductase. One study suggests that lifibrol’s weak inhibition of HMG-CoA synthase alone is insufficient to explain its LDL cholesterol-lowering ability.574 The investigators also demonstrated lifibrol’s powerful ability to upregulate LDL receptor expression in an in vitro study. Although lifibrol’s definitive mechanism of action is still unknown, recent evidence suggests that the drug’s LDL cholesterol-lowering ability lies in its ability to upregulate LDL expression, with a lesser ability to inhibit HMG-CoA synthase.

No severe adverse effects were reported during 4 weeks of treatment with this drug. The only statistically significant adverse effects noted were skin reactions observed in 9.8% of patients, as compared to 5.5% of patients taking the placebo.567 Further studies hope to unlock the key to lifibrol’s mechanism of action.

Inhibition of Squalene Synthase and Other Downstream Enzymes of the Cholesterol Synthesis Pathway

Although relatively safe and effective, the available statins can cause elevations in liver enzymes and myopathy. Squalene synthase is another enzyme that is downstream to HMG-CoA reductase in the cholesterol synthesis pathway;575 it modulates the first committed step of hepatic cholesterol biosynthesis at the final branch point of the cholesterol biosynthetic pathway. Squalene epoxidase and oxidosqualene cyclase are other enzymes that act distally to squalene synthase. Pharmacologic inhibitors of these downstream enzymes have been developed that may reduce LDL cholesterol and reduce the myopathy adverse effect seen with upstream inhibition of HMG-CoA. At this juncture, 1 squalene synthase inhibitor, lapaquvastat (TAK-475), is in active clinical trials as a monotherapy, but there have been suggestions of increased hepatotoxicity with the drug.

Thus far, squalene synthase inhibitors have shown more clinical promise than inhibitors of other enzymes further along in the cholesterol synthesis pathway. While squalene synthase inhibitors may not be as efficacious in decreasing absolute values of total cholesterol or LDL levels when compared to HMG-CoA reductase inhibitors, they do show the additional benefit of decreasing triglyceride levels and increasing HDL levels.576–578 In the future, the ability to decrease LDL and triglyceride levels could provide an alternate monotherapy to patients afflicted with mixed hyperlipidemia who cannot tolerate statin therapy.

The greatest benefit of squalene synthase inhibitors over statins is their potential to reduce the risk of myotoxicity due to the sustained synthesis of non-sterol products of mevalonate. Therefore, these drugs could be beneficial in patients who have statin-induced myotoxicity or in patients with suboptimal LDL goals who cannot tolerate an increase in statins due to elevated CK levels. Although squalene synthase inhibitors may prevent statin-induced myotoxicity in vitro and in vivo, it is not yet known whether this is a temporary effect due to the accumulation of mevalonate, farnesyl pyrophosphate, and geranylgeranyl or is one that can be sustained over the long-term.

The safety profile of squalene synthase inhibitors is not completely elucidated; however, the known safety profile of squalene synthase inhibitors makes this a more appealing treatment option than squalene epoxidase inhibitors and oxidosqualene cyclase inhibitors. The metabolic product farnesyl pyrophosphate appears to be secreted freely in the urine. While no toxicities were reported in the study of BMS-188494 in healthy male volunteers, the study subjects were healthy and capable of increasing their fluid intake to promote urinary excretion. Although toxic urinary levels of dicarboxylic acid were not specifically reported in animal model studies of lapaquvastat, this complication should be carefully monitored. Acidosis could be a limiting factor to the use of lapaquvastat in the long-term, at high doses, in patients with comorbidities, or in patients with renal disease.

One disadvantage of squalene synthase inhibitors is that they do not appear to be as effective as statins in monotherapy to decrease cholesterol or LDL. The results of the lapaquvastat trials show lesser decrease in cholesterol and LDL levels compared to low doses of atorvastatin. This may be the result of a downregulation of squalene synthase in patients with elevated cholesterol levels. In vitro, cells incubated with sterols showed a suppression of squalene synthase enzyme. Therefore,
that the inhibition of the enzyme ACAT will lead to an-
eter accumulation and foam cell formation leads to plaque
within the arterial intima. The intracellular cholesteryl es-
trophages and smooth-muscle cells to produce foam cells
atherosclerosis.580 Cholesteryl esters accumulate in mac-
cholesteryl esters is an early step in the development of
and in macrophages. The intracellular accumulation of
lesteryl esters in the intestine, liver, and adrenal gland,
sponsible for the acylation of free cholesterol into cho-

Acyl-Coenzyme A Transferase Inhibitors

The acyl-coenzyme A transferase (ACAT) enzyme is re-
ponsible for the acylation of free cholesterol into cho-
lesterol esters in the intestine, liver, and adrenal gland,
and in macrophages. The intracellular accumulation of
cholesterol esters is an early step in the development of
atherosclerosis.580 Cholesteryl esters accumulate in mac-
rophages and smooth-muscle cells to produce foam cells
within the arterial intima. The intracellular cholesteryl es-
ter accumulation and foam cell formation leads to plaque
initiation and atherosclerotic progression. It is believed
that the inhibition of the enzyme ACAT will lead to an-

Studies show the existence of several isoforms of
ACAT with different expression sites in tissues. ACAT-
1 is preferentially expressed in macrophages, the adrenal
gland, and in the kidney, while ACAT-2 exists in the liver
and intestinal epithelium. Inhibition of ACAT-1 may lead
to beneficial reductions in foam cell formation and chole-
sterol storage within macrophages. Inhibition of ACAT-
2 decreases absorption of cholesterol in the intestine and
decreases the VLDL cholesteryl ester content.

The ACAT inhibitor avasimibe (CI-1011) has dem-
strated an ability to dramatically reduce plasma lipid
concentrations in animals. Avasimibe decreased plasma
cholesterol by > 56% in cholesterol-fed mice.584 The mice
treated with avasimibe also showed an enrichment of
VLDL/LDL with triglycerides. The enrichment and ob-
served decrease in cholesteryl esters in the VLDL/LDL
particles results in molecules that are potentially less ath-
erogenic. Mice fed high-cholesterol diets and treated with
avasimibe had a 92% reduction of atherosclerotic lesion
area measured in cross-sections at the aortic valve area.
The avasimibe-treated mice had an average lesion area
per section of 7.6 ± 7 µ2 x 1000 compared to 95.5 ± 35.2
µ2 x 1000 measured in the control group. The atheroscle-
rotic lesions of the avasimibe-treated mice also contained
smaller numbers of foam cells and a reduced lipid pool
when compared to the control group. Avasimibe also
showed a significant reduction in the number of mono-
cytes adhering to the endothelium. The mechanism by
which avasimibe reduces endothelial adhesion is cur-
cently unknown.

However, all clinical studies in humans with the avail-
able ACAT inhibitors have failed to show favorable lipid
profile changes as well as improvements in surrogate
markers for CAD.585-588 The studies demonstrated an in-
crease in atheroma burden. In addition, the inhibition of
this pivotal enzyme in cholesterol esterification may in-
terfere with reverse cholesterol transport.585

It is suggested that the combination of a selective
ACAT2 inhibitor with compounds enhancing reverse
cholesterol transport may be of clinical benefit.585

Cholesteryl Ester Transfer Protein Inhibition

The available cholesterol-lowering drugs (niacin, fibrates,
statins, and ezetimibe), although effective for reduc-
LDL-C and triglycerides, are not effective in causing
major elevations in HDL-C.589 During the last 2 decades,
cholesteryl ester transfer protein (CETP) inhibition has
received attention as a potential pharmacologic approach
for causing major elevations of HDL-C. A genetic deficiency of CETP activity in a long-living Japanese population without CAD was found to be associated with substantial elevations in HDL-C.

CETP is a plasma hydrophobic glycoprotein that is secreted by the liver and is bound to HDL in the plasma. Its biologic role is to facilitate the net mass transfer of cholesteryl esters from HDL to Apo B-containing and triglyceride-rich lipoproteins such as LDL and VLDL, and reciprocal transfer of triglycerides from VLDL to LDL and HDL. CETP inhibition due to a genetic deficiency or by pharmacologic inhibition will result in larger HDL-C particles with an elevated cholesteryl ester and decreased triglyceride content, and a non-HDL fraction with elevated triglycerides and decreased cholesteryl ester. These changes lead to an increased HDL-C due to its delayed clearance from plasma.

In animal studies with mice, a species naturally lacking CETP, transduction with the human CETP gene resulted in dose-related reductions in HDL-C and the development of atherosclerosis. When rabbits, a species with naturally high levels of CETP, were given a synthetic CETP inhibitor, JTT-705, the animals demonstrated a 90% increase in HDL-C as well as a 70% reduction in experimentally induced aortic atherosclerotic lesion area.

In humans, Boekholdt et al were the first to demonstrate a direct link between baseline CETP levels and the risk of future CAD. Likewise, an analysis of data from the Regression Growth Evaluation Study (REGRESS) revealed that a high CETP concentration was associated with a faster progression of coronary atherosclerosis in men who were followed with angiographic studies.

Human interventions have been carried out with 3 different orally active synthetic selective CETP inhibitors: dalcetrapib (Roche, Basel, Switzerland); torcetrapib (Pfizer, New York); and anacetrapib (MK-0859, Merck & Co., Whitehouse, New Jersey). The largest experience accrued to date has been with torcetrapib.

In phase 1 clinical trials, compared to the placebo, torcetrapib has been shown to cause substantial elevations in HDL-C and modest reductions in non-HDL-C, including LDL-C. Used in combination with atorvastatin in phase 2 clinical trials in dyslipidemic patients, the combination resulted in additional increases in HDL-C and additional decreases in LDL-C beyond those seen with atorvastatin alone.

However, the results from a series of large phase 3 clinical trials with torcetrapib plus atorvastatin versus atorvastatin alone demonstrated unexpected results on measured clinical endpoints with the combination regimen. The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) study evaluated 15,000 subjects with CAD or high-risk equivalents. Excessive deaths were found in the combination treatment group, as well as an increase in the incidence of heart failure, MI, angina, and the need for revascularization procedures. In addition, an increase in systolic blood pressure of 4 to 6 mmHg was observed in the combination group.

Nissen et al reported on the results of an independent parallel study called the Investigation of Lipid Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE), which showed no difference using combination torcetrapib-atorvastatin therapy versus atorvastatin alone on atherosclerosis plaque burden, using intravascular ultrasound to image plaque. The adverse outcomes found in the ILLUMINATE trial cannot be attributed to the worsening of atherosclerotic plaque burden. However, the ILLUSTRATE study did not provide any data regarding stability of thrombogenic potential of the plaques.

Finally, the results of 2 double-blind, randomized trials in patients with heterozygous familial hypercholesterolemia (RADIANCE 1) and mixed dyslipidemia (RADIANCE 2) using torcetrapib and atorvastatin in combination showed no change in the progression of carotid intima-media thickness compared to the results with atorvastatin alone. In RADIANCE 1, the average increase in systolic blood pressure was 2.8 mmHg; in RADIANCE 2, the average increase was 8.4 mmHg.

The findings in the torcetrapib-atorvastatin clinical program have thrown an unfavorable light on the clinical development program of CETP inhibition. With torcetrapib, was it the molecule or the mechanism? In other words, was the increase in the number of deaths in the ILLUMINATE study related directly to an unforeseen blood-pressure-raising adverse effect and completely unrelated to torcetrapib’s mechanism for raising HDL? Torcetrapib may raise blood pressure by causing an unexpected rise in aldosterone levels. Are the hopes of those who once believed in the clinical promise of CETP inhibition as a meaningful mechanism to raise HDL shattered? Perhaps the larger cholesterol-laden HDL produced in the setting of pharmacologic CETP inhibition in vivo becomes dysfunctional and is not capable of unloading cholesterol from the vessel walls and/or has pro-inflammatory properties as has been recently suggested by others.

The findings of ILLUMINATE, ILLUSTRATE, and RADIANCE have clearly been disappointing regarding the potential benefit of torcetrapib in preventing CAD. However, the other orally active CETP inhibitor, anacetrapib, does not adversely affect blood pressure. Recently it was shown that anacetrapib caused a powerful HDL-C lowering effect and a modest LDL-C effect in a placebo-controlled study of dyslipidemic patients, and in a parallel study reported in the same article, no change in
blood pressure was observed in normotensive individuals using ambulatory blood pressure monitoring. Dalteparin, the first CETP inhibitor, also causes elevations in HDL-C and reductions in LDL-C, and to date no reports of the drug’s effect on blood pressure have been reported on.607

Although the promise of pharmacologic CETP inhibition to prevent CAD is now unclear, safer compounds in the class, used judiciously, could still be shown to provide a clinical benefit from the marked elevations in HDL-C.608,609

**Lipoprotein-Associated Phospholipase A2**

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a specific marker of vascular inflammation that has been shown in numerous large epidemiological studies to be an independent predictor of various cardiovascular events, over and above the traditional risk factors and inflammatory biomarkers, including high-sensitivity C-reactive protein.610 Such results have been reported in both primary and secondary studies including the healthy young and the elderly, patients with stable CAD and stroke, and those with sub-clinical disease. Furthermore, the adjusted measure of association (HR versus OR versus RR) for Lp-PLA2 generally ranged between 1.5 and 2 (OR 1.60 as reported in the meta-analysis)—a value typical for common risk markers.611 The prevalence of patients with elevated levels of Lp-PLA2 (in the highest tertiles or quartiles) is appreciable, and recent but limited data suggest stability and good reproducibility of serial Lp-PLA2 measurements.612 As for measurement, the only commercially available Lp-PLA2 immunoassay test approved by the FDA (the PLAC test) currently lacks adequately established receiver-operating characteristics; sensible cut-off points should be implemented before it could be clinically useful. Altogether, though, the current data suggest that Lp-PLA2 levels, if used judiciously, may indeed be useful, together with their Framingham Score, in further stratifying patients with an intermediate to high probability of developing cardiovascular disease events. Additional studies, however, must examine the receiver-operating characteristics curves in order to evaluate the incremental benefit of Lp-PLA2 in predicting incident CAD.

In tackling the second question, it is worth noting that currently, even with aggressive risk management and polypharmacotherapy, significant residual cardiovascular risk is present in high-risk patients. In diabetic patients, for example, even intensive treatments including tight lipid control, blood pressure, glucose, and lifestyle were still associated with a 19% cardiovascular disease event rate over 5 years compared with 32% in the conventionally treated group.613 Unfortunately, the individual risk reduction achieved by each drug group does not add up and, at best, leads to a 30% to 40% reduction in relative risk.614 Such data support the argument for developing drugs with novel targets that would be complementary to the currently available treatments.

Ascribing a role for Lp-PLA2—as an atheroprotective versus pro-atherogenic agent—in the development of atherosclerosis has been controversial. Initial studies focusing on the role of Lp-PLA2 in PAF degradation suggested an anti-inflammatory role. Evaluation of Lp-PLA2 in mice studies has been limited due to the predominant association of this enzyme with HDL cholesterol. Results from the genetic polymorphism studies have been contradictory and highlight the need for a comprehensive examination of Lp-PLA2 genetic variants. Numerous other preclinical studies, however, including Lp-PLA2 inhibition studies, endothelial function studies, and studies analyzing the function of pro-inflammatory active byproducts of this enzyme, have all strongly implicated Lp-PLA2 as a pro-atherogenic agent and perhaps the missing link between oxLDL and local inflammation in the atherosclerosis process. To this end, darapladib (SB-48048), a selective inhibitor of Lp-PLA2, has been shown to substantially inhibit the plasma activity of this enzyme and possibly modulate the inflammatory response as measured through surrogate markers in the presence of intensive statin therapy.614 Although no safety concerns were noted in the 3-month period of the darapladib trial, the long-term potential for adverse effects is unclear. More importantly, additional studies are needed to determine whether Lp-PLA2 plasma inhibition is associated with a favorable effect on CAD events above and beyond the current available therapies.

Darapladib is an orally available, selective reversible inhibitor of Lp-PLA2 manufactured by GlaxoSmithKline and is currently in phase 2/3 of clinical development.615 In a phase 1 clinical trial, the administration of darapladib to healthy volunteers reduced the plasma enzyme activity in a dose-dependent manner by up to 95%, rendering darapladib a very potent selective inhibitor of Lp-PLA2.616 Furthermore, the results from an early phase 2 clinical trial involving patients undergoing carotid endarterectomy showed that administering 40 and 80 mg of darapladib for 14 days before the surgery reduced plasma Lp-PLA2 activity by 52% and 81% respectively and also inhibited the Lp-PLA2 activity within the atherosclerotic plaque by 52% and 80%, respectively, compared with the placebo.617 More recently, Mohler et al618 conducted a large multicenter, randomized, double-blind, placebo-controlled study to examine the effects of darapladib on plasma Lp-PLA2 activity and select biomarkers of cardiovascular risk. CAD and CAD-risk equivalent patients (n = 959) receiving atorvastatin (20 or 80 mg) were randomized to receive 40, 80, or 160 mg oral darapladib or the placebo once daily for 12 weeks. Darapladib 40, 80, and 160...
mg significantly inhibited Lp-PLA₂ activity by approximately 43%, 55%, and 66% respectively compared with the placebo. Sustained dose-dependent inhibition was noted in both atorvastatin groups at different baseline LDL cholesterol but without affecting LDL levels. Darapladib 160 mg at 12 weeks significantly decreased interleukin-6 levels by 12.3% (95% confidence interval, -22% to -1%, P = .028) and showed a non-significant trend in lowering CRP compared with the placebo, suggesting a possible reduction in the inflammatory burden. There were, however, no significant changes in plasma levels of myeloperoxidase and matrix metalloproteinase—two other inflammatory markers implicated in the atherosclerosis-atheroma pathway. Given the concern that Lp-PLA₂ inhibition might enhance platelet aggregation (prompted by preclinical data implicating Lp-PLA₂ in PAF inactivation), several biomarkers of platelet activity were also measured; no increase in any of these markers was noted during and at the end of the trial as compared with the placebo. Lastly, no major safety concerns were noted during this 3-month study.

The effects of darapladib on human coronary atherosclerotic plaque was assessed in a placebo-controlled study of 330 patients with angiographically documented CAD.⁶¹⁹ Patients were treated with either the placebo or darapladib 160 mg daily for 12 months. There was no difference from the placebo in coronary total volume measured by serial intravascular ultrasound. However, an increase observed in the estimated necrotic core volume in the placebo-treated patients was not observed in patients receiving darapladib, suggesting that a more stable plaque was created with the active drug. An intervention trial with darapladib, powered to assess its effects on coronary disease events (STABILITY), is now in progress.⁶²⁰,⁶²¹

**HDL Infusions**

Most pharmacological agents used in hyperlipidemia exert their benefit by lowering LDL-C. A promising new approach is the use of HDL infusions.⁶²²,⁶²²a Several epidemiological studies have shown an inverse relationship between HDL cholesterol levels and CHD.⁶²³-⁶²⁵ HDL and its major structure protein, Apo A-I, are believed to act by promoting reverse cholesterol transport: a process whereby free cholesterol from peripheral tissues such as the arterial wall is taken by HDL molecules to the liver and other steroidogenic tissues.⁶²⁶-⁶²⁹ Furthermore, HDL has been found to have anti-inflammatory, anti-oxidant, and anti-thrombotic actions and can correct impaired vasodilation due to endothelial dysfunction.⁶³⁰-⁶³⁶

In 1980, investigators from Milan reported on a family from the village of Limone sul Garda, in which 3 members had very low levels of HDL cholesterol (< 15 mg/dL) but no clinical signs of cardiovascular disease as would be expected by these levels.⁶³⁷ They were found to have a mutant form of Apo A-1 (Apo A-1 Milano) with substitution of cysteine for arginine at position 173. This substitution conferred very different properties allowing Apo A-1 Milano to form homodimers (with other Apo A-1 Milano proteins) and heterodimers (with Apo A-II). The mutant form was found to have a higher capacity to extract cholesterol from peripheral cells when compared to the wild-type protein. Apo A-1 Milano homodimers were also found to have slow turnover in carriers.⁶³⁸

Several preclinical studies have shown the potential benefit of HDL therapy. Repeated intravenous injection of a crude preparation of homologous HDL has been found to inhibit the progression and induce the regression of early aortic fatty streaks in cholesterol-fed rabbits.⁶³⁹,⁶⁴⁰ Injecting the protein Apo A-I produced similar results.⁶⁴¹ In another study, reconstituted HDL containing Apo A-I Milano given intravenously to genetically hyperlipidemic ApoE–null mice, prevented progression and caused regression of aortic atherosclerosis without changing the high circulating total cholesterol levels.⁶⁴²

The results of the first clinical trial assessing the effect of administering Apo A-I Milano in humans provided promising data regarding the use of HDL as a therapeutic agent. A prospective, randomized, double-blind, placebo-controlled trial by Nissen et al found regression of coronary plaque lesions after 5 infusions of recombinant Apo A-I Milano/phospholipid complex (ETC-216, Esperion Therapeutics, Ann Arbor, Michigan).⁶⁴³ In this multicenter study, patients who needed diagnostic coronary angiography within 14 days of an acute coronary syndrome were enrolled. The patients were randomized into 3 treatment groups: the placebo (0.9% normal saline) (n = 12; 11 included in analysis), low dose ETC-216 (15 mg/kg) (n = 23; 21 included in analysis) or high dose ETC-216 (45 mg/kg) (n = 22; 15 included in analysis). Treatment was administered weekly for 5 weeks. A baseline angiogram including intravascular ultrasound of a segment within a target vessel that did not undergo revascularization was obtained within 2 weeks following acute coronary syndrome and was then repeated at the end of 5 weeks of treatment. The study found statistically significant regression in coronary atheroma volume in the groups treated with high dose and low dose ETC-216 when compared to baseline. The placebo group had no significant change in atheroma volume. This pilot study did not have sufficient power to directly compare the treatment group and the placebo group with respect to change in atheroma volume. Interestingly, there was no evidence of greater regression in the high dose group.

GI adverse effects included nausea, vomiting, or abdominal pain and occurred in all 3 groups. One patient in the high-dose group developed an elevated aspartate aminotransferase (> 3x the upper limit of normal),
accompanied by nausea, vomiting, and cholelithiasis. Another patient in the high-dose group experienced a reaction consisting of nausea, chills, diaphoresis, rigors, vomiting, and mild rash. Other adverse effects observed were headaches, arthralgias, and fluid retention.

In another study, the short-term infusion of reconstituted HDL resulted in no significant reductions in percentage change in atheroma volume or nominal change in plaque volume compared with the placebo. However, there was improvement in the plaque characterization index and coronary index on quantitative coronary angiography. The absence of published data linking intravascular ultrasound changes in plaque volume to morbidity and mortality limits the extrapolation regarding the clinical relevance of the changes found in the studies. Furthermore, there are no data comparing Apo A-I Milano and Apo A-I to see if Apo A-I Milano is in fact more efficient than the normal form. However, this study provides evidence for the potential benefit of exogenous HDL as a therapeutic agent in the treatment of hyperlipidemia. These results still need to be confirmed in a larger, long-term study. The investigators speculate that if these results are confirmed, HDL may serve as an emerging therapeutic target in the management of patients with acute coronary syndrome.

**Toll-Like Receptor Modulators**

The toll-like receptors are a class of transmembrane molecules that have important function in both innate and acquired immunity. As part of the body’s normal immune defense against microbial pathogens, stimulation of these receptors will trigger the inflammatory response cascade and the release of cytokines. Activation of these receptors also plays a role in a variety of systemic inflammatory diseases such as atherosclerosis, acute CAD, and left ventricular remodeling. Pharmacologic approaches to modify the actions of toll-like receptors are now under consideration as potential treatments for inflammatory systemic diseases that include atherosclerosis. At the same time, it is essential to characterize the benefits and risks of modifying such an important part of the body’s innate immune system.

**Apolipoprotein A-I Mimetic Peptides**

Apo A-I is largely responsible for the beneficial effects of HDL and has been shown to have therapeutic potential in reversing atherosclerosis in both animal and human models. Due to Apo A-I’s large size and the difficulty and expense to manufacture, Apo A-I mimetic peptides are likely to provide the best alternative method to use the favorable effects of apoA-I. D-4F is an Apo A-I mimetic peptide that can be administered orally, and phase 1 trials using an oral preparation are being conducted. Anti-inflammatory and anti-atherogenic effects of 4F include increasing pre-β HDL formation, increasing cholesterol efflux, converting pro-inflammatory HDL to anti-inflammatory HDL, and reducing lipoprotein oxidation. Improved arterial vasoreactivity is another important function of 4F. In a rat model of diabetes mellitus, D-4F increased arterial concentrations of heme oxygenase-1 and superoxide dismutase, decreased superoxide levels, reduced levels of circulating endothelial cells, decreased endothelial cell fragmentation, and restored arterial vasoreactivity to normal. In a mouse model of systemic sclerosis, D-4F functioned to improve vasodilation, angiogenic potential, myocardial inflammation, and oxidative stress. With respect to mouse models of heart-transplant–associated atherosclerosis, D-4F induced heme oxygenase-1. D-4F also improved cognitive performance in LDL receptor–null mice with Western diet-induced cognitive decline. D-4F also reduced the kidney content of oxidized phospholipids in a mouse model of hyperlipidemia-induced renal inflammation. In humans with significant cardiovascular risk, a single dose of oral D-4F was found to safely improve the inflammatory index of HDL. The conglomeration of these findings suggests that Apo A-I peptide mimetics, particularly 4F, may have a future role in the prevention and treatment of atherosclerosis.

The recent data on L-4F could also have broad clinical implications for the epidemic of obesity in this country. L-4F has been shown to reduce weight, improve insulin sensitivity, reduce inflammatory cytokines, reestablish hormonal levels and nitric oxide/superoxide ratios, and reduce consequent cardiovascular risk. L-4F is currently in clinical trials and is especially promising as a potential treatment for obesity and the metabolic syndrome.

**Ileal Na+/Bile Acid Cotransporter Inhibitors**

The ileal Na+/bile acid cotransporter (IBAT) contributes to the enterohepatic circulation of bile acids by exchanging bile acids in the ileal brush-border membrane for Na+. IBAT is bile-acid specific and Na+ dependent. The BASs interrupt the enterohepatic circulation of bile acids, but are nonspecific anion exchange resins with the bulkiness of the agents being a common patient complaint.

A study using the IBAT inhibitor S-8921, a ligand derivative, showed a dramatic decrease of serum cholesterol concentrations in hamsters. Hamsters treated with S-8921 also showed an increased fecal excretion of bile acids. While S-8921 has a potent cholesterol-lowering activity in vivo, it also has an antioxidative property against LDL oxidation in vitro. S-8921 both inhibits cholesterol absorption and enhances cholesterol elimination, thereby suppressing plasma total and VLDL/LDL cholesterol levels in rats. A study assessing the effects of the administration of S-8921 in the diet (0.01% to 0.1%) given to hyperlipidemic rabbits showed an increased fecal excre-
tion of measured bile acids of 60% to 180% and a decrease in serum cholesterol of 29% to 37%. The study also found that 0.01% S-8921 suppressed the development of hypercholesterolemia to a greater extent than did 1.5% cholestyramine. This finding suggests that S-8921 may have a greater potency than cholestyramine.

Passive diffusion along the entire intestine or active transport at the terminal ileum accounts for 90% of bile acid absorption. Free bile acids are absorbed to a larger extent via passive diffusion, while conjugated bile acids are mainly absorbed by active transport. S-8921 inhibits the active reuptake of bile acids at the terminal ileum without inhibiting the passive absorption of bile acids.

When the enterohepatic circulation of bile acids is interrupted, the liver increases the biosynthesis of bile acids from cholesterol to compensate for the loss. The liver LDL receptor increases the uptake of plasma LDL cholesterol. There is also a decrease in the bile acid concentration in bile leading to an overall decreased cholesterol absorption in the intestine. The bile acid sequestrants cholestyramine, colestipol, and colesevelam are the only drugs in clinical use that disrupt the enterohepatic circulation of bile acids. The drugs can effectively lower LDL cholesterol plasma concentration but frequently have associated gastrointestinal adverse effects (cholestyramine and colestipol), and impaired taste is often a common patient complaint. Investigators are seeking drugs that interrupt the enterohepatic circulation of bile acids with higher potency and less GI adverse effects. IBAT inhibitors such as S-8921 show promise as a new class of effective hypocholesterolemic drugs. S-8921 is currently in the preclinical development phase.

**Bile Acid Sequestrants**

SK&F 97426 is a BAS that has higher affinity for the trihydroxy bile acids and slower rates of dissociation from this resin when compared to cholestyramine. This property of SK&F 97426 is believed to account for its having threefold greater potency than cholestyramine. In animal models, it increases bile acid secretion and has been shown to reduce total cholesterol by 37 to 58%, LDL cholesterol by 56% to 75%, and VLDL cholesterol by 25% to 41%.

GT16-239, a novel BAS, is nonabsorbable, with a unique affinity for binding conjugated primary bile acids. At half the dose of cholestyramine, it was more effective in preventing diet-induced hypercholesterolemia and the development of early aortic atherosclerosis in hamsters.

**Lipoprotein Lipase Activators**

Lipoprotein lipase is an important protein involved with regulating the levels of HDL cholesterol seen in plasma. The enzyme has been cloned, and its regulation is being studied on the molecular level. LPL-mediated lipolysis of chylomicrons and VLDLs contributes to the plasma HDL level. The concentration of HDL cholesterol also depends on HDL production by the liver and small intestine and CETP metabolism, as mentioned in the previous section. LPL digests chylomicrons and VLDLs into remnants and LDL. Conversion of HDL into a less-dense HDL, then ensues. Low levels of HDL have been consistently linked to patients with extensive CHD. LPL is also a strong modulator of triglyceride metabolism. LPL hydrolyzes triglycerides within lipoproteins into nonesterified fatty acids and glycerol. The free fatty acids are then absorbed in adjacent tissues by diffusion.

An enhancement of LPL activity could favorably influence the level of triglycerides and other atherogenic lipoproteins in the plasma. A team of researchers recently developed the compound NO-1886, an agent that enhances the activity of LPL. Investigators have demonstrated in the rat, hamster, and rabbit models, that NO-1886 elevates HDL cholesterol by the selective enhancement of LPL independent of the CETP pathway. NO-1886 given to rabbits for 20 weeks resulted in reductions of aortic atheromatosus lesions, with a concomitant increase in HDL and a decrease in triglycerides. NO-1886 also demonstrated a strong ability to decrease triglyceride levels in both normal and streptozotocin-induced diabetic rats. Other studies show that NO-1886 results in reduced insulin resistance along with decreased triglyceride levels in rats fed a high-fat diet. NO-1886 may be an important drug in the future for diabetics with poor lipid profiles and insulin resistance.

**Enhancers of 7α-Hydroxylase**

The enzyme 7α-hydroxylase is the regulatory substance in the conversion of cholesterol to bile salts. Bile-acid biosynthesis represents the major route of catabolism and removal of cholesterol in the body. Since reporting the cloning of the regulatory enzyme in 1989, several molecular mechanisms that regulate the enzyme have been described. Bile acids have been shown to bind and activate the farnesoid X receptor, which represses the transcription of CYP7A1 that encodes 7α-hydroxylase. Downregulation of CYP7A1 transcription can also occur via activation of the JNK/c-Jun pathway, whereas activation of CYP7A1 transcription occurs through the activity of hepatocyte nuclear factor-4. These are significant findings because an understanding of the molecular mechanisms would provide a strategy for developing drugs, such as a farnesoid X receptor antagonist, that could enhance the activation of 7α-hydroxylase. This drug would potentially reduce plasma cholesterol levels while having a preventive influence on gallstone production.

Previous studies showed an increase in the activity of 7α-hydroxylase with the administration of cholestyramine. Recent studies demonstrate that direct
augmentation of hepatic 7α-hydroxylase markedly lowers plasma LDL concentrations in animals with diet-induced hypercholesterolemia, as well as in animals that genetically lack LDL receptors.\cite{673} This finding suggests that the combination of 7α-hydroxylase gene transfer and a cholesterol synthesis inhibitor might prove useful in familial hypercholesterolemia patients without LDL receptors.

New studies also indicate that polymorphism of the gene encoding hepatic 7α-hydroxylase contributes significantly to the interindividual variation in plasma LDL cholesterol concentration, and a specific CYP7A1 allele associated with increased plasma LDL cholesterol concentrations has been identified.\cite{674}

**Peroxisome Proliferator-Activated Receptor Modulators**

The PPARs are members of the nuclear hormone receptor family that regulate glucose and lipid homeostasis, including receptors for steroid hormones, retinoids, thyroid hormones, vitamin D, and fatty acids.\cite{675,676} The 3 subtypes identified to date are PPARα, PPARδ (also referred to as PPARγ), and PPARγ.\cite{677,679,678} Although the role of PPARδ is unclear, PPARα appears to have a catabolic role in lipid metabolism and PPARγ has an anabolic role.\cite{678}

The PPARs form heterodimers with other nuclear receptors and subsequently bind peroxisomal proliferation response elements (PPREs) to their promoters.\cite{677,679} The binding of PPRE agonists leads to the transcription of proteins that are then involved with metabolism of lipid and carbohydrates.

It has been discovered that FADs act at the level of PPARα and that the glitazone drugs target PPARγ.\cite{680,681,682} The favorable antiatherogenic properties of FADs are partly a result of PPARα-mediated hepatic gene expression.\cite{682} It has also been recognized that PPARα plays an important role in the downregulation of fibrinogen expression seen with the FADs.\cite{683}

PD 72953, an ether diacid, is a PPAR agonist that is believed to affect PPARα. PD72953 caused the downregulation of Apo C-III expression and the consequent reduction of plasma triglyceride levels observed in PD 72953-treated rats.\cite{684} It is known that Apo C-III acts to inhibit triglyceride clearance; the reduction of Apo C-III seen in the PD 72953 rats was then followed by a reduced level of hypertriglyceridemia.\cite{685} PD72953 also resulted in an elevation of HDL cholesterol in the treated rats.\cite{684} These findings are consistent with the triglyceride reductions and HDL elevations observed with FADs and PPARα activation.

PPARγ activators (glitazones) are used in type 2 diabetics to increase insulin sensitivity and improve glycemic control. Recently, it was learned that while PPARγ is needed in the formation of adipose depots, agonists for PPARγ are used to treat the insulin resistance and hyperglycemia seen in type 2 diabetes mellitus.\cite{686} It has also been noted that PPARγ is highly expressed in macrophages and the foam cells of atheromatous lesions.\cite{687,688} PPARγ is involved in the regulation of the influx and efflux of cholesterol for macrophages. PPARγ agonists raise HDL cholesterol in humans, and their ability to enhance cholesterol efflux from macrophages and endothelial cells may prevent the development of atherosclerosis.\cite{686}

GW501516 was recently developed as a selective PPARδ agonist that may be effective in increasing the reverse cholesterol transport pathway.\cite{689} An 80% increase in HDL cholesterol was seen in GW501516 (3 mg/kg)-treated monkeys, who had significant increases in Apo A-I and Apo A-II, both components of HDL. GW501516 (3 mg/kg) caused reductions in triglyceride levels and a 50% decrease in VLDL. Interestingly, GW501516 raised serum Apo C-III levels while simultaneously experiencing a reduction of serum triglyceride levels. As mentioned above, it is believed that a possible mechanism for the ability of PPARα to reduce levels of triglycerides is by decreasing levels of Apo C-III and thereby removing the inhibition of triglyceride clearance. It is believed, therefore, that PPARα and PPARδ operate in different pathways to achieve similar triglyceride reductions.

Researchers are also involved with a new class of drugs that exhibit dual PPARα/γ agonist activity. Propionic acid derivative 8, also known as compound 8, is one of the drugs synthetically designed to stimulate both PPARα and PPARγ.\cite{690,691} Compound 8 was tested in the diabetic animal model, the EOB mouse. Compound 8 (30 mg/kg), fenofibrate (100 mg/kg), and rosiglitazone (30 mg/kg) were orally dosed in the mouse model for a period of 7 days and then compared to control. These studies showed a 48.4% increase in HDL cholesterol in the compound 8-treated mice, a greater increase than in the fenofibrate-treated mice. The compound 8-treated mice also showed a greater decrease in plasma glucose level than achieved in the rosiglitazone-treated mice. Serum triglyceride levels were markedly reduced in all the treated mice when compared to control, with the greatest decrease observed in the compound 8-treated mice. Compound 8 shows great promise for a new class of drugs that can result in powerful reductions in hyperglycemia combined with favorable changes in plasma HDL cholesterol and triglyceride levels.

These combined PPARα/γ agonists show potential as important drugs of the future for helping type 2 diabetics achieve manageable serum glucose controls while also addressing their increased risks for CAD and atherosclerosis. The ability to focus on the PPARs and their subclasses may provide a new class of specific and more powerful drugs in the treatment in both atherosclerosis and diabe-
Cholesterol Vaccines

The use of various types of vaccines to prevent and treat atherosclerotic vascular disease appears to be an innovative and promising new endeavor in cardiovascular medicine. Existing vaccines, such as the influenza and pneumococcal vaccines, appear to reduce the risk of stroke and cardiovascular death in elderly subjects by a mechanism that is unknown. A nicotine vaccine is in development where an exogenous antibody binds to nicotine, preventing its passage through the blood–brain barrier, thereby reducing the urge to smoke. An anti-angiotensin II vaccine is now in clinical trials, as well as an anti-obesity vaccine with ghrelin. Only the vaccines involved with HSPs directly target the molecular development of atherosclerosis.

Cholesterol vaccines have been proposed and tested as a technique for lowering serum cholesterol by enhancing clearance of serum lipoprotein via the reticuloendothelial system. Two synthetic antigens containing cholesterol esters covalently coupled to various carrier proteins (bovine albumin, human β-lipoprotein) were synthesized. Groups of rabbits immunized with these preparations were fed atherogenic diets up to 15 weeks. Reduction in serum cholesterol of 25% to 35% and suppression of atherosclerotic plaque formation up to 90% were observed in immunized animals, as compared with controls. Another study demonstrated inhibition of the neointimal response to balloon injury in hypercholesterolemic rabbits after immunization with homologous oxidized LDL. In the future, cholesterol immunization procedures should be tested for more typical hyperlipidemias occurring in human populations.

Somatic Gene Therapy

There are several techniques currently being investigated as possible approaches to treat atherosclerosis via gene therapy. Gene transfer to somatic cells can be performed by an ex vivo or an in vivo approach. Ex vivo approaches require expensive and complicated procedures that may be unacceptable to the patient. These procedures, for instance, may require a partial hepatectomy, followed by the transfection of target cells in vitro and the reimplantation of the organ. The in vivo approach is conducted in a much-less-invasive manner, involving the direct administration of the gene locally or systemically. The in vivo approach can be performed by using viral or nonviral delivery strategies. An exciting development in gene therapy involves using chimeraplasty as an alternative to viral gene therapy.

Adenoviruses are useful viral vectors for achieving hepatic transgene expression. Human adenovirus is a double-stranded DNA virus, nonenveloped and icosahedral, approximately 36 kb in length. First-generation adenovirus vectors were designed with the E1 region of viral DNA deleted in an effort to inhibit viral gene expression. The results of in vivo experiments demonstrated the occurrence of serious hepatotoxicity and adverse effects resulting in morbidity and mortality in humans treated with the first-generation adenovirus vectors. This led to the development of second-generation adenovirus vectors that were designed with further deletions of the viral DNA. Recently researchers developed helper-dependent adenoviral vectors designed for the removal of all viral protein genes as an attempt to further decrease toxicity.

Initial experiments demonstrated that adenoviruses could transfer foreign genes to the mouse model for the expression of the human LDL receptor (LDLR) gene. A drawback to adenovirus-mediated gene transfer is the short-lived expression of the transgene. Some studies show that after the first week of transduction, gene expression would be below the levels necessary for therapeutic benefit.
expression declines greatly.701 There is evidence that the elicitation of the host’s immune responses against the vector and viral proteins expressed by the transduced cells are major factors in the observed drop in gene expression.702 New studies are in progress to prevent the immune response leading to the loss of adenovirus-mediated gene expression. One study demonstrated long-term cholesterol reduction in LDLR-deficient mice via the transfer of the LDLR gene coupled with a blocking antibody directed against CD154, in order to achieve suppression of the immune response.703 This study demonstrated that the anti-CD154-treated mice continued to have significant cholesterol reductions 93 days after the adenovirus-mediated transfer of LDLR and anti-CD154.

Further promising studies with adenovirus-mediated gene transfer have observed regression of atherosclerotic lesions in animal models. One group of experimenters observed plaque regression in apoE-deficient mice infected with adenovirus encoding the human apoE gene.704 apoE-deficient mice are hypercholesterolemic and develop atherosclerosis spontaneously on a cholesterol-rich diet.705 Researchers demonstrated dose–dependent reductions in total cholesterol and triglyceride levels, along with atherosclerotic growth regression in the arterial walls of the infected mice. At the time of adenoviral introduction of the human Apo E gene, the mice had fatty streak lesions averaging 220 ± 37 mm² via histologic analysis. The arterial lesion sizes of mice treated with 5 x 10⁸ and 10⁹ pfu of adenovirus measured 147 ± 76 and 28 ± 6 mm² at day 199 of the experiment. In comparison, the control mice had an average lesion size of 1172 ± 255 mm² at day 199. Histologic analysis demonstrated the complete remodeling and re-endothelialization of the arterial wall along with a disappearance of macrophages, foam cells, and cholesterol crystals. This study provides physical evidence of the antiatherogenic potential of adenovirus-mediated gene therapy.

A different strategy to gene therapy involves the inhibition of gene expression of certain genes. Potential use of this technique involves incorporating antisense oligonucleotides to control c-myb and c-myc gene expression and protein synthesis at several points.706 By this method, it could be possible to inhibit smooth-muscle cell proliferation in the arterial wall to decrease atherosclerosis.

ISIS 301012 ( mipomersen) is an antisense oligonucleotide developed to reduce the hepatic synthesis of Apo B-100. Promising results have been demonstrated in animal models and in clinical trials where it has been shown to cause a reduction in Apo B-100, LDL cholesterol, and triglycerides.707-709 However, the drug can cause an increase in enzymes.

Chimeraplasty, or targeted gene correction, involves the use of synthetic DNA-RNA oligonucleotides (chimeraplasts) for targeted gene repair of mutant genes. Chimeraplasty is a novel approach to gene correction that does not rely on a viral delivery strategy. This method to gene correction uses synthetic DNA-RNA oligonucleotides (chimeraplasts) that target a specific mutated gene sequence.708 The use of the chimeraplast offers an advantage to traditional gene therapy that normally requires delivery of much larger amounts of genetic material. The chimeraplasts bind to the mutant gene sequence resulting in the activation of the cell’s DNA repair machinery.709 The cell repairs the mutant gene in situ to match the correct version delivered by the chimeraplast. This targeted gene therapy has an advantage over viral vectors because viruses can integrate at random locations in chromosomes, which can make it difficult to regulate gene expression.

Initial studies in chimeraplasty have been successful in gene transfer. Studies provide evidence that targeted gene therapy can restore tyrosinase activity in the melanocytes of albino mice.710 A recent study also described the correction of the genetic lesion responsible for Crigler-Najjar syndrome in a rat model via chimeraplasty.711 The scientists observed that in rats previously expressing the faulty gene, there was restoration of normal enzyme expression with consequent improvement in the metabolic abnormality after chimeraplasty.

Chimeraplasty has shown promise in early studies for the correction of the enzymatic defect attributed to be a major cause of type III hyperlipidemia. ApoE has antiatherogenic properties associated with the promotion of cholesterol efflux from cells. Having low levels of ApoE is associated with hyperlipidemia and atherosclerosis. ApoE2 is a dysfunctional form of apoE expressed in patients with Type III hyperlipidemia, whereas the wild-type protein, apoE3, is a functional form.709 Scientists were able to target the apoE gene in the liver of transgenic mice overexpressing human apoE2.712 The researchers injected 1000 nm of a chimeraplast, the 68-mer oligonucleotide, into the transgenic mice overexpressing human apoE2. The researchers analyzed the DNA taken from the liver of the treated mice 7 days later and determined approximately 25% of the hepatic apoE2 converted to apoE3. This study provides early evidence that chimeraplast can be used in the future as a possible tool to correct mutant genes in patients with dyslipidemias. One concern of chimeraplasty is the possibility that infusion of the chimeric molecules may lead to the unintentional binding to similar genes with large stretches of DNA identical to the target sequence. Scientists are working on newer ways to deliver the chimeraplasts to the targeted cells, with the hope that the development of these small chimeric molecules will result in a more efficient means of gene transfer.

RNA interference has also become an accepted approach to manipulate gene expression in mammalian systems. In experimental models, Apo B messenger RNA has
been silenced in the liver, resulting in decreased plasma levels of lipoprotein and total cholesterol.\textsuperscript{713}

Heme-oxygenase-1 has been claimed to be protective against atherosclerosis. It has been suggested that heme-oxygenase-1 activation protects against oxidative stress, and the adenovirus mediated gene transfer of heme-oxygenase-1 has been shown to reduce atherosclerotic lesions.\textsuperscript{714,715}

**Other Approaches for Reducing LDL**

Other approaches to reducing LDL cholesterol include the inhibition of microsomal triglyceride transfer protein that mediates the transfer of cholesterol esters and triglycerides to nascent Apo B\textsuperscript{716} and the inhibition of proprotein convertase subtilisin kexin type 9, which negatively modulates LDL receptor expression.\textsuperscript{717}

**Conclusion**

One of the most important breakthroughs in clinical medicine over the last 30 years has been the confirmation of the cholesterol hypothesis by the demonstration that lipid-lowering drug therapy could affect morbidity and mortality from CAD. The drugs will also serve as pharmacologic probes for helping to understand the pathogenesis of atherosclerosis and its major vascular complications.

*Note: References for this chapter can be found here: www.cvpct3.com*
New Aspects of Combination Therapy

Focus on Hypertension

Michael A. Weber, MD

The use of combinations of antihypertensive drugs is growing, particularly with the increasing clinical availability of fixed-dose products that provide 2 or more drugs in 1 tablet or capsule. But despite this trend, a recent statement by an authoritative European guidelines group acknowledges that progressing too rapidly to combination therapy, or initiating antihypertensive treatment with 2 drugs, could cause some patients who might be controlled with just 1 well-selected drug to get more drug exposure than required. On the other hand, from a public health perspective, these experts argue that early or initial combination treatment would sharply increase blood pressure control rates among the large numbers of hypertensive patients currently not achieving desirable blood pressure targets and so provide overall greater cardiovascular protection.

Both the United States and European hypertension guidelines committees have embraced this strategy and recommend initiating treatment with a 2-drug combination in those patients in whom a single drug is unlikely to achieve the target blood pressure. Importantly, the US Food and Drug Administration (FDA) has agreed with these concepts and a number of 2-drug fixed-dose combinations have recently been approved for initial therapy by this agency. Although there is a lack of objective evidence to confirm the outcomes benefits of this approach, the arguments that early blood pressure responses are predictive of long-term control rates support these new trends, as does the argument that the use of modern combinations as initial therapy appears to be safe and well tolerated.

Practical Reasons for Combination Therapy

There are several reasons supporting use of combination therapy in hypertension (Table 21-1). As already discussed, achieving aggressive blood pressure goals early in the treatment process rather than using a long-term deliberative approach, has been accepted by influential experts in the field.

It should be acknowledged that the evidence supporting a blood pressure target < 140/90 mmHg comes from studies in which the starting blood pressures were > 160 mmHg; it is not certain that patients with starting blood pressures between 140 and 160 mmHg should have the same target. In addition, in the case of high-risk hypertensive patients with such conditions as diabetes mellitus or chronic kidney disease, evidence supporting a target

Table 21-1. Advantages of Multidrug Therapy in Hypertension

<table>
<thead>
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<th>Advantage</th>
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<tr>
<td>Increased efficacy of each drug versus either as monotherapy</td>
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<tr>
<td>Complementary mechanisms of action</td>
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<tr>
<td>More prompt achievement of goal blood pressure</td>
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<tr>
<td>Reduced adverse effects, both clinical and metabolic</td>
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<tr>
<td>Alterations of pharmacodynamics, possibly allowing for longer duration of action</td>
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<tr>
<td>Broader spectrum of response</td>
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<tr>
<td>If given as a fixed-dose combination, potential for improved adherence to therapy</td>
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<td>Fewer copays if given as a fixed-dose combination and often less expensive than buying each individually</td>
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<130/80 mmHg is rather meager. However, the VALUE trial indicated not only the general benefits of achieving systolic blood pressures < 140 mmHg but also observed that blood pressures achieved by 1 month of treatment were predictive of major clinical events during the subsequent 5 years. Clearly, there could be reasons other than the effectiveness of blood-pressure lowering to explain the link between strong blood pressure responses and good outcomes, not the least of which is that a rapid normalization of blood pressure during treatment identifies those patients with relatively healthy arterial circulations who, in any case, were destined to have a better cardiovascular prognosis than patients with lesser or slower blood pressure responses. Still, given the good tolerability and convenience of modern drugs, advocating forceful antihypertensive drug strategies appears to be a reasonable approach.

Other potential advantages of combination treatment are discussed later in this brief chapter. The use of drug combinations also broadens the spectrum of patients who respond to treatment. Some patient types are known to respond best to particular drug classes; other patient types respond to different drug classes. Combining 2 drug types into a single therapeutic entity increases the probability of an acceptable blood pressure outcome regardless of patient demographics or other clinical characteristics.

**Beneficial Interactions**

Another advantage of combination therapy is that one of the active drugs may be able to offset or minimize the adverse effects of the other. One example of this beneficial relationship is that the use of a diuretic in combination therapy can prevent the fluid-retaining properties of the other antihypertensive drug. Certainly, diuretics were very valuable treatment adjuncts to the early direct vasodilatory drugs that caused sodium and water retention. On the other hand, the antihypertensive benefits of diuretic therapy were often reduced by the stimulatory effects on the renin angiotensin system of the induced volume depletion, thus making blockers of this system including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and even beta blockers desirable partners of the diuretics.

Another example is the symptomatic complaint of pedal edema produced by calcium channel blockers, especially the dihydropyridine agents. Drugs that block the renin angiotensin system are useful when combined with the calcium channel blockers because they produce venodilation as well as arterial dilation, thereby enhancing central return of circulating fluid from the periphery. Likewise, the deleterious effects of diuretic therapy on glucose and electrolyte metabolism can be partly mitigated by concomitant therapy with blockers of the renin angiotensin system.

**Advantages**

Further advantages of combination therapy include patient convenience and reduced cost. These attributes are particularly evident with fixed combinations in which 2 drugs are combined into 1 tablet or capsule. The ability to take 1 tablet rather than 2 appears to be attractive to patients: There is a higher probability of therapeutic success than if the 2 medications are prescribed to be taken separately. It is not clear whether this enhanced patient adherence with treatment reflects the ease of following a more simple regimen or whether being required to take 1 rather than 2 units creates the sense of a less-threatening, and thus more acceptable, disorder.

Cost is often a consideration in the care of hypertension. There is now such a wide availability of effective agents, many of them older and inexpensive, that it should not be difficult for most patients to be prescribed an affordable regimen. In addition, particularly for newer drugs, the cost of 2-drug combinations is often only marginally more expensive than for the primary drug dispensed as a single agent, making the therapy more affordable.

The following short sections provide examples of these concepts and underscore some relatively recent data regarding the use of combination therapy in managing hypertension.

**Antihypertensive Efficacy of an ACE Inhibitor or ARB Combined with a Diuretic**

Although single-agent therapy can be beneficial in many patients with milder forms of hypertension, most patients whose pretreatment blood pressures are at least 20/10 mmHg above their treatment targets will require more than 1 drug. It is well established that diuretics are logical partners with such agents as ACE inhibitors and ARBs, at least in part because these blockers of the renin angiotensin system are able to neutralize the stimulatory effects of diuretic therapy on renin release. The study in Figure 21-1 is typical of this type of combination, showing that a starting dose, and then a higher dose of the ARB, olmesartan, is effective at reducing systolic and diastolic blood pressures. However, in patients with more severe forms of hypertension, it can be seen that adding hydrochlorothiazide 12.5 mg, and if necessary, 25 mg, adds significant further blood pressure-lowering efficacy. Based on this type of experience, there are currently numerous fixed combinations of ACE inhibitor or ARBs with diuretics available for prescription.
Efficacy of an ACE Inhibitor or ARB and a Diuretic in White and Black Hypertensive Patients

Diuretic therapy tends to be more effective in black patients than white patients, whereas blockers of the renin angiotensin system tend to be more effective in white patients than black patients. Although these generalizations do not always apply to individual patients, the concept of using these 2 drug classes in combination is attractive, for it should provide efficacy across a broad range of patient types. Figure 21-2 shows that having the ability to use the ARB telmisartan alone or in combination with the diuretic, hydrochlorothiazide, provides valuable flexibility in achieving blood pressure goals. It is evident in the large community-based clinical trial represented in this figure that black and white patients experience closely similar beneficial blood pressure reductions when this type of therapeutic approach is used.

Combination of an ACE Inhibitor or ARB with Amlodipine

Although diuretics make obvious partners with blockers of the renin angiotensin system in managing hypertension, calcium channel blockers such as amlodipine also are efficacious when combined with ACE inhibitors or ARBs. This may partly reflect a natriuretic action of calcium channel blockers. Figure 21-3 demonstrates that the ARB olmesartan and the calcium channel blocker, amlodipine, exhibit meaningful dose-dependent antihypertensive efficacy when given to hypertensive patients as monotherapies. Of note, when either the lower or the higher amlodipine dose is added to olmesartan, there is clear evidence of powerful further blood pressure reduction. The antihypertensive efficacy demonstrated in this figure is equivalent to the efficacy demonstrated when diuretics have been combined with blockers of the renin angiotensin system and indicates that this newer type of combination treatment may be a valuable alternative.

Peripheral Edema During Calcium Channel Blocker Treatment

Although calcium channel blockers such as amlodipine generally are well tolerated and perhaps avoid some of the unwanted metabolic effects of diuretic therapy, they can produce peripheral edema. It is believed, however, that this finding reflects the fact that calcium channel blockers have vasodilatory effects on arterial vessels but do not have corresponding effects on venous tissue. This potentially causes some peripheral pooling. Since blockers of the renin angiotensin system have dilatory effects in the venous circulation, they may compensate for the edema caused by calcium channel blockers. The study shown in Figure 21-4 is a meta-analysis of data regarding peripheral edema in patients treated with amlodipine alone, the ARB valsartan alone, and the 2 drugs in combination. The combination is associated with a significantly lower edema rate than with amlodipine (either 5 mg or 10 mg) alone, although the incidence of edema may still be higher than with the placebo or valsartan alone. However, this type of combination therapy adds usefully to the tolerability of amlodipine therapy and may be valuable in...
expanding the clinical utility of the higher 10 mg amlodipine dose.

Effect on Left Ventricular Mass

Combinations of ACE inhibitors and calcium channel blockers appear to be effective in reducing blood pressure. Beyond that, there has been strong interest as to whether such combinations might have vasculoprotective properties that go beyond blood pressure reduction. Figure 21-5 shows the effect of full doses of the ACE inhibitor benazepril and the calcium channel blocker amlodipine on left ventricular mass in a cohort of hypertensive patients.10 It is noteworthy that beyond their individual effects on this measurement, the combination of the 2 drugs—employing only half the doses used in the mono-therapies—shows complete additivity of their effects on left ventricular muscle mass. This finding raises the possibility that this type of combination could have therapeutic benefits beyond those predicted simply by its blood pressure effects.

Effect on Arterial Distensibility

In the same study as just discussed above, the effects of treatment with benazepril, amlodipine, and their half-dose combination on arterial distensibility was measured by a noninterventional technique.10 Figure 21-6 shows that each drug as a monotherapy produced significant improvements in this interesting measurement, but at the same time, the half-dose combination produced a beneficial effect that was at least additive when taking the monotherapies into account. This finding adds a further incentive to believe that this type of combination, for reasons not yet fully defined, could provide outcomes benefits beyond those anticipated by its blood pressure effects.

Exploring Outcomes Effects of Innovative Combinations

The Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) compared cardiovascular outcomes in hypertensive patients treated with a so-called older drug combination, a beta blocker plus a thiazide diuretic, with a so-called newer combination, amlodipine plus an ACE inhibitor. These 2 types of combinations have well-established antihypertensive efficacy. As shown in Figure 21-7, it is clear that across the 5 years of this study, both treatment combinations had significant and approximately similar blood pressure effects.13 This represented an important background to then allow a comparison of the 2 regimens in their effects on major clinical outcomes. It should be noted, however, that the beta-blocker combination might not have had the same antihypertensive efficacy when
measured by an innovative noninterventional method in the central aortic circulation.\textsuperscript{12}

Combination of Amlodipine and an ACE Inhibitor: Effects on Cardiovascular Outcomes

The ASCOT study just discussed was designed primarily to explore major outcomes. Figure 21-8 demonstrates that patients randomized to the amlodipine/ACE inhibitor combination experienced significantly lower cardiovascular mortality than those receiving the beta blocker/diuretic combination.\textsuperscript{11} In fact, the study was stopped prematurely because of this significant mortality difference between the 2 treatment arms. Interpretation of

Figure 21-7. Changes in systolic and diastolic blood pressures during 5.5 years of therapy in hypertensive patients treated with atenolol plus a thiazide or amlodipine plus perindopril. ASCOT=Anglo Scandinavian Cardiac Outcomes Trial; BP = blood pressure.


Figure 21-8. Cardiovascular mortality during 5.5 years in hypertensive patients treated with atenolol plus a thiazide or amlodipine plus perindopril.

these results, however, has been complicated. Did these outcomes, including significantly lower stroke incidence and other event reductions in the amlodipine/ACE inhibitor group, simply reflect an inadequate central blood pressure effect of the beta blocker,\textsuperscript{12} or might there have been some beneficial attribute of the combination of amlodipine with a blocker of the renin angiotensin system? This issue will be assessed in the next section.

Combining Amlodipine and a Blocker of the Renin Angiotensin System: Further Exploration

Recently, the Avoiding Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared 2 antihypertensive combinations based on a blocker of the renin angiotensin system.\textsuperscript{13,13a} One combination was the ACE inhibitor benazepril, together with the diuretic hydrochlorothiazide; the other used the same ACE inhibitor but with the calcium channel blocker amlodipine. This allowed a determination of whether amlodipine or hydrochlorothiazide would represent a better partner with the renin angiotensin blocker as measured by fatal and nonfatal cardiovascular outcomes. Figure 21-9 shows the blood pressure values across 3.5 years of study, indicating excellent and closely similar blood pressure effects in the 2 regimens. This represents an excellent background, as discussed in the next section, to determine whether there are fundamental differences in major outcomes between these 2 types of combination therapies.

The ACCOMPLISH Trial, Definitive Evidence

This clinical trial, like ASCOT before it, was stopped before completion owing to a significant difference in outcomes between the 2 treatment regimens. Figure 21-10 shows that those patients receiving amlodipine in addition to the ACE inhibitor, as compared to those receiving the ACE inhibitor/diuretic combination, had a significantly lower event rate.\textsuperscript{13} These patients experienced a 20% reduction in the primary composite endpoint of myocardial infarction, stroke, cardiovascular mortality, revascularization, and hospitalized angina pectoris. This provided a powerful conclusion that amlodipine, when combined with a blocker of the renin angiotensin system, was associated with clear cardioprotective benefits. This finding might influence future recommendations regarding the selection of optimal antihypertensive combination therapies and should provoke further research into the particular attributes of amlodipine that, beyond its blood pressure actions, appears to provide important clinical advantages.

Combining 2 Types of Blockers of the Renin Angiotensin System

There are theoretical reasons why this type of combination might be valuable despite employing 2 agents with apparently similar mechanisms of action. The most obvious and most tested combination is of an ACE inhibitor and an ARB. A major rationale for the anticipated benefit of this combination is based on the observation that enzymes other than the ACE can convert angiotensin I to angiotensin II, thus suggesting that the cardiovascular and blood pressure benefits of the ACE inhibitors might
at least partly depend on the effects of these agents on nonangiotensin mechanisms, namely those that reduce the breakdown of bradykinin and thereby increase its availability. So, adding an ARB to an ACE inhibitor could provide the advantage of effectively blocking the actions of the remaining angiotensin II.

In reality, this type of combination has not provided substantial antihypertensive additivity, although there have been some outcome benefits in patients with chronic heart failure. Of concern, however, is a recent report from a study of patients at high cardiovascular risk in whom the combination provided no further reduction in events as compared with the single agents, but in whom there was an increased incidence of adverse renal outcomes. Although it would be inappropriate to overinterpret the unexpected results of a single trials, there has been an understandable reduction in enthusiasm for using ACE inhibitor/ARB combinations.

However, another type of combination, an ARB with a direct renin inhibitor, has emerged as an effective treatment for hypertension. As shown in Figure 21-11, the combination of maximum doses of these agents is significantly more efficacious than either one alone. In fact, this new treatment, composed of 2 blockers of the renin angiotensin system, has been approved by the FDA as a fixed-dose combination. Importantly, this approval includes its use—similar to a variety of ARB combinations with thiazides or amlodipine—as initial treatment in patients whose pretreatment blood pressures are sufficiently high to make them unlikely to respond adequately to just 1 drug. Beyond the practicality of this combination, it is very interesting to note that there is hemodynamic activity of the renin angiotensin system that cannot be fully blocked by an ARB and likewise that cannot be fully blocked by a renin inhibitor. The physiological implications of this interesting finding deserve further study.

Re-Emergence of the Triple

With the exception of about 3 or 4 decades ago, almost all fixed antihypertensive combinations have been based on 2 drugs. With a growing belief in the importance of achieving aggressive blood pressure goals, it is now recognized that a meaningful number of patients will require at least 3 agents.

Recently, 3 products incorporating 3 separate drugs were approved and released for patients in whom such treatment would be of value. Not surprisingly, these products, like others that are expected to follow soon, are comprised of an ARB (valsartan or olmesartan) and aliskiren, combined with both amlodipine and hydrochlorothiazide. Obviously, the usual test of a 2-drug combination’s value—that it exhibit significantly greater efficacy than each of its individual components—would not be applicable to a 3-drug combination. Instead, it was necessary to demonstrate that these products had significantly greater efficacy than each of the 3 possible 2-drug combinations that could be formed by its components: the ARB plus amlodipine; the ARB plus hydrochlorothiazide; and amlodipine plus hydrochlorothiazide.
The data from these comparisons are shown in Figure 21-12. It is evident that the 3-drug combination has superior efficacy to each of its 2-drug components, hence making it a valuable tool in patients who require 3 drugs to control their blood pressures. Such patients are provided the convenience of taking 1 rather than 3 tablets.

**Looking Forward**

The use of fixed-dose drug combinations for managing hypertension has increased sharply in the last few years. The available combination regimens for treatment of hypertension are listed in Appendix 2 of this textbook. Much attention is now being focused on our aging population that not only must deal with hypertension, but typically such other conditions as diabetes mellitus, lipid disorders, arthritis, eye conditions and emotional issues. Certainly, the use of rational, well-tolerated drug combinations will reduce the pill burden of these patients and should contribute to more effective therapy.

*Note: References for this chapter can be found here: www.cvct3.com*
During World War I, cigarette smoking escalated and a sharp increase in the incidence of cardiovascular disease was noted. However, it was not until 1958 that the first major epidemiological study demonstrated a strong correlation between smoking and cardiovascular disease. The study found that the risk of dying from coronary artery disease (CAD) was 70% greater in smokers than in nonsmokers. Although not providing definitive evidence that tobacco smoke was responsible for the increased coronary risk, it prompted the first antismoking measures by the Surgeon General in a 1964 report. Acumulating evidence in subsequent years led to the 1979 report proposing a definite association between smoking and CAD.

The harmful effects of smoking cigarettes or cigars is not confined to CAD incidence; the practice also accelerates the development of other atherosclerotic vascular diseases, including vascular dementia, and can greatly increase the risk of acute coronary events, particularly sudden cardiac death (SCD). Evidence suggests that cigarette smoking is an independent predictor of SCD in patients with known CAD. Smoking has also been shown to increase the risk of hospitalization for heart failure, atrial fibrillation, myocardial infarction, and death in patients with left ventricular dysfunction.

Patients with CAD who quit smoking are at no greater risk of SCD than those who never smoked. Cessation of cigarette smoking has been estimated to increase the life expectancy among smokers who stopped at age 35 compared with those who continued to smoke by 6.9 to 8.5 years for men and 6.1 to 7.7 years for women. For patients with left ventricular dysfunction, a 41% reduction in all-cause mortality has been observed in those who stop smoking compared to those who continued, there being no significant difference between ex-smokers and individuals who had never smoked. Smoking cessation appears to be a more powerful risk-factor intervention for coronary artery protection than dietary modifications. Aggressive smoking-cessation intervention has proved superior to a conservative approach for smokers who had undergone coronary artery bypass surgery.

The life-threatening effects of smoking are attributed to increased sympathetic outflow and heightened activation of the blood coagulation system. The biomarkers of inflammation and atherosclerotic disease high-sensitivity C-reactive protein and fibrinogen in blood and the 24-hour urine 8-epi-prostaglandin F2a and 11-dehydrothromboxane B2 are elevated in smokers compared with nonsmokers.

Homocysteine is another biomarker of cardiovascular risk that has been shown to be elevated in the blood of smokers. These biomarkers are thought to be involved in the mechanism promoting atherosclerotic disease progression via endothelial dysfunction. Endothelial dysfunction is not only a precursor of CAD but can also result in peripheral artery disease, chronic renal disease, and erectile dysfunction. Disturbingly, elevated levels of these biomarkers have also been detected in individuals exposed to second-hand smoke.

Mechanisms of Nicotine Addiction

The benefits of smoking cessation include not only reduction in cardiovascular risk, but also reduction in the risk of pulmonary disease and cancer. Ethnic differences in risk have been identified: Japanese smokers are least susceptible to lung cancer. Blacks have a lower incidence of and higher mortality from chronic obstructive pulmonary disease (COPD) than white Americans but a higher incidence of and higher mortality from lung cancer. Although sociocultural factors may be contributory, there

Pharmacotherapy for Smoking Cessation

William H. Frishman, MD
may be ethnic differences in nicotine metabolism that may contribute to nicotine addiction.

Nicotine addiction is a complex bio-psychosocial problem. Once an addiction to nicotine develops, it is difficult to break. Cessation rates are very low when compared with the proportion of smokers who wish to stop and repeatedly try to do so. The effects of nicotine are centrally mediated, with biochemical and physiological functions reinforcing drug-taking behavior. Smoking motives scales allow the measurement of private events mediated by the proposed neuroregulatory effects of nicotine on neuropetides. Questionnaires have been used to identify pharmacological and nonpharmacological motives for smoking. The most commonly identified motives are classified as automatic (ATM), addictive (ADD), sedative (SED), stimulatory (STM), psychosocial (SOC), indulgent (IND), and sensorimotor manipulation (SMM). In 1974, it was proposed that social and other nonpharmacological rewards motivate smoking initially and account for the stronger role of the SOC, IND, and SMM motives early in a smoker’s career. By examining the pattern of correlations between factor scores and criterion variables, Tate suggested that ATM, ADD, SED, and STM and their underlying second-order factors are more closely related to nicotine pharmacology and the mood-altering effects of nicotine than SOC, IND, and SMM and their underlying second-order factors. Eventually, the positive rewards of nicotine, mediated via its direct and indirect effects on the brain, exert more control as the smoker increasingly uses nicotine to modulate arousal and affective tone. This accounts for the stronger role of the SED and STM motives as the addiction progresses.

Recent efforts have concentrated on elucidating some of the underlying neural circuits responsible for nicotine addiction. These include the brainstem pedunculopontine tegmental nucleus (also implicated in drug addiction), activation of nicotinic acetylcholine receptors, endocannabinoid receptors, gamma-aminobutyric acid (GABA) mechanisms, and dopaminergic pathways. A genetic mechanism has also been proposed to explain smoking initiation and nicotine dependence.

An important component of reducing tobacco use in the general population is to prevent the development of nicotine addiction in young people. It is also important to reduce the effects of passive smoking, which has been proved to be harmful to the cardiovascular system of nonsmokers and may aggravate the nicotine load in current smokers.

**Nicotine Pharmacokinetics**

Nicotine in cigarette smoke is absorbed in the pulmonary alveoli and passes into the blood. Blood nicotine levels rise rapidly after smoking a cigarette (a phenomenon known as a “nicotine boost”), with concentrations in the arterial plasma being about twice those in the venous plasma. The extent of the nicotine boost can vary in different individuals. Thereafter, it takes less than 10 seconds for nicotine to reach the brain. Blood levels of cotinine, the main metabolite of nicotine, are directly related to nicotine intake. Smokers of < 5 cigarettes per day have an average blood cotinine level of 54 ng/mL. The reasonable threshold for the addictive cotinine is 50 to 70 ng/mL, but there appears to be no sharply demarcated value.

**Nicotine Withdrawal Symptoms**

Withdrawal symptoms develop in addicted patients within a few hours of the last cigarette. Symptoms vary in different individuals, with some being relatively short-lasting and others persisting for several months (Table 22-1). In most smokers, the addiction is aggravated by the need to avoid the discomfort of withdrawal.

**Treatment of Smoking Cessation**

Numerous factors should be taken into consideration when developing a rational approach to the treatment of nicotine addiction. First, the objectives of the treatment need to be established: namely, stopping smoking completely. Then, the appropriate medication needs to be identified to achieve this objective. The medication needs to be matched to the pathophysiology of the disease. Also, the optimal dosing regimen must be selected. The thera-

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Duration</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightheadedness</td>
<td>&lt; 48 h</td>
<td>10</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>&lt; 1 week</td>
<td>25</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>&lt; 2 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Craving for nicotine</td>
<td>&lt; 2 weeks</td>
<td>70</td>
</tr>
<tr>
<td>Irritability or aggressiveness</td>
<td>&lt; 4 weeks</td>
<td>50</td>
</tr>
<tr>
<td>Depression</td>
<td>&lt; 4 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt; 4 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>&lt; 10 weeks</td>
<td>70</td>
</tr>
</tbody>
</table>

The use of nicotine replacement therapy (NRT) can help reduce the severity of withdrawal symptoms that patients find distressing and, in some cases, unacceptable. NRT should be introduced to patients in a supportive and motivational manner, and they should receive counseling from their healthcare provider. The odds of successfully quitting smoking increase approximately 1.5- to 2-fold with the use of NRT. It’s important to recognize that even when abstinence for several months has been achieved, the risk of relapse remains high. Patients often may need to try several times to attain complete abstinence from smoking.

Smokeless tobacco, predominantly in the form of snuff or chewing tobacco, re-emerged as a popular form of tobacco use in the 1980s, particularly among male adolescents. Smokeless tobacco is associated with fewer and less serious health problems than cigarette smoking, but new evidence for cardiovascular disease is not conclusive. Some data from small-scale studies suggest that the risk of cardiovascular mortality and myocardial infarction is greater in smokeless tobacco users than in smokers. Higher nicotine levels detected in the blood of smokeless tobacco users than in smokers suggest that cardiovascular risk may be greater. However, further rigorous studies with adequate sample sizes are required to establish a firm link between smokeless tobacco and cardiovascular disease.

Nicotine Patches

Transdermal nicotine delivery systems were approved by the US Food and Drug Administration (FDA) in 1991, to provide support for smoking cessation. In recent years, patches of various designs and different pharmacokinetic properties have become available. The low-dose patches are designed to produce blood nicotine levels that are less than those resulting from smoking. The rate of nicotine absorption is maximal between 6 and 7 hours.
12 hours after application, with an absolute bioavailability of about 82%. Blood nicotine levels peak after 16 to 24 hours and then decline. The skin may serve as a reservoir for nicotine because about 10% of transdermal nicotine is systemically absorbed after the patch is removed.

A review of the findings of double-blind studies concluded that prescription nicotine patches are an effective aid to tobacco dependence treatment. However, since success rates varied greatly across studies, it was concluded that the results may be influenced by the nature and intensity of adjuvant smoking cessation counseling. An analysis of over-the-counter products showed that their use resulted in cessation rates by a factor of 2.8 compared with the placebo and proved as effective when given on prescription (Table 22-3). Higher-dose nicotine (44 mg/day) can achieve blood concentrations similar to those resulting from smoking, and clinical data from 3,575 patients suggest that smoking cessation may be enhanced. Patches are designed for 16- or 24-hour wear. No significant difference was found in cessation rates or withdrawal symptoms between the 2 types, and both proved effective by more than doubling 6-month cessation rates. Success with nicotine patches was also shown to be enhanced in those who were slow metabolizers of nicotine. Fast metabolizers of nicotine may be better candidates for non-nicotine treatment formulations.

The most frequently reported adverse effects with all 24-hour patches, but not with 16-hour formulations, are local skin irritation and contact sensitization. These events may be reduced by applying the patch to a different site each day. Use of 24-hour patches may also result in sleep disturbance; an effect that appears to be dose-dependent. For patients experiencing sleep disturbances, a 16-hour patch may prove more acceptable. Alternatively, the 24-hour patch should be removed before bedtime. Patients who continue to smoke while using nicotine patches should be warned that they may experience nausea, abdominal pain, diarrhea, vomiting, dizziness, profuse perspiring, flushing, hearing and vision disturbances, confusion, weakness, palpitations, altered respiration, and hypotension; all of these are signs and symptoms of nicotine toxicity. These events may be confused with nicotine withdrawal (Table 22-1).

Transdermal nicotine has less effect on platelet activation and catecholamine release than does cigarette smoking; thus the use of patches as a smoking-cessation treatment in the patient with CAD is likely to be safer than cigarette smoking. NRT proved safe in a study of the use of the transdermal nicotine patch or the placebo in patients with known CAD and a history of smoking more than 1 pack of cigarettes per day. This has been confirmed in another study. However, use of nicotine

### Table 22-3. 6-Month Cessation Rates (%) in Minimal Contact Studies of Nicotine Gum and Nicotine Patches*

<table>
<thead>
<tr>
<th>Nicotine Gum</th>
<th>Cessation Rate</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OTC NRT</td>
<td>Placebo</td>
</tr>
<tr>
<td>OTC Nicorette data summary 1995</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>Schneider et al 1983</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Nicotine Patch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hays et al 1997</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Nicoderm data summary 1996 (GlaxoSmithKline, Pittsburgh, Pa)</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>Leischow et al 1997</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Nicotrol data summary 1996 (Pfizer Inc., New York, NY)</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Sonderskov et al 1997</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

OTC = over the counter; NRT = nicotine replacement therapy

*Rates are given in percentages. Due to differences in study design and in data collection, quit rates can be compared within rows, but not across rows.

†These studies were surveys, not experimental trials. Because so few surveys were returned for carbon monoxide verification, these are self-reported quit rates. With carbon monoxide verification, they are likely to be somewhat lower.

Reprinted with permission from Hughes JR, Goldstein MG, Hurt RD, Shiffman S. Recent advances in the pharmacotherapy of smoking. JAMA. 1999;281:72. Copyright © 1999 American Medical Association. All rights reserved. (Papers cited within this table are referenced in Hughes et al.)
patches should not be started around the time of an acute myocardial infarction or in patients undergoing coronary artery surgical procedures.  

**Nicotine Gums**

Approved by the FDA in 1984 and now widely available on an over-the-counter basis, the nicotine strengths of the gums (nicotine polacrilex, nicotine resin complex) are 2 mg (1.4 mg nicotine extracted) or 4 mg (3.4 mg nicotine extracted). Highly addicted individuals, defined as smoking > 25 cigarettes daily or with a Fagerstrom Tolerance Questionnaire Score ≥ 7, should initially use the 4 mg strength; for others, the 2 mg nicotine gum is sufficient. The 4-mg strength increased cessation rates by a pooled factor of 2.2 over the 2 mg gum in highly dependent smokers but showed no statistical difference over the 2 mg gum among low-dependence smokers. A summary of 6-month cessation rates with nicotine gum is provided in Table 22-3.

It is recommended that normally 9 to 12 pieces of gum should be chewed daily, but the maximum can be 20 to 30. Even with extensive use of gum, chewers do not match the daily blood nicotine levels achieved by smoking cigarettes considering that the smoke from 1 average cigarette provides 0.8 mg. Unlike normal chewing gum, each piece should be chewed intermittently for about 30 minutes to allow absorption through the buccal mucosa. One piece of gum should provide nicotine replacement for 1 to 2 hours, but an additional piece may be chewed during the hour if a strong craving arises. The rate of nicotine release is dependent on the speed of chewing. Rapid chewing may result in the shallowing of nicotine-loaded saliva and can result in gastrointestinal adverse effects and headaches. It is important that patients should learn to chew slowly and understand the importance of self-titrating the nicotine dose. To assist in the so-called “chew and park” technique, patients should be advised to stop chewing once a peppery taste or tingling in the mouth develops and only start chewing again once the sensation disappears. It was recently found that starting nicotine gum treatment 4 weeks before the target quit date was more effective than starting treatment on the proposed quit date.

Some people find adherence with nicotine gum difficult because of the need for oral manipulation, unappealing flavor, jaw fatigue, jaw and mouth soreness, and headaches (because of excessive chewing). Other adverse effects that are usually only mild and transient include hiccups, burping, and nausea. A low pH suppresses the buccal absorption of nicotine. Patients may also find it difficult to observe the recommended avoidance of carbonated drinks, coffee, beer, wine, or any other acidic drinks 15 minutes before and during gum chewing, especially if they previously associated such activities with smoking a cigarette. Nicotine gum has been reported to be associated with habitual abuse, but prospective data indicate that there is no increased risk of cardiovascular or other diseases with the use of nicotine gum for as long as 5 years, even with concurrent use of cigarettes.

**Nicotine Lozenges**

Nicotine lozenges may be suitable for a patient who prefers oral NRT but is intolerant of gum. An over-the-counter nicotine lozenge was approved by the FDA in 2002. In a placebo-controlled clinical trial, lozenges containing 2 and 4 mg nicotine were shown to be effective, with adverse effects similar to those of the gum. The lozenge can also be “parked” to facilitate absorption through the buccal mucosa.

**Nicotine Nasal Spray**

A nicotine nasal spray is approved for clinical use as an aid to smoking cessation and for the relief of nicotine withdrawal symptoms. One dose consists of 2 squirts (1 in each nostril), each squirt delivering 0.5 mg nicotine. The nicotine nasal spray can replace about 50% of the blood nicotine concentrations that occur with smoking. Smokers normally use 1 to 2 doses per hour, but this may be increased to 40 doses per day for 3 months.

Peak concentrations of nicotine in the blood occur 5 to 10 minutes after use; thus, delivery is faster than gum or an inhaler, but slower than cigarettes. The nasal spray can be used in association with nicotine patches to achieve increased efficacy—a decrease in breakthrough cravings. Originally, it was thought that the dependence potential of nasal spray would be high because of the rapid nicotine absorption and the need for frequent administration. Studies have shown that this is not the case and have found no evidence of abuse liability. Cessation rates at 6 months of between 25% and 35% have been reported (Table 22-4).

Local irritation of the nose and throat are the most common adverse effects. The incidence of moderate to severe irritation usually disappears or becomes mild within a few days of starting the spray. Other events include watery eyes, runny nose, coughing, and sneezing. Long-term nasal complications have not been reported.

**Nicotine Inhaler**

The nicotine inhaler became available by prescription in 1998 and was developed to mimic the hand-to-mouth ritual. It looks very much like a cigarette and comprises a nicotine cartridge attached to a mouthpiece. Inhalers may need to puff, not inhale, vigorously and frequently to achieve a 30% replacement of blood nicotine levels; 80 deep puffs deliver 4 mg nicotine. Unlike cigarettes, the inhaler delivers more nicotine by the buccal (36%) than...
pulmonary (4%) route, with absorption being temperature-dependent and with poor bioavailability below 10°C. Successful use of inhalers depends on the number of doses taken; typically 6 to 16 cartridges per day are required to be successful in preventing smoking.

As is common with other NRTs, the nicotine inhaler results in cessation rates that are double those achieved with the placebo (Tables 22-3 and 22-4). If used concurrently with nicotine patches, high cessation rates may be achieved. E-cigarettes are also available.

Some patients experience local irritation, such as a burning sensation in the throat, as well as sneezing, coughing, and hiccups. These adverse effects may compromise adherence with heavy use and reduce the efficacy of an inhaler.

### Nicotine Partial Agonist

#### Varenicline

Varenicline (Chantix), the most recently approved smoking cessation preparation, is a nicotine receptor partial agonist. The novel prescription drug for smoking cessation received FDA approval in May 2006 after a priority FDA review because of its significant potential benefit to public health. Varenicline is an analog of cytisine. Cyto sine is derived from a weed called “false tobacco” and is a competitive partial agonist at the nicotinic acetylcholine receptor (nAchR).

Varenicline is a selective partial agonist for the α4β2 nAchR and does not bind to other common nicotine receptors or to non-nicotine receptors and transporters. Varenicline also has moderate affinity for the 5-hydroxytryptamine-3 receptor. Stimulation of the α4β2 nAchR by varenicline produces some of the effects of nicotine but reduces cravings and withdrawal symptoms. Unlike NRTs, which require the patient to stop smoking, an individual who smokes while taking varenicline will experience a decline in the sense of satisfaction associated with smoking.

The recommended dose of varenicline is 1 mg twice daily. In the first week of administration, the dose is gradually increased from 0.5 mg once daily on days 1 to 3, 0.5 mg twice daily on days 4 to 7 and then to 1 mg twice daily on day 8. The recommended duration of treatment is 12 weeks. If a patient succeeds in stopping smoking after 12 weeks, varenicline should be given for an additional 12 weeks to increase further the likelihood of long-term smoking abstinence. Patients who are unsuccessful in stopping smoking after the initial therapy, or who relapse after the initial course of treatment, should be encouraged to try again after the factors that contributed to the relapse have been addressed.

Varenicline has been evaluated in over 3,500 chronic cigarette smokers. To date, there has been no direct comparison of varenicline with nicotine patches, but it has been compared with the other first-line non-nicotinic preparation, bupropion. Formal combination efficacy studies using varenicline and other smoking cessation therapies have not been performed. The smoking-cessation rate at the end of 12 weeks of twice-daily varenicline 1 mg treatment was twice that achieved with twice-daily bupropion 150 mg and 4-fold greater than that with the placebo. At a 40-week post-treatment follow-up, those patients on varenicline who had stopped smoking at the end of treatment were more likely to remain abstinent than those on the placebo.
In clinical trials, varenicline was well tolerated. The most common adverse effects were nausea, changes in dreaming, constipation, flatulence, and vomiting. No drug–drug interactions have been detected, although when used in conjunction with nicotine patches, incidences of nausea, headache, and vomiting are greater than those experienced with the patch alone.

In a recent placebo-controlled clinical trial, the drug was shown to be both effective and safe in patients with sable coronary disease. A notice posted in November 2008 on the FDA's MedWatch advises health care professionals to monitor patients taking varenicline for behavior and mood changes and recommends that people taking the drug should contact their physicians if they experience moods or behavioral changes.

The FDA has also added a warning to the varenicline package insert about neuropsychiatric symptoms and exacerbations of pre-existing psychiatric illness associated with its use. Recent data have shown that varenicline is effective and safe in patients with known cardiovascular disease, and 33.2% of those treated with varenicline achieved 1-year cessation rates of at least 10%.

Non-Nicotine Preparations

Bupropion

Bupropion is available in 2 sustained-release forms (Wellbutrin and Zyban) and a generic form. It is an atypical antidepressant with dopaminergic and adrenergic actions; bupropion was originally marketed for the treatment of depression. Evidence also suggests that bupropion antagonizes a brain nicotinic receptor and blocks the reinforcing effects of nicotine, hence, a sustained-release formulation, Zyban was developed specifically for use in smoking cessation. Zyban first became available in 1998. Using sustained-release bupropion for smoking cessation does not involve the replacement of nicotine and may be appropriate for patients who dislike or who have failed NRT. For patients interested in reducing rather than quitting smoking altogether, bupropion can help them to achieve this during the treatment course. Bupropion also may reduce the time to the next attempt to stop and increase short-term abstinence rates. When combined with NRT, greater effects on smoking cessation are seen than with either treatment alone. It may be especially beneficial for patients concerned about weight gain associated with stopping smoking, as bupropion appears to blunt this effect. Within 1 week of starting bupropion, many smokers note that their craving for cigarettes is altered and their satisfaction derived from tobacco decreased.

Smokers using the sustained-release formulation of bupropion (which is approved for clinical use) begin treatment 1 week prior to the date they plan to stop smoking. Dose titration is performed, starting at 150 mg for 3 to 5 days before an increase to 150 mg twice daily. The recommended duration of treatment is 7 to 12 weeks, but this may be extended to 12 months to prevent relapse dependent on the individual’s nicotine withdrawal phase. Its long-term safety for the treatment of chronic depression has already been determined. There is no rebound phenomenon upon abrupt discontinuation of the drug, because bupropion is a non-nicotine-based therapy. Some clinicians use Wellbutrin XL 150 mg once daily, which is off label for tobacco dependence treatment; it may decrease insomnia.

In comparison with a cessation rate of 19.05% with the placebo, treatment with bupropion 100, 150, and 300 mg/day for 7 weeks produced cessation rates of 28.8%, 38.6%, and 44.2% respectively in a study of more than 600 patients. A history of major depression was an exclusion criterion in this study, thus suggesting that the beneficial effect of bupropion was not explained by its antidepressant activity. Another study has shown that bupropion was equally effective in smokers whether or not they had a history of depression. In a randomized study of over 1,500 smokers, 1-year cessation rates after bupropion and minimal to moderate counseling were between 23.6% and 33.2%. The study also demonstrated that bupropion provided effective treatment in the primary-care setting and did not require intensive counseling. Smoking cessation rates at 6 months are similar to those achieved with NRT and were greater than observed in the placebo (Table 22-4). In a study of patients with known cardiovascular disease, cessation rates were more than doubled in the bupropion than in the placebo between 4 and 52 weeks after the start of treatment.

Adverse effects observed in clinical trials include insomnia (30% to 42%), headache (26%), and dry mouth (10.7%) using the sustained-release formulation. Insomnia can be overcome by taking the evening dose > 4 hours before bedtime. Initial studies with higher-dose, immediate-release bupropion have shown a higher frequency of seizures. More recent data with sustained-release preparations at doses of ≤ 150 mg twice daily showed that the risk of seizures was no greater than that of typical antidepressants. Patients with a history of seizures or suicide ideation should not use bupropion. Bupropion is also contraindicated if there is a history of head trauma, heavy...
alcohol use, or anorexia. Furthermore, bupropion must not be used in combination with monoamine oxidase inhibitors or in patients with schizophrenia. Bupropion has been assigned a class C category for pregnancy by the FDA.

Bupropion can safely be used in combination with nicotine patches; a 1-year cessation rate of 25% to 30% has been recorded as opposed to 15% to 20% when monotherapy with counseling was employed. It is the author’s opinion that concurrent bupropion and nicotine patches should be considered for patients who have failed prior therapy, have high levels of nicotine dependence, or a history of psychiatric problems.

**Clonidine**

Clonidine is an α2 adrenergic agonist developed originally as an antihypertensive agent (Prichard 1988), but it has also been recommended for the treatment of chronic pain syndromes, menopausal flushing, Tourette syndrome, opiate or alcohol abuse withdrawal, and other neuropsychiatric conditions. More recently, studies have investigated clonidine for use as a smoking-cessation therapy. Clonidine suppresses the acute symptoms of nicotine withdrawal, such as tension, irritability, anxiety, cravings, and restlessness.

Clonidine’s recommended dose for smoking cessation is 100 μg given twice daily, but it can be titrated to a maximum of about 400 μg per day according to toleration. Treatment should commence before stopping smoking so that steady-state plasma concentrations can be achieved before the onset of nicotine withdrawal symptoms. The maximum duration of treatment should not be more than 3 to 4 weeks. Physicians should be vigilant as to the potential for rebound hypertension on withdrawal in hypertensive patients; therefore, treatment should not stopped abruptly but should be gradually down-titrated. A meta-analysis of 10 small-scale and 2 large-scale trials revealed a trend for improved smoking cessation rates, although efficacy at 6 months was demonstrated in only 1 study.

Adverse effects have restricted use of clonidine in smoking-cessation therapy to second-line treatment. The important adverse effects include orthostatic hypotension, dizziness, fatigue, sedation, and dry mouth. Situations where clonidine may be considered appropriate include the failure of NRT or bupropion and the presence of multiple drug-abuse problems; this is because clonidine relieves the withdrawal symptoms of other drugs besides nicotine.

Clonidine might be used in combination with NRT or bupropion as its mechanism of action is different from that of either therapy. However, to the author’s knowledge, no relevant studies have been reported. Before it can be considered as a first-line therapy for smoking cessation, future studies will have to show that clonidine is clinically effective and is associated with fewer adverse effects than other treatments.

**Nortriptyline**

Nortriptyline is a noradrenergic tricyclic antidepressant drug that can have a beneficial impact on nicotine withdrawal symptoms. It is not approved currently by the FDA for nicotine dependence and should be considered only as second-line treatment for smoking cessation.

Nortriptyline, compared with the placebo, doubled the continuous 1-year smoking abstinence rate from 12% to 24% when used in association with intensive individual counseling sessions. Although excessive hunger and increased eating and drowsiness were unchanged, significant reductions in impatience, irritability/anger, anxiety/tension, restlessness, and insomnia and an improvement in the ability to concentrate was noted in other studies. One study found that 14% of nortriptyline-treated patients remained abstinent after 6 months, but only 3% remained abstinent in the placebo group. The other study (n = 144) demonstrated a 6-month abstinence rate of 20.6% for nortriptyline and 5.3% for the placebo.

Overall efficacy was similar to that of bupropion and appeared unrelated to nortriptyline’s antidepressant activity. The study participants had histories of depression; thus, the findings may not be applicable to the general smoking population. An improved smoking-cessation rate has been recorded when nortriptyline was used in conjunction with nicotine patches.

Adverse effects are frequent and include dry mouth, distortion or decrease in taste sensation, gastrointestinal disturbances, drowsiness, and sleep disruption. Some patients report lightheadedness, shaky hands, and blurry vision. Disturbances of cardiac rhythm can occur, and overdose can result in serious and possible life-threatening toxicity.

**Selective Serotonin Reuptake Inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) are used to treat depression and anxiety and to regulate mood. After stopping smoking, many people experience mood changes resembling subclinical depression. It is theoretically possible; therefore, that SSRIs such as fluoxetine, paroxetine, or sertraline may help patients overcome these symptoms.

Fluoxetine 60 mg improved both the positive and negative mood states in a clinical trial conducted in smokers without clinically significant depression. In a study of only 15 patients, Doxepin resulted in significantly less craving for cigarettes. However, fluoxetine proved not to be effective. Results of other studies evaluating fluoxetine, paroxetine, or sertraline in the management of smoking cessation failed to establish any benefit. In the light of
these inconclusive findings, the use of SSRIs in smoking-cessation therapy is not currently recommended.

**Monoamine Oxidase Inhibitors**

Animal and human studies have shown that exposure to tobacco smoke reduces the levels of monoamine oxidase (MAO) in the brain. The reversible MAO type A inhibitor moclobemide, given at doses of 400 mg/day for 2 months and 200 mg/day during the third month, has been evaluated when given as an aid to smoking cessation in heavily dependent smokers in a preliminary study and proved successful. However, study subjects tended to experience insomnia and dry mouth.

Under laboratory conditions, the MAO type B inhibitor selegiline reduced smoking behavior as well as cravings. At a daily dose of 10 mg for 8 weeks, a pilot study in hard-to-treat smokers found that selegiline improved smoking-cessation rates and was well tolerated. Further analysis showed that 45% of the participants receiving selegiline had not smoked during the preceding week when questioned at the end of treatment. When asked again 6 weeks later, 20% were still not smoking.

**Bromocriptine**

Researchers have hypothesized that dopamine mediates the reinforcing effects of stimulant drugs, including nicotine, suggesting that a dopamine antagonist could increase smoking and that an agonist could reduce smoking. Subfertile women (using bromocriptine to help conceive) were half as likely to smoke as those taking other drugs or those conceiving without medication. In a laboratory study of heavy smokers, bromocriptine use was linked to reduced smoking.

**Anxiolytics**

The efficacy of benzodiazepine as a tobacco cessation treatment has not been demonstrated, and prolonged use of the drug may lead to physical and psychological dependence, so its use for smoking cessation is contraindicated. The results of treatment with a nonbenzodiazepine anxiolytic such as buspirone have been inconsistent, and the current recommendation is that this type of drug should be limited to use as an alternative, second-line treatment.

**Glucose**

Oral glucose tablets have been proposed as a possible aid to smoking cessation that would be very inexpensive and might be used by some smokers as well as or instead of medications. It is hypothesized that a single dose of nicotine will relieve hunger in a smoker, so that over time smokers come to interpret sensations associated with hunger as craving for a cigarette in certain situations. Some studies have shown that chewing glucose tablets can reduce the desire to smoke during abstinence. Definitive trials are now required, but given their low cost, glucose tablets may be a useful aid for some smokers.

**Upper Airway Stimulants**

The stimulation of the sensory receptors located in the pharynx and larynx could contribute to tobacco addiction. Inhaled preparations of ascorbic acid, citric acid, and extract of black pepper have been evaluated, although currently no study results are available to justify their use.

**Experimental Formulations That Affect Nicotine**

**Inhibition of the Hepatic Cytochrome P-450 System**

As mentioned earlier, approximately 80% of nicotine is metabolized to the inactive metabolite cotinine by way of C-oxidation, and CYP2A6 is responsible for 90% of this process. Variations in the activity of this enzyme account for individual differences in the rate of nicotine metabolism and have been shown to influence various aspects of smoking behavior, such as the ability to start smoking and become addicted to tobacco, as well as the maintenance of higher or lower levels of tobacco use. Many individuals who lack the enzyme either do not smoke or smoke very little. Researchers theorized that if they could block the enzyme from being produced or prevent its activity, it would reduce a person’s desire to smoke. The agent methoxsalen was shown to inhibit the metabolism of orally administered nicotine and reduce the rate of smoking in study subjects. The drug works indirectly to decrease the desire to smoke by slowing the removal of nicotine from the body, so individuals have less urge to smoke and therefore will have less exposure to it. In addition, CYP2A6 activates procarcinogens, so that blocking the enzyme may not only decrease smoking levels, but also may make cigarette smoke safer because there would be less activation of these procarcinogens. Research with this approach is still in its early phase.

**Nicotine Vaccines**

In the context of drug addiction, the aim of a therapeutic vaccine is to stimulate the production of specific antibodies that will fix the target drug and alter its pharmacokinetic properties. The principal objective is to reduce the quantity of the substance available or its distribution to the brain. High doses of nicotine produce reward
stimuli much greater than low doses, and rapid delivery of nicotine to the brain stimulates a much greater reward response than slow delivery.\textsuperscript{146} For example, a cigarette produces a much greater reward response than a nicotine patch. The nicotine vaccine stimulates the production of nicotine-specific antibodies that can bind nicotine with a high affinity and fix it in plasma. Because of their high molecular weight, these antibodies are too large to cross the blood–brain barrier so that the nicotine fixed by the antibody is thus blocked from entering the central nervous system (CNS).\textsuperscript{146} Nicotine is a small molecule that is not very antigenic. In order to augment the immune response, nicotine can be bound to larger molecules, usually proteins founds in bacterial toxins. In animal studies, the nicotine vaccine has been shown to be effective in reducing the distribution of nicotine to the brain by 60%,\textsuperscript{149,150} Vaccination of rats against nicotine has been shown to reduce nicotine distribution to the brain\textsuperscript{151,152} even with nicotine doses that are twice the estimated binding capacity of the antibodies. This suggests that the vaccine not only sequesters nicotine but may also direct it away from the brain by some other mechanism.\textsuperscript{153} In animals, antibodies to nicotine were produced even with the continued administration of nicotine to the subject. Therefore, these vaccines could be used even in individuals continuing to smoke and the antibodies would be present when a cessation attempt was made.

Some pharmaceutical companies are currently developing nicotine vaccines for human use.\textsuperscript{143} TA-NIC, a novel nicotine vaccine that has undergone Phase 1 studies, has been shown to be safe and immunogenic when using up to 6 vaccinations during weeks 0–8, with a booster at 9 months.\textsuperscript{154} The TA-NIC vaccine has been shown to have a 12-month abstinence rate of 19% to 38% with 250 and 1000 μg doses versus 8% with the placebo in clinical trials.\textsuperscript{114} Enrollment for a large phase 2b trial in the United States has been completed. This placebo-controlled, double-blind, multicenter study is evaluating the safety and efficacy of TA-NIC in managing smoking cessation when given in combination with current standard support treatment. The primary endpoint of the study is a 6-month smoking abstinence rate.\textsuperscript{155}

The nicotine vaccine (Nic V AX) is a nicotine recombinant Pseudomonas aeruginosa ex protein A conjugate vaccine.\textsuperscript{156} Phase 1 studies have shown safety and antibody response up to 63 days post-vaccination. A single dose of the vaccine produced antibodies within 7 days, which were maintained in the blood over 4 months.\textsuperscript{157} In a Phase 2, double-blind, placebo controlled, randomized study with 68 smokers, the vaccine was found to be well tolerated, with adverse effects similar to the placebo. Vaccine immunogenicity was dose-related, with the highest dose eliciting antibody concentrations within the anticipated range of efficacy.\textsuperscript{158} Preliminary reports showed that 38% of smokers taking the vaccine stopped smoking for at least 30 consecutive days versus 9% of the placebo subjects. Patients were given 4 injections over a 6-month period. The results represented a vaccine-only effect, as patients were given the vaccine without any supplemental treatment, behavioral support, or counseling. The vaccine received fast track designation from the FDA.

CYT-002-NicQb is a vaccine based on the virus-like particle formed by the recombination coat protein of the bacteriophage Qb. Preclinical studies in mice have demonstrated the efficacy of CYT-002-NicQb in producing nicotine-specific antibodies and reducing penetration of the brain by circulating nicotine. In a phase 1 study, the vaccine produced an immunogenic response of 100%.\textsuperscript{159} In a phase 2 trial, abstinence correlated significantly with antibody levels as smokers in whom high antibody levels were achieved showed significant improvements in continuous abstinence over 6- and 12-month periods compared with subjects receiving the placebo and subjects treated with active vaccine showing medium and low antibody levels.\textsuperscript{159} In those individuals who resumed smoking, there was no evidence for increased smoking activity to compensate for the neutralizing effect of nicotine.\textsuperscript{159}

With these vaccines, achievement of high antibody levels is essential for efficacy. Subjects often require multiple injections over 4-6 weeks to achieve sufficient antibody titers. In addition, there seems to be great interindividual variability in the immunogenicity of the vaccine, which could provide a challenge in clinical practice.

The clinical benefit for smokers with this approach is that in a vaccinated individual, nicotine will not have the same effect on the brain and thus, smoking may not become addictive.\textsuperscript{148} The implications for current smokers as a tool for cessation, former smokers as tool for relapse prevention, and those who have never smoked (possibly youth) as a tool for primary prevention are numerous. This vaccination has potential benefits for both pregnant smokers and the developing fetus, as nicotine has been implicated as a neurotoxin in developing fetal tissues. Vaccinated pregnant smokers might be more likely to quit and remain abstinent, with a reduction of nicotine exposure to the brain of the fetus.\textsuperscript{143,160} Additional studies are required to assure the safety and efficacy of the vaccine in humans.

Vaccination against nicotine appears very effective and poses relatively few side effects because the antibody itself does not appreciably enter the brain. Because nicotine vaccines target the drug rather than the brain, and the antibodies themselves do not cross the blood–brain barrier, immunization should circumvent the CNS adverse effects that limit the usable dosage of other medications for tobacco dependence. The antibodies are also highly specific for nicotine and do not bind other ligands, endogenous neurotransmitters, or receptors.
While the effects of the vaccine could be nullified with enough nicotine ingestion to overpower the antibody response produced, it is unlikely that this would happen. Possible target groups for the vaccine include an experimenting teenage population, a recently abstinent smoker, or patients trying to quit smoking. In any case, the effect is similar in that a risk factor for atherosclerosis is nullified.

### Additional Drugs Under Investigation

#### Rimonabant

Endocannabinoid receptors have recently been implicated in nicotine addiction. Hence, drugs affecting cannabinoid receptors may aid smoking cessation. The selective cannabinoid-1 receptor blockers (CB1) are thought to modulate systems in the brain that are altered by cigarette smoke. Rimonabant (Acomplia) is the first CB1 receptor and was available in the UK as an antiobesity drug. In animals, rimonabant reduced self-administration of nicotine and release of dopamine in the nucleus accumbens induced by nicotine. The drug had been proposed not only as an aid for smoking cessation and atherosclerosis reduction, but also in the maintenance of abstinence. Clinical trials have shown success regarding its use in smoking cessation; however, results from Europe showed that its use was associated with a significantly increased rate of psychiatric adverse effects, and the drug, for now, will not be approved for clinical use in the United States.

#### Reboxetine

Reboxetine is a selective inhibitor of the norepinephrine transporter and also has been shown to be a noncompetitive antagonist of nAChRs. Animal studies have found that reboxetine inhibits nAChR function, suggesting that it may have potential as a smoking cessation agent.

#### Naltrexone

Opioid treatments have been investigated for smoking cessation as the reinforcing properties of nicotine may be mediated through release of various neurotransmitters that impact the endogenous opiate system. Naltrexone use in a laboratory study was associated with a reduction in the number of cigarettes smoked, but the drug was associated with significant adverse effects, especially sedation.

In a preliminary study, naltrexone in combination with NRT for smoking cessation reduced the likelihood of relapse and the desire to smoke; it also prevented weight gain following smoking cessation.

### Conclusions

Cigarette smoking is strongly associated with an increased risk of developing CAD, COPD, vascular dementia, and cancer. Ex-smokers with CAD have significantly lower mortality, fewer ischemic events, and better cardiac function than individuals with CAD who continue smoking. Because of the clear health benefits of smoking cessation, the importance of encouraging patients to stop cannot be overemphasized. The effectiveness of current therapies to help smokers to achieve this goal is reflected in Medicare policies. Medicare currently reimburses health-care providers for counseling sessions for smoking cessation and, as of January 1, 2006, prescription smoking-cessation medications were covered for eligible Medicare beneficiaries in accordance with the Medicare prescription drug benefit.

Nicotine, together with carbon monoxide and tar, is one of the substances in cigarette smoke that contributes to the increased mortality risk in smokers. Furthermore, nicotine appears to contribute most to the addictive nature of cigarette smoking. A variety of pharmaceutical nicotine formulations are available for use in replacement therapy for cigarette smoking to help smokers who wish to eliminate their addiction to smoking and nicotine. In patients with known CAD, NRT appears to be an effective and safe approach to smoking cessation, along with behavioral modification and other pharmacologic interventions. Many new NRTs are available, and research is being undertaken to understand more fully the neural circuits and pathways involved in smoking and drug addiction. With this knowledge, we should be able to develop newer and better therapies. Currently, NRT with the nicotine patch and gum are first-line therapies in smoking cessation (Table 22-5).

Varenicline, a nicotine receptor partial agonist, was approved for use in smoking cessation as a first-line therapy, and has been shown to be safe when used in patients with CAD. However, there may be an increase in suicide ideation with its use. Bupropion, a non-nicotine therapy that was originally given to treat depression, is another first-line therapy that can be employed in combination with NRT. Another antidepressant, nortriptyline, has been shown to be as effective as bupropion, although it is not a first-line agent. The proven efficacy of bupropion and nortriptyline appears to be independent of their antidepressant activity.

Research into genetics may provide an empirical approach by enabling various pharmacologic treatments to be tailored to the individual with tobacco dependency.
Using genetic association studies of smoking initiation and dependence, genetic polymorphisms have been identified. Pharmacogenetics may help to predict responses to different medications used as part of a smoking-cessation program. Nicotine in cigarette smoke is acknowledged as a pharmacologic substance and, as are other drugs, needs to be regulated more stringently.

With the recent passage of the Family Smoking Prevention and Tobacco Control Act (2009), the government granted permission for the FDA to regulate the nicotine content in tobacco products. It will allow the FDA to ban certain ingredients in cigarettes, push for tougher product labeling, and create an FDA Center for Tobacco Products.

Table 22-5. Possible Pharmacotherapies to Aid Smoking Cessation*

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Precautions/Contraindications</th>
<th>Adverse Effects</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line NRT</strong></td>
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<td></td>
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<tr>
<td>Nicotine patches</td>
<td>Local skin reaction; insomnia</td>
<td>21 mg/24 h</td>
<td>4 weeks then</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>14 mg/24 h</td>
<td>2 weeks then</td>
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<tr>
<td></td>
<td></td>
<td>7 mg/24 h</td>
<td>2 weeks;</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>15 mg/16 h</td>
<td>8 weeks</td>
<td></td>
</tr>
<tr>
<td>Nicotine gums</td>
<td>Mouth soreness; dyspepsia</td>
<td>1–24 cigarettes/day: 2-mg gum (up to 24 pieces/day);</td>
<td>≤ 12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 25 cigarettes/day: 4-mg gum (up to 24 pieces/day)</td>
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<tr>
<td>Nicotine lozenges</td>
<td>Mouth soreness; dyspepsia</td>
<td>2-4 mg (up to 24 pieces/day)</td>
<td>6 weeks then</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>down-titrte</td>
<td></td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>Nasal irritation</td>
<td>8–40 doses/day</td>
<td>3–6 months</td>
<td></td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>Local irritation of mouth and throat</td>
<td>6–16 cartridges/day</td>
<td>≤ 6 months</td>
<td></td>
</tr>
<tr>
<td><strong>First-line Non-Nicotine Preparations</strong></td>
<td></td>
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<tr>
<td>Varenicline</td>
<td>Nausea, headache, vomiting, behavior &amp; mood changes, suicide ideation</td>
<td>0.5 mg od for 3 days, then 0.5 mg bid for 4 days, then 1 mg bid thereafter</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Sustained-release bupropion</td>
<td>History of seizure; History of eating disorder</td>
<td>Insomnia; dry mouth, behavior changes &amp; suicide ideation</td>
<td>7–12 weeks Maintenance ≤6 months.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>150 mg od for 3 days then 150 mg bid (begin treatment 1-2 weeks before stopping smoking)</td>
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<tr>
<td><strong>Second-line Non-Nicotine Preparations</strong></td>
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<tr>
<td>Clonidine</td>
<td>Rebound hypertension</td>
<td>Dry mouth, drowsiness; dizziness; sedation</td>
<td>0.15–0.75 mg/day</td>
<td>3–10 weeks</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Risk of arrhythmias</td>
<td>Sedation, dry mouth</td>
<td>75–100 mg/day</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*The information in this table is not comprehensive. Please see package insert for additional information. First-line pharmacotherapies have been approved for smoking cessation by the FDA; second-line pharmacotherapies have not.

Adapted from The Tobacco Use and Dependence Clinical Practice Guidelines Panel, Staff and Consortium Representatives. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. JAMA. 2000;283:3244-3254. Copyright © 2000 American Medical Association. All rights reserved.
The past two decades have heralded a new era in obesity research with unprecedented progress being made regarding knowledge of pathophysiology and potential treatments for this previously neglected metabolic disorder. Exciting new molecular targets for intervention have been identified including leptin, the leptin receptor, the cannabinoid receptor, human growth hormone, hormone PYY, the β3 adrenergic receptor, the melanocortin receptors (MCR-3 and 4), fatty acid synthase, uncoupling proteins (UCPs) that stimulate energy expenditure, and ghrelin.

Several factors underlie the explosion in obesity research and its legitimacy as a subject for scientific investigation. These include: (1) alarming increases in prevalence estimates of overweight and obesity in all age ranges from a survey of systematically sampled United States residents (the National Health and Nutrition Survey [NHANES] III); (2) evidence from a variety of longitudinal studies of a causal relationship between obesity and important adverse health consequences that increase premature mortality in industrialized nations; and (3) a myriad of new molecular findings, including the elucidation of the neural circuitry of appetite regulation and the identification of specific genetic defects related to energy expenditure.

The prevalence of obesity has increased dramatically in the past 5 decades. The most recent prevalence estimates from population-based studies indicate that 129.6 million adults are overweight (body mass index [BMI] 25.0 to 29.9 kg/m²) and 61.3 million adults are obese (BMI ≥ 30 kg/m²). From 1999 to 2002, more than 65% of adults aged 20 to 74 residing in the United States were categorized as either overweight or obese, and 31.1% were categorized as obese. This is a dramatic increase, as reported in the National Health and Nutrition Survey (NHANES) III, which compared the prevalence of weight abnormalities by age-range and ethnic groups with NHANES II and demonstrated an equally dramatic increase in the prevalence of obesity (22.9% compared to 14.5%). These weight trends were perplexing, as they followed 2 decades of a formal public health campaign to improve the nation’s physical activity levels and nutrition practices through increased intake of complex carbohydrates (fruits, vegetables, and whole grains) in combination with a reduction of total caloric intake and dietary fat (as outlined in Healthy People 2000 and 2010).

The implications of these findings in the context of longitudinal studies established obesity as an important risk factor for cardiovascular disease, type 2 diabetes mellitus, cancer, disabilities, and all-cause mortality. The changing awareness of obesity facts has led public health officials to designate obesity an important health priority of “epidemic” proportion. This also culminated in the creation of a national task force of obesity experts in the United States in 1996 to evaluate potential causes and cures. Studies by the US Task Force and results of a similarly convened study group in Canada were formulated into publications that provide excellent overviews of the magnitude and complexity of obesity in industrialized society with specific clinical guidelines for the management of overweight and obese adults. The 1998 US Report, issued by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health, included a consensus statement, evidence-based treatment algorithms, and diagnostic and therapeutic recommendations that became the foundation for current obesity management guidelines.

The NHLBI report served a pivotal role in the redefinition of obesity as a chronic medical condition. The perception of obesity as a chronic clinical disorder encouraged physicians to adopt a more realistic approach to the treatment of obesity, and ultimately, increased the
acceptability of medication as adjunct to diet and exercise in lifelong obesity management. Comprehensive treatment guidelines outlined in the report provided a systematic approach to obesity management that is relevant to cardiologists as well as to all primary care specialists. As with published national guidelines for the treatment of cholesterol and blood pressure abnormalities, these recommendations now enable clinicians to initiate appropriate dietary and pharmacological therapies as part of an integrated weight-management strategy that could ultimately reduce the risk of obesity-related comorbidities, including cardiovascular disease for the 65% of American adults who are currently overweight or obese.

Although lifestyle modification and long-term dietary vigilance will, inevitably, remain the cornerstone of lifetime weight regulation, the continued availability of pharmacotherapies approved by the US Food and Drug Administration (FDA) along with the promising development of new drugs has further expanded current therapeutic options for the management of obesity. This chapter will summarize current recommendations regarding the diagnosis and drug treatment of obesity.

### Obesity and Cardiovascular Disease: Epidemiologic Evidence

Obesity is a well-established risk factor for cardiovascular disease. Several large longitudinal studies have documented the relationship between obesity and cardiovascular mortality, including the Framingham Study, the Nurses Health Study, and the Harvard Alumni Study. In addition, adiposity predisposes to diabetes mellitus, hypertension, and lipid abnormalities that act as additional independent putative risk factors for various cardiac outcomes. With the rising prevalence of obesity and its associated cardiovascular risk factors, the metabolic syndrome is also increasing as a risk factor for coronary artery disease and stroke, as described by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP ATP III). The metabolic syndrome is defined by several lipid and nonlipid risk factors that increase the risk for cardiovascular disease. The presence of 3 or more of the following risk factors is sufficient for diagnosis of the metabolic syndrome: (a) abdominal obesity (waist circumference in men > 102 cm; women > 88 cm); (b) elevated triglycerides (> 150 mg/dL); (c) low high-density lipoprotein (HDL) (men < 40 mg/dL; women < 50 mg/dL), (d) blood pressure ≥ 130 mmHg systolic and 85 mmHg diastolic, and (e) fasting glucose ≥ 110 mg/dL.

### Defining Obesity: New Criteria

The definition of obesity is critical to both clinician and clinical researcher and has evolved over the past 2 decades. For most of the 1900s, obesity was defined in terms of variance from the population mean that was believed to represent "desirable weight." The latter was based on actuarial data reflecting the distribution of weight in the United States population according to an estimate of body frame category for a given height. Clearly, the reliance on an imprecisely derived weight range for a given individual precluded a definitive assessment of the relationship between obesity and disease outcomes. It was not until the late 1980s that more specific measures incorporating height were introduced. This led, initially, to use of the Quetelet Index and, more recently, to the concept of BMI. The latter is equivalent to weight (in kilograms) divided by the height (in meters) squared and may be also be calculated by the following nonmetric conversion formula: 704.5 times the weight (pounds)/height (inches). However, universal acceptance of the BMI as a definitive measure of obesity has been relatively recent as evidenced by earlier epidemiologic studies in the decade that utilized the Quetelet. The BMI is considered an indirect measure of body fat and should be calculated as part of obesity management.

The NHLBI task force has adopted the following classification system for adults (18 years of age or older):

- BMI 25.0 to 29.9 kg/m² overweight
- BMI 30.0 to 34.9 kg/m² moderate obesity
- BMI 35.0 to 39.9 kg/m² extreme obesity
- BMI > 40.0 kg/m²

### Medical Interventions

Energy expenditure must exceed energy intake to achieve weight loss. Evidence-based medicine dictates that effective obesity management must incorporate an integrated program of calorific and fat restriction in combination with exercise and behavior modification in addition to pharmacotherapy.

### Dietary Interventions

Dietary interventions form the cornerstone of the comprehensive management of obesity. Two aspects of diet are typically considered as part of dietary recommendations: (1) total caloric content and (2) the composition of the diet, ie, nutrient partitioning between fats, carbohydrates, and protein. At the current time, most obesity experts recommend a caloric deficit tailored to baseline body weight in the range of 600 calories/day. There is con-
Pharmacotherapy

The recognition that obesity is a chronic condition that merits a comprehensive management approach comparable to those used in the treatment of hypertension, hypercholesterolemia, and diabetes mellitus has produced a dramatic resurgence of interest in nonprescription and prescription pharmacotherapies. After an analysis of 813 obesity treatment studies, 39 of which met inclusion criteria, the Canadian Task Force on Obesity concluded that insufficient data were available to evaluate the long-term effectiveness of obesity treatment methods and did not present guidelines for therapeutic intervention. In contrast, how and when to treat overweight and obese Americans was an important focus of the NHLBI guidelines, and following the evaluation of 44 randomized clinical trials, the NHLBI study group did issue federal guidelines regarding the initiation of pharmacotherapies.

These treatment recommendations were based on calculation of the BMI, measurement of waist circumference, and assessment of comorbidities defined specifically as established coronary heart disease, other atherosclerotic disease, Type 2 diabetes mellitus, and sleep apnea. Accordingly, the task force recommended pharmacotherapy for individuals with a BMI > 30 Kg/m² or a waist circumference > 35 inches (women) or 40 inches (men), and for patients with a BMI > 27 Kg/m² with the presence of an additional comorbid condition or more than 1 risk factor for “weight-related” disease, eg, hypercholesterolemia, diabetes mellitus, or hypertension. In addition, the NHLBI guidelines specifically state that FDA-approved weight-loss drugs must be employed in conjunction with concomitant lifestyle modification that includes dietary intervention, behavioral therapy, and increased physical activity. The patient’s motivation and willingness to adopt an integrated lifestyle modification program should also be assessed as part of the evaluation.

Currently, 3 categories of drug therapies have received FDA approval for the treatment of obesity. The medications include (a) anorexiants, which target neurotransmitters; (b) thermogenic drugs, which increase energy expenditure; and (c) lipid-partitioning medications, which diminish energy intake. Sibutramine and orlistat are approved for long-term use (up to 2 years), while phentermine is approved for short-term use (3 months) (Table 23-1).

Anorexiant Agents: The history of commonly used anorexiant agents has been presented in several reviews. The appetite-suppressant effect of sympathomimetic amines was first identified in 1938 and 1939 when this side effect of Benzedrine was reported. However, the potential abuse of this compound and related Class II agents has limited its efficacy for weight reduction.

Sympathomimetic Agents: These medications suppress appetite through the stimulation of sympathetic activity. Older noradrenergic drugs, formerly approved for short-term use, included phentermine and diethylpropion. Phentermine (Fastin, Ionamin) is the only noradrenergic drug currently approved and is the most affordable of the FDA-approved weight-loss medications. It was previously employed in combination formulations with fenfluramine (Pondimin) and dexfenfluramine (Redux), which were subsequently withdrawn by the FDA because of intolerable adverse effects, as described below.

Serotonergic Agents: Fluoxetine (Prozac) and fluvoxamine (Luvox) are selective serotonin reuptake inhibitors that have been studied in clinical trials for the treatment of binge eating disorder. Fluoxetine has been approved for this indication. The drug requires therapeutic dosing in a range that exceeds that of its typical use as an antidepressant (60 mg per day). In placebo-controlled, double-blind trials at a dosage of 60 mg, fluoxetine was associated with decreased food intake and a decline in body weight in healthy volunteer obese participants and a reduced rate of type 2 diabetics (where it was also associated with improved insulin sensitivity and reduced insulin requirement). However, weight gain after the first 6 months was observed in a subset of participants despite continuation of the drug, and adverse events that included sexual dysfunction, somnolence, agitation, diarrhea, and tremor have been reported by many investigators. Therefore, it is not approved for general use as an anorexiant.

In a multicenter, placebo-controlled, double-blind study, fluvoxamine (50 to 300 mg/day) was associated with a significant decrease in the frequency of binge episodes; participants who completed the 9-week study achieved a reduction in BMI. A significantly greater number of participants receiving medication discontinued therapy due to adverse events. These included nausea, sedation, and light-headedness.

Sibutramine: Sibutramine (Meridia) inhibits the reuptake of both serotonin and norepinephrine (Table 23-2). Sibutramine is also believed to increase resting energy expenditure and suppress appetite by inducing early satiety. The drug has shown a statistically significant effect as an adjunct to a calorie-restricted diet in placebo-controlled, randomized clinical trials of healthy individuals conducted in the United States. Its clinical efficacy as an adjunct to dietary management was defined in an initial 12-week dose-finding study and a 12-month multicenter study conducted in France. Using an intention-to-treat analysis, sibutramine at a dose of 10 mg per day was superior to the placebo in promoting and maintaining weight loss in 160 obese (mean BMI 35.5) young adults.
Table 23-1. Medications Approved for the Long- and Short-Term Treatment of Obesity

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</thead>
<tbody>
<tr>
<td><strong>Long-Term Treatment</strong></td>
<td></td>
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</table>
| Orlistat | Xenical | 120 mg orally with each meal | Peripheral lipase inhibitor (30% of consumed fats passed unabsorbed/undigested) | Maintain diet of ≤ 30% fat, not safe in pregnancy | • Fatty/oily stools, loose stools, flatulence (temporary), reduced absorption of fat soluble nutrients eg, vit E, K, Beta Carotene  
• May complicate gall bladder problems or history of kidney stones  
• Body ache/chills  
• Less common: chest tightness or trouble breathing | • Cyclopamin  
• Statins (additive antilipemic effects with statins)  
• Warfarin (reduced Vitamin K absorption) | None |
| Alli | | 60 mg orally with each meal | |
| Sibutramine* | Meridia | 5 to 15 mg orally once a day | Central-inhibits reuptake of serotonin and norepinephrine | May be habit-forming. Use with caution in patients with hypertension, stroke, heart disease, hx of gallstones, liver or kidney disease. Not safe in pregnancy | Dry mouth, constipation, drowsiness, insomnia, headache, increased blood pressure, tachycardia | • Decongestants, eg, pseudoephedrine, phenylpropanolamine  
• Cough suppressants, eg, dextromethorphan  
• Antidepressants  
• Lithium  
• MAOIs  
• Migraine drugs, eg, ergots, tryptans  
• Select opioids  
• Ketoconazole  
• Erythromycin  
• Antihypertensives  
• Certain antihistamines  
• Antiepileptic drugs  
• Sedatives  
• Serotonergic agents  
• Tryptophan | None |
| **Short-Term Treatment** |
| Phentermine | Ionamin, Fastin, Adipex | 15 to 37.5 mg single or split dose | Stimulates central release of norepinephrine | Contraindicated sympathomimetics/MAOIs; furazolidone | CNS stimulation, palpitations, tachycardia, dry mouth, insomnia | • SSRIs  
• Tricyclics  
• Guanethidine  
• Any sympathomimetic | None |

MAOIs = monoamine oxidase inhibitors; CNS = central nervous system; SSRIs = selective serotonin reuptake inhibitors

* Sibutramine was recently removed from the market in the U.S. and Europe.

Adapted with permission from Palamara KL, Mogul HR, Peterson SJ, Frishman WH. Obesity: New perspectives and pharmacotherapies. *Cardiol in Rev.* 2006;14:238.
### Table 23-2. Comparison of Various Features of the Antiobesity Drugs Orlistat and Sibutramine

<table>
<thead>
<tr>
<th>Feature</th>
<th>Orlistat</th>
<th>Sibutramine*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
<td>Gastric and pancreatic lipase inhibitor</td>
<td>Noradrenaline (norepinephrine) and serotonin reuptake inhibitor (via active metabolites M1 and M2)</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Prevents absorption of ≈ 30% dietary fat</td>
<td>Enhances satiety (decreases food intake)</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Initial BMI of ≥ 30 kg/m² or ≥ 27 kg/m² (US) or ≥ 28 kg/m² (UK) with risk factors†</td>
<td>Initial BMI of ≥ 30 kg/m² or ≥ 27% kg/m² with risk factors**</td>
</tr>
<tr>
<td><strong>Usual dose’</strong></td>
<td>120 mg orally thrice daily with each main meal</td>
<td>10 to 15 mg orally once daily with or without food</td>
</tr>
<tr>
<td><strong>Special instructions</strong></td>
<td>Patients must take a multivitamin Should be taken if a meal is missed or contains no fat</td>
<td>Blood pressure monitoring is required before and during supplement (2 h before dose). No dose therapy</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Chronic malabsorption syndrome, cholestasis, pregnant/nursing women, hypersensitivity to the drug or other serotonergic drugs</td>
<td>CAD, CHF, arrhythmias, stroke, severe renal or hepatic impairment, poorly controlled or uncontrolled hypertension, anorexia nervosa, patients taking MAOIs†</td>
</tr>
<tr>
<td><strong>Use with caution</strong></td>
<td>History of hyperoxaluria or calcium oxalate nephrolithiasis</td>
<td>History of hypertension, seizures, narrow angle glaucoma</td>
</tr>
<tr>
<td><strong>Use in children</strong></td>
<td>Safety and efficacy not established (US)</td>
<td>Safety and efficacy in patients &lt; 16 yrs of age not established (US)</td>
</tr>
<tr>
<td><strong>Abuse potential</strong></td>
<td>As with any weight loss agent, the potential exists for misuse in inappropriate patient populations (eg, with anorexia nervosa or bulimia)</td>
<td>Physicians should evaluate patients for history of abuse and observe closely for signs of misuse or abuse</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Gastrointestinal (oily spotting or stool, flatus, increased fecal urgency)</td>
<td>Headache, dry mouth, anorexia, insomnia, constipation</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>None</td>
<td>Increase in blood pressure and heart rate</td>
</tr>
<tr>
<td><strong>Potential drug interactions</strong></td>
<td>Decreased absorption of fat-soluble vitamins by CYP3A1 inhibitors</td>
<td>May potentiate action of MAOIs and drugs that increase blood pressure or heart rate; metabolism may be inhibited</td>
</tr>
</tbody>
</table>

* Sibutramine was recently removed from the market in the U.S. and Europe.

** Hypertension, diabetes mellitus, dyslipidemia

† Taken in conjunction with a reduced-calorie diet. In patients taking orlistat, the diet should contain ≈ 30% of calories from fat.

‡ Or within 2 weeks of MAOI therapy

BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; US = United States; UK = United Kingdom; MAOIs = monoamine oxidase inhibitors; CYP = cytochrome P450.

who had been randomized to treatment after following a very-low-calorie diet for 4 weeks. At 12 months, the mean absolute weight change in the sibutramine group was −5.2 (+7.5) kg compared to a weight gain of +0.5 (+5.7) kg in the placebo group (P = .004). However, follow-up visits at 1 and 3 months after completion of the study indicated that after discontinuation of therapy, neither placebo- nor sibutramine-treated participants maintained this weight loss. Even with the extension of therapy for a second year, participants had a 50% average weight regain.87 A patient’s response to sibutramine is best described as variable; those who are able to lose at least 4 lbs in 4 weeks are considered "responders" and are usually continued on the drug for longer time periods. Recently it was shown that the presence of G-protein β3 subunit gene polymorphism was a partial explanation for the lack of responsiveness to sibutramine.79

Placebo-controlled studies have also evaluated continuous and intermittent sibutramine as part of a long-term weight-control program for up to 2 years. Weight loss was sustained in those continuing on treatment, and favorable effects on plasma lipids and insulin levels were observed.80,81 In 1 study, 3% of participants were withdrawn because of significant increases in blood pressure.84 Intermittent sibutramine treatment (weeks 1 to 12, 19 to 30, 37 to 48) was found to be as effective as continuous treatment with fewer adverse effects observed.80

In one reported placebo-control study in obese participants with high triglycerides and low serum HDL cholesterol levels, treatment with sibutramine was associated with significant improvements in body weight, serum triglycerides, and HDL cholesterol.82 In a randomized, double-blind, placebo-controlled trial designed to evaluate the effects of sibutramine in participants with type 2 diabetes mellitus, plasma glucose and HbA1c levels decreased to a greater degree with sibutramine than with the placebo.83 In the Sibutramine Cardiovascular Outcomes trial (SCOUT) of overweight or obese participants, 10,744 participants received sibutramine for 6 weeks. Sibutramine and lifestyle modifications resulted in small reductions in body weight, waist circumference, and blood pressure, with a small increase in heart rate.84 In this study, participants with pre-existing cardiovascular conditions demonstrated an increased risk of non-fatal myocardial infarction and non-fatal stroke, but not of cardiovascular death or death from any cause.85 Based on the results of this study, the drug was reassessed by the FDA. In the U.S. and Europe, the drug has been taken off the market because of safety concerns.86

As might be anticipated in other studies, given the sympathomimetic actions of the drug, baseline increases in supine diastolic pressure were modest but statistically and significantly higher in the treatment group at month 6 (+1.5 ± 2.0 versus −1.9 ± 2.2 mmHg; P ≤ .05).77 New onset hypertension secondary to sibutramine treatment was found to be well controlled in all cases and participants with pre-existing hypertension responded well to subsequent alterations in their antihypertensive regimen.84,85 Pulse rates (which increased in both groups) were significantly increased in the sibutramine compared to the placebo group at all time-points during one trial.82 Otherwise, the drug was fairly well tolerated, with a low frequency of reported adverse events including anxiety, depression, dry mouth, and constipation. With the exception of constipation (15 sibutramine participants versus 4 placebo participants), statistically significant adverse events were not reported in association with the drug use.

Orlistat: Orlistat (Xenical), a gastrointestinal (GI) lipase inhibitor (Table 23-2), represents a category of pharmacotherapies targeted at the promotion of negative energy balance through “drug-mediated inhibition of nutrient absorption” and increase in fecal fat excretion.86 The medication, which reduces dietary fat absorption by approximately 30%, was evaluated in a 2-year randomized, double-blind, placebo-controlled trial conducted at 18 clinical research centers in the United States. Using an intention-to-treat analysis, 880 obese participants (BMI 36.3, range 30 to 43 kg/m²) were initially randomized to the placebo or to treatment with orlistat 120 mg three times a day in combination with a controlled energy diet for 1 year. Subjects were rerandomized to orlistat 60 or 120 mg three times a day or the placebo in combination with a weight-maintenance diet for an additional year. Orlistat-treated participants who received the 120 mg three times daily lost more weight compared to the placebo in year one (8.7 compared to 5.8 kg, P < .001) and regained less weight (3.2 kg, 35% regain) compared to the participants who received the 60 mg three times daily dose (4.3 kg, 51% regain) or the placebo (5.6 kg, 63% regain).

It has also been shown that 2-year treatment with orlistat plus diet significantly promotes weight loss, lessens weight regain,87 and improves fasting low density lipoprotein (LDL) cholesterol and insulin levels.88 The drug, in addition to a conventional weight-loss program, has also been shown to improve glucose tolerance and diminish the rate of progression to the development of impaired glucose tolerance and type 2 diabetes mellitus.89 In addition, the drug has been shown to be safe and more effective than diet alone in modifying some of the risk of coronary artery disease by reducing LDL cholesterol, fasting glucose, and HbA1c levels.90 In a 1-year, randomized, double-blind, placebo-controlled trial investigating orlistat’s effect on cardiovascular disease risk, the orlistat group demonstrated significant changes in several cardiovascular risk factors, including total cholesterol, LDL cholesterol, glucose, HbA1c, insulin, body weight, and waist circumference when compared to the placebo.90

The use of orlistat is often limited as a result of its GI
adverse effects that include flatulence, abdominal pain, increased stool frequency, steatorrhea, fecal incontinence, and oily anal discharge. Fat-soluble vitamin supplementation is also necessary when using orlistat, as its mechanism of action interferes with the absorption of vitamins A, D, E, and K.

In 2007, the FDA Non-Prescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee voted in favor of approval of orlistat as an over-the-counter formulation (alli). This formulation is at half the dose (60 mg) of the prescribed formulation.91

**Drugs in Development**

β3-adrenergic receptor agonists

Knowledge about the biologic processes underlying the regulation of fat stores and energy balance and the role of catecholamines as mediators of thermogenesis and lipolysis has led to new therapeutic targets for the treatment of obesity that are the subject of several excellent reviews (Table 23-3).92-95 Contemplation of using β3-adrenergic receptor agonists as antiobesity agents is a byproduct of intensive investigation on the nature and function of the adipocyte and relates to the observation that β3-adrenergic receptors are mediators of both catecholamine-stimulated thermogenesis in brown adipose tissue96-99 and stimulation of lipolysis in white adipose tissue,95 in addition to their effects on GI motility.94

The β3-adrenergic receptor is a seven-transmembrane G-coupled protein receptor. Stimulation of the receptor causes the induction of adenylyl cyclase100 that leads to numerous downstream metabolic events that have been summarized in various reviews92,94,101 and include stimulation of both cAMP dependent lipoprotein lipases responsible for triglyceride lipolysis and the newly described uncoupling protein-1 that has been shown to be associated with increased thermogenesis. Activation of the receptor also improves insulin sensitivity. The association of polymorphisms in the β3-adrenergic receptor gene with obesity in insulin-resistant Finns,102 with weight gain in participants with morbid obesity103 and the early occurrence of diabetes mellitus in other populations,104 has provided additional evidence for a role of the receptor in energy regulation in humans. A paired sibling analysis of 45 Mexican Americans demonstrated that the presence of the substitute tryptophan for arginine at codon 64, the so-called “Trp64arg” point mutation, in the β3-adrenergic receptor gene was associated with a significantly higher BMI, waist circumference, and fat mass in the affected sibling.105 This genetic variant has been associated with the Pro12Ala variant of the peroxisome proliferator-ac-

<table>
<thead>
<tr>
<th>Table 23-3. Examples of Antiobesity Agents Under Investigation</th>
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<tbody>
<tr>
<td>I CNS agents that can affect neurotransmitters or neural ion channels</td>
</tr>
<tr>
<td>Antidepressants (bupropion, fluoxetine)</td>
</tr>
<tr>
<td>Antiepileptics (topiramate, zonisamide)</td>
</tr>
<tr>
<td>II Leptin/Insulin/CNS Pathway agents</td>
</tr>
<tr>
<td>Leptin analogues</td>
</tr>
<tr>
<td>Leptin transport and/or receptor promoters</td>
</tr>
<tr>
<td>CNTF (Axokine)</td>
</tr>
<tr>
<td>NPY antagonists</td>
</tr>
<tr>
<td>AgRP antagonists</td>
</tr>
<tr>
<td>POMC promoters</td>
</tr>
<tr>
<td>CART promoters</td>
</tr>
<tr>
<td>MC4 receptor agonists</td>
</tr>
<tr>
<td>III Agents that affect insulin metabolism/activity</td>
</tr>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td>IV Gastrointestinal-neural pathway agents</td>
</tr>
<tr>
<td>Agents that increase CCK and PYY activity</td>
</tr>
<tr>
<td>Agents that increase GLP-1 activity (exenatide)</td>
</tr>
<tr>
<td>Agents that decrease ghrelin activity (vaccine)</td>
</tr>
<tr>
<td>Amylin (pramlintide)</td>
</tr>
<tr>
<td>V Agents that increase thermogenesis</td>
</tr>
<tr>
<td>Selective β3 agonists</td>
</tr>
<tr>
<td>UCP homologues</td>
</tr>
<tr>
<td>Thyroid receptor agonists</td>
</tr>
<tr>
<td>VI Other agents</td>
</tr>
<tr>
<td>Growth hormone fragments</td>
</tr>
<tr>
<td>Inhibitors of fatty acid synthesis (C75)</td>
</tr>
<tr>
<td>Apo-1 mimetic peptides</td>
</tr>
</tbody>
</table>


As noted in a comprehensive review of the biologic activities of the more than 20 β3-adrenergic receptor agonists developed since 1984, the first generation β3-adrenergic receptor agonists were developed from compounds that had demonstrated efficacy in rodent obesity models. These drugs proved disappointing when employed in preliminary clinical trials of obese human participants.94 With subsequent biochemical modification, newer agonists were developed with increased tivated receptor-γ2 gene, suggesting convergent pathways that can produce synergistic effects on obesity.106
potency in combination with enhanced selectivity for the β₃-adrenergic receptor.

The latest β₃-adrenergic receptor agonists have additional pharmacological properties that suggest that this category of pharmacotherapies could be useful as antiobesity agents. Some of these agents can dramatically enhance (e.g., 800-fold increases) selectivity for the β₃-adrenergic receptor with the elimination of cardiovascular effects typically associated with β₁ and β₂ adrenergic stimulation. In addition, they have been shown to resist desensitization following chronic agonist exposure in contrast to other β-adrenergic receptors. Finally, there is evidence that β₃-adrenergic receptor agonists may have independent beneficial effects on blood pressure and myocardial function as has been recently outlined.

Although the initial results of clinical trials that used the first β₃-adrenergic receptor agonists were disappointing, biochemical modifications have dramatically enhanced selectivity and pharmacological activity. The newest generation of modified β₃-adrenergic receptor could offer promise as potentially selective, safe, and effective therapies for the treatment of obesity.

**Leptin**

Leptin, the adipocyte-derived gene-product of the ob gene, is a catabolic hormone that plays an important role in energy regulation and has been a focus of intensive investigation in obesity research for the past 2 decades. Leptin’s prominence in current theories of obesity has been a topic of several reviews, one of which summarized more than 1,300 studies that had evaluated the action of leptin in the previous 2 years. The actions of leptin and its relationship to other hormones and neuropeptides in the hypothalamic regulation of appetite are summarized in Figures 23-1 and 23-2. Leptin circulates in the serum as a free bioavailable form and as an inactive bound form. It acts to inhibit feeding and increase energy expenditure through inhibition of neuropeptide Y gene expression and to cause anorexia and thermogenesis through the promotion of pro-opiomelanocortin (POMC) derivate α-MSH and cocaine- and amphetamine-regulated transcript (CART). Further actions of leptin include suppression of endocannabinoid synthesis and release. The plasma concentration of leptin is proportional to the amount of body fat and BMI, given that leptin is released as adipocytes increase in size.
The administration of human recombinant leptin to a morbidly obese, genetically leptin-deficient female in a dose sufficient to produce serum leptin levels equivalent to one-tenth of the typical age-appropriate leptin level produced a dramatic reduction in body weight and a predisposition for selective loss in body fat mass. However, in a 6-center, randomized, double-blind, placebo-controlled trial, human recombinant leptin (administered by daily injection in escalating doses) induced weight loss in a relatively small percentage of obese participants after 24 weeks of treatment. Lack of efficacy was attributed to the presence of leptin resistance in this subset of participants.

The theory of leptin resistance in obesity-prone individuals was developed after realizing that while the hyperleptinemia found in obese patients should be antilipogenic, adipocytes in these patients continued with fat storage. However, in a 6-center, randomized, double-blind, placebo-controlled trial, human recombinant leptin (administered by daily injection in escalating doses) induced weight loss in a relatively small percentage of obese participants after 24 weeks of treatment. Lack of efficacy was attributed to the presence of leptin resistance in this subset of participants.

The theory of leptin resistance in obesity-prone individuals was developed after realizing that while the hyperleptinemia found in obese patients should be antilipogenic, adipocytes in these patients continued with fat storage. The problem is multifactorial and does not lie in the lack of leptin production. It is suggested that high-fat diets impair downstream leptin signaling and transport of leptin across the blood–brain barrier. Studies have found that obese patients have blockades on both the postreceptor and receptor levels. In 1 animal study, after 6 days of feeding rats a high fat diet, the mRNA of a postreceptor leptin inhibitor (SOCS-3, Suppressor of Cytokine Signaling-3) increased 22-fold in white adipose tissue, despite plasma leptin levels increasing 10-fold. In addition, after several weeks of this high-fat diet, the expression of Lepr-b (specific leptin receptor responsible for leptin signaling in brain) continually decreased until it was undetectable. Other inhibitors to leptin signaling have been found, including tyrosine phosphatases protein tyrosine phosphatase 1B and SH-containing protein tyrosine phosphatase. Future research is now being focused on overexpression of Lepr-b, suppression of known postreceptor inhibitors, and identification of additional downstream signaling inhibitors.

**Rimonabant**

A potential antiobesity drug is the selective cannabinoid receptor-1 antagonist rimonabant (Acomplia). Endocannabinoids act as agonists to regulate food intake, energy balance, and lipid and glucose metabolism. Food intake is stimulated via the cannabinoid receptor-1, located centrally in several areas of the brain, including the hypothalamus, adipocytes, the GI tract, and muscle. Stimulation of the cannabinoid-receptor-1 in fat cells signals lipogenesis and inhibits adiponectin, a cytokine with antidiabetic and antiatherosclerotic properties (Figure 23-3). The endocannabinoid system was found to be overactivated in several studies using genetic and diet-induced animal models of obesity. Animal models with genetic deletion of cannabinoid receptor-1 resulted in a lean phenotype that was resistant to diet-induced obesity. As a result of these and other studies, a search began to develop a cannabinoid receptor antagonist that could potentially promote weight loss and improve cardiovascular risk factors associated with obesity.

After Phase 2 trials with SR141716A (rimonabant) were successful, 3 large multicenter, international, randomized, double-blind, placebo-controlled trials were initiated, all given the initials of RIO (rimonabant in Obesity) trials, with the similar primary endpoint of weight lost after 1 year in the intention-to-treat population, and differing secondary endpoints. In each trial, obese participants (BMI 27 to 40) were randomized to the placebo, 5 mg rimonabant, or 20 mg rimonabant and placed on a 600 kcal reduction/day diet for 1 year. After 1 year of treatment, weight loss was significantly greater and dose-dependent in the rimonabant treatment group as compared to the placebo. The average weight loss was 3.4 kg with 5 mg rimonabant (P = .002 versus the placebo), 6.6 kg with 20 mg rimonabant (P < .001 versus the placebo) and 1.8 kg with the placebo.
In addition, treatment with rimonabant 20 mg resulted in significantly greater improvements than both the 5 mg and placebo doses in parameters of waist circumference, HDL cholesterol, triglycerides, insulin resistance, and prevalence of the metabolic syndrome. While 5 mg of rimonabant did result in significant weight loss, its effects on secondary endpoints were insignificant. In phase 3 trials of sibutramine, there was a question whether its positive effects on HDL cholesterol and triglycerides were secondary to weight loss and not the drug itself. With this in mind, RIO-Europe used logistic regression models to assess whether the improvement in HDL cholesterol and triglycerides seen with 20 mg rimonabant treatment after 1 year were partly independent from weight loss, and it was found that one-half of the HDL and triglyceride effects were independent of weight loss.120

RIO-Lipids was designed to investigate the effects of rimonabant on weight loss and metabolic risk factors in obese or overweight participants with untreated dyslipidemia.119 Secondary endpoints were identical to RIO-Europe with the addition of measurements of adiponectin and leptin levels and additional cardiovascular risk factors after 12 months of rimonabant treatment. Similar to the results of RIO-Europe, participants randomized to 20 mg rimonabant showed an average weight loss of 8.6 kg compared to 4.2 kg with 5 mg (P < .001 compared to the placebo for both) and 2.3 kg with the placebo. Other statistically significant similarities included decreased waist circumference, elevated HDL, decreased triglycerides, the prevalence of metabolic syndrome, and fasting serum insulin levels.125 There was no change in the quantitative LDL cholesterol, but it was noted that the particle size in the 20 mg group had changed from a predominance of small-particle LDL to a predominance of large-particle LDL. Unique to RIO-Lipids was the discovery that treatment with 20 mg rimonabant resulted in increased adiponectin levels (2.7 µg/ml compared to +0.8 µg/ml with the placebo) and decreased leptin (-4.8 compared to -0.3 with the placebo) (P < .001 compared to the placebo for both).119 Increased adiponectin levels have been found to correlate with a decreased rate of both diabetes mellitus and cardiovascular events since adiponectin is a regulator of hyperglycemia, hyperinsulinemia, and fatty acid oxidation in adipocytes.119

Both RIO-Europe120 and RIO-Lipids119 were designed to have 1 year of treatment without follow-up. As the long-term efficacy of weight-loss medications is often challenged along with the ability to sustain weight loss after discontinuation of medication, RIO-North America125 was designed exactly the same as RIO-Europe, but after 12 months of treatment participants were randomized again—those on the placebo remained on the placebo, those randomized to 5 mg and 20 mg of study drug initially were either randomized to continue with their current dosage or to the placebo. Using this study design, the RIO-North America study was able to simultaneously assess long-term efficacy of rimonabant as well as a patient’s ability to maintain weight loss after stopping treatment. The results for year 1 were similar to the other RIO trials. The nonplacebo group maintained their weight loss compared to the placebo in year two. The results were classified as the percentages of participants who lost ≥ 5% and ≥ 10% of their initial baseline weight. After year two, 62.5% of participants in the 20 mg group lost ≥ 5% of their initial weight, compared to 36.7% and 33.2% with 5 mg and the placebo, respectively (P < .001 versus the placebo). In addition, it was found that 32.8% of participants lost ≥ 10% of their initial body weight with the 20 mg dose, compared to 20% and 16.4% with the 5 mg dose and the placebo, respectively (P < .001 versus placebo).126

Rimonabant treatment was associated with favorable effects on waist circumference, triglyceride levels, and HDL cholesterol levels. Rimonabant-treated participants who were subsequently rerandomized to the placebo group in year two of the study were found to regain nearly all of the weight lost during year 1. These study results were disconcerting as the weight-loss effects of rimonabant appear to be lost with discontinuation of active treatment. In addition, the long-term safety of rimonabant beyond 2 years is still unknown.

The most frequent adverse effects of rimonabant reported in the RIO trials were nausea, dizziness, diarrhea, and joint pain, which were described as “mild and transient.”127 The most common reasons for treatment discontinuation were depression, anxiety, and nausea. There were no deaths related to treatment. At this juncture, the drug’s neuropsychiatric toxicity has prevented FDA approval, and for the same reason, the drug is no longer marketed in Europe.

Lorcaserin

Lorcaserin is an investigational serotonin receptor agonist similar to fenfluramine and dexfenfluramine, but designed to avoid the serotonin-related valvulopathy associated with those drugs. In a clinical trial, the drug was shown to produce significant weight loss compared to placebo.127 However, the FDA has not recommended approval of the drug.

Off-Label Use of Available Medications as Antiobesity Agents

Mounting concerns over the health implications of obesity and the paucity of FDA-approved therapies has spawned clinical research initiatives to evaluate medications that are known to induce weight loss when used for other clinical indications (Table 23-4). Accordingly, a number of studies have been conducted to determine the efficacy...
and tolerability of such drugs when used in the primary treatment of obesity. Drugs with documented long-term safety and tolerability with biological plausibility and/or prior evidence of potential therapeutic efficacy have been the focus of these research endeavors. These agents include metformin, topiramate, zonisamide, bupropion, and fluoxetine in combination with phentermine.

**Metformin**

Metformin (Glucophage) is an insulin-sensitizing agent that received FDA approval for the management of type 2 diabetes mellitus (see Chapter 24, Heart Disease and Treatment of Diabetes Mellitus). When used in clinical trials for the treatment of diabetes mellitus, metformin has been associated with a statistically significant weight loss in actively treated participants. Metformin-induced weight reduction is also consistent with data from studies of nondiabetic populations with hyperinsulinemia, including participants with human immunodeficiency virus (HIV)-related lipodystrophy, impaired glucose tolerance, and most, but not all, studies of women with polycystic ovarian syndrome. The majority of these studies did not incorporate a formal weight-reduction program or evaluate weight loss as a primary outcome variable.

Metformin has been evaluated as a primary treatment for weight reduction in an open-label, 1-year study of euglycemic, hyperinsulinemic women with midlife weight gain, where metformin was combined with a carbohydrate-modified, hypocaloric diet to address the hypothesis that pharmacologic and dietary strategies that target hyperinsulinemia might promote weight loss in distinct patient subpopulations. Subsequent studies suggest that metformin may be an important and effective therapeutic adjunct to dietary interventions and other lifestyle modifications and promote long-term weight management in hyperinsulinemic participants. Metformin is being evaluated in a large long-term randomized clinical trial of obese preadolescents.

The multiple mechanisms of action of metformin in glucose homeostasis have been well elucidated, but the major mode of action of metformin in weight regulation has not been conclusively defined. Metformin reduces food intake in diabetic and nondiabetic patients and has many desirable, well-delineated pharmacological effects that include a decrease in hepatic glucose output and a reduction of free fatty acids. Free fatty acids augment hyperinsulinemia in the basal and postprandial state, and free fatty acid elevations have been linked to central obesity and are considered an important component in the pathogenesis of insulin resistance. In addition, recent studies have demonstrated that metformin improves endothelial dysfunction.

Metformin has had a long-term safety profile. It has been associated with a reduction in cardiovascular risk factors in numerous prospective European and US studies, suggesting it might be uniquely suited for the treatment of obese individuals who typically have significant risks for these obesity-related comorbidities. In a large, 4-year, multicenter study of more than 3,000 participants with impaired glucose tolerance, metformin decreased the progression to type 2 diabetes mellitus by 31% compared to the placebo. Complications of lactic acidosis with a related compound, phenformin, used as an oral agent for the treatment of type 2 diabetes mellitus in the 1970s, created initial concern about the safety profile of metformin. However, following the presentation of long-term safety data, the FDA approved revised package inserts and warnings about the relationship between metformin and lactic acidosis in 1998. Large studies conducted in Europe, Canada, and the United States have demonstrated that metformin has an excellent safety profile when used in healthy individuals. Metformin is well tolerated, and adverse effects are limited essentially to the GI tract, including nausea and diarrhea.

**Exenatide and Liraglutide**

Exenatide (Byetta) is an injectable incretin mimetic agent for the treatment of diabetes mellitus (see Chapter 24, Heart Disease and Treatment of Diabetes Mellitus). It improves glucose control by mimicking the effects of glucagon-like peptide-1.

In a multicenter clinical trial of 551 type 2 diabetic participants who tested exenatide against insulin, it was observed that the exenatide-treated participants lost, on average, 2.3 kg after 6 months, while insulin-treated participants gained 1.8 kg over the same time period. Another clinical study in 163 participants demonstrated an average 3.6 kg weight loss after 1 year of exenatide treatment.

At this time, exenatide is approved only for clinical use in diabetic patients not well controlled on maximum doses of metformin and/or sulfonylurea therapy. It is not approved for weight loss in nondiabetics, and there is a risk of hypoglycemia with the agent.

Liraglutide, another incretin mimetic agent, was recently approved by the FDA for clinical use. In clinical trials for treatment of diabetes mellitus, it was also shown to cause weight loss, similar to exenatide. Specific weight-loss studies need to be carried out in both diabetic and nondiabetic patients with these agents.

**Pramlintide**

Pramlintide (Symlin) is a modified version of the pancreatic hormone amylin and is approved for subcutaneous use in patients with either type 1 or type 2 diabetes mellitus being treated with insulin. Unlike insulin, which is
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</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Glucophage</td>
<td>Initiate with 500 mg/day and increase weekly to 1000 – 2000 mg/day in divided doses.</td>
<td>Reduces food intake. Also lowers insulin and free fatty acids. Exact primary mechanism in weight reduction not identified</td>
<td>Contraindicated in patients with renal impairment (creatinine &gt; 1.5), hepatic disease, congestive heart failure, chronic pulmonary disorders, or alcohol abuse. Discontinue 48 hours before and after general anesthesia or use of iodinated contrast materials. Discontinue with severe fever or dehydration secondary to vomiting or diarrhea.</td>
<td>• Diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia (generally transient) • Pregnancy can occur due to increased fertility</td>
<td>• Iodinated contrast materials • Sulfonylurea and/or insulin—hypoglycemia • Furosemide—increases plasma concentrations of both drugs • Nifedipine—increases plasma concentrations of metformin with minimal change in pharmacokinetics • Cimetidine—increases plasma concentration of metformin • Adrenergic-blocking agents—beta blockers increase the frequency and severity of hypoglycemia • alcohol—increased risk of hypoglycemia and acidosis • clomiphene—increased ovulatory response</td>
<td>None</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Topamax</td>
<td>25 to 100 mg</td>
<td>GABAergic</td>
<td>drowsiness, blood dyscrasias, LFT abnormalities</td>
<td>Confusion, dizziness, nervousness, paresthesias, breast pain, nausea, tremors, memory, and cognitive impairment</td>
<td>None listed</td>
<td>None listed</td>
</tr>
<tr>
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<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Zonisamide</td>
<td>Zonegran</td>
<td>100–600mg/day</td>
<td>Serotonergic and dopaminergic</td>
<td>Contraindicated in patients with hypersensitivity to sulfonamides; discontinue if skin rash develops. Caution in patients with renal and hepatic impairment. May cause kidney stones. Discontinue if patient develops ARF or sustained elevated BUN/creatinine. Teratogenic.</td>
<td>Somnolence, dizziness, headache, nausea, agitation/irritability, fatigue</td>
<td>None listed</td>
<td>None listed</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Wellbutrin</td>
<td>100 mg B.I.D.</td>
<td>Precise mechanism not known</td>
<td>Do not use in patients with renal and hepatic impairment. Avoid alcohol. Monitor for seizures</td>
<td>Agitation, anxiety, abdominal pain, anorexia, constipation, dizziness, dry mouth, increased sweating, insomnia, nausea, tremors, vomiting, weight loss</td>
<td>MAOI's—contraindicated Ritonavir—moderate</td>
<td>None</td>
</tr>
</tbody>
</table>

SSRI = selective serotonin reuptake inhibitors; MAOIs = monoamine oxidase inhibitors; GABA = γ-aminobutyric acid; ARF = acute renal failure; BID = twice daily; OD = once daily

often associated with weight gain, patients on pramlintide have been shown to lose weight, especially those with higher body mass indices.\textsuperscript{164-167}

At this juncture, pramlintide is indicated as an adjunct treatment in type 1 and type 2 diabetic patients who use mealtime insulin therapy and have not achieved desired glucose control. It is not approved for weight loss in non-diabetics and appears to cause less weight loss than exenatide in diabetic patients. Specific weight-loss studies need to be conducted with pramlintide.

**Psychotropic and Antiepilepsy Medications**

Weight loss has been reported as a common side effect in patients treated with topiramate (Topamax), an anticonvulsant with GABAergic and antiglutamatergic effects. Isolated case reports suggested that topiramate could promote significant weight loss,\textsuperscript{168-170} and the weight-reducing properties of this medication in combination with diet and behavioral therapy have been investigated in several randomized clinical trials.\textsuperscript{171-173} In currently published trials of participants with binge-eating disorder, topiramate reduced the frequency of binge eating, and participants randomized to topiramate have been shown to have significant weight loss in comparison to the placebo, as well as an improvement in blood pressure. In addition, topiramate holds promise for the future of long-term obesity treatment, as these trials also demonstrated continual weight loss beyond a 1-year period.\textsuperscript{82} The frequency of CNS adverse effects (paresthesias, somnolence, memory loss) halted Phase 3 trials. A controlled-release formulation is under development at this time. The FDA recently rejected the application of a combination product of phenotrmine and controlled-release topiramate for weight loss.

Zonisamide is another antiepileptic currently being studied for its potential use for treatment of obesity and binge-eating disorders.\textsuperscript{82,118} In a 16-week randomized clinical trial, the use of zonisamide resulted in a 6% weight loss compared to 1% with the placebo.\textsuperscript{174} Although zonisamide has similar actions as topiramate, it is associated with fewer CNS effects, namely fatigue. Slightly elevated serum creatinine was also noted in the zonisamide group.\textsuperscript{82,174}

Results from antidepressant trials with bupropion suggest that treatment with the drug was associated with moderate dose–related weight loss in a significant number of participants.\textsuperscript{175} In addition, bupropion treatment was not associated with weight regain at the conclusion of treatment.\textsuperscript{82} In short- and long-term studies of bupropion specifically designed to evaluate weight loss in obese participants as the primary outcome variable, those randomized to bupropion lost significantly more weight than the placebo (4.9% compared to 1.3% respectively) and maintained this weight-loss trend for up to 48 weeks of treatment.\textsuperscript{176} In a second study, participants randomized to the bupropion group were then randomized to either 300 mg or 400 mg.\textsuperscript{177} This study not only produced similar results in comparison to the placebo, but weight loss was stratified in the bupropion group in a dose-dependent manner. The medication was well tolerated, with the most frequently reported adverse effect being dry mouth.

In a recent study of overweight and obese adults, the combinations of sustained-release naltrexone plus bupropion (Contrave) were shown to be both effective and safe in causing weight loss in adults with both overweight and obesity conditions.\textsuperscript{177a} The combination drug is now under FDA review.\textsuperscript{177b}

An improvement in binge-eating behaviors as determined by a reduction in the number of binges has been reported in studies of fluoxetine (Prozac),\textsuperscript{71} as previously noted. Although fluoxetine is not approved for weight loss, a randomized clinical trial carried out before dexfenfluramine was removed from the market showed that the combination of the 2 drugs resulted in significant weight loss in comparison to fluoxetine alone after 8 months of use. Since this trial, physicians have reportedly had some success with the combination of fluoxetine and phentermine for weight loss.

**Growth Hormone**

Data from several placebo-controlled randomized clinical trials have demonstrated the efficacy of human recombinant growth hormone (hrGH, Humatrope, Nutropin, Protropin) in promoting loss of fat body mass in combination with increased lean body mass in GH-deficient children and adults.\textsuperscript{178} However, hrGH, when used in obese individuals, is not an effective weight-loss drug, and its use also results in increased insulin resistance. In addition, hrGH cannot be contemplated as a treatment of obesity in view of its cost and the impractical nature of having to use daily injections.

AOD9604, a synthetic fragment of hGH, is currently being studied in Phase II trials. It has been found to induce weight loss and decrease body fat in the Zucker rat and ob/ob mouse, without compromising insulin sensitivity.\textsuperscript{118}

**Additional New Targets for Pharmacotherapies**

**Uncoupling Proteins**

Three members of the uncoupling proteins (UCP) gene family have now been described in humans.\textsuperscript{179} These include UCP-1, which is found in brown adipose tissue\textsuperscript{180} and is activated by the β\textsubscript{3} adrenergic receptor, and UCP-2 and UCP-3,\textsuperscript{181} which are structurally and functionally ho-
mologous but found respectively in white adipose tissue (in addition to liver, lung, spleen, and macrophages) and muscle, as well as brown adipose tissue. Although the functional significance of UCPs in human obesity has not been definitely established, there is growing consensus that these proteins may contribute to thermogenesis and the maintenance of basal metabolic rate. UCP-2 expression is modulated by diet and both proteins are upregulated by a high fat diet.

Inhibitors of Fatty Acid Synthase

Malonyl-coenzyme A (malonyl-CoA) is an inhibitor of carnitine palmitoyltransferase 1 (CPT1), the enzyme controlling the rate-limiting step in fatty acid oxidation. Accumulation of malonyl-CoA in the brain leads to inhibition of CPT1, which prevents lipid synthesis and is believed to generate a satiety signal. Moreover, investigators have produced a synthetic inhibitor, C75, that prevents malonyl-CoA from being converted to fat, causing it to build up in the body (Figure 23-4), which in turn spurs a dramatic but reversible drop in appetite, weight, and body fat in animal models. C75 does not appear to work via effects on leptin but by inhibiting neuropeptide Y formation. Its effects on the body’s metabolism are not known, and longer-term efficacy and safety studies need to be done. In addition, newer fatty acid synthase inhibitors are currently being developed for future investigation.

Other Novel Pharmacotherapeutic Targets: Regulatory Gut Peptides and Other Mediators of Leptin and Neuropeptide Y

New therapeutic targets for obesity treatment have been summarized in several recent reviews. These include neuropeptide Y receptor antagonists, apolipoprotein A1 mimetic peptides, melanocortin receptor 3 and 4 (MC3 and MC4) agonists, agouti-related peptide inhibitors, ghrelin antagonists, and analogues for various regulatory gut peptides that have been long been known to promote satiety, such as cholecystokinin. Clinical trials with preprandial intranasal PYY are underway to evaluate its ability to decrease food intake and possibly induce earlier meal termination. Ghrelin, a gut peptide originally discovered as the endogenous ligand for the GH secretagogue receptor, is increasingly being focused on for its role in feeding behavior. Ghrelin decreases the production of leptin and neuropeptide Y and is associated with meal initiation in humans. Ghrelin is secreted by the stomach in response to decreased food intake, such as in diet-induced weight loss. In response to increased ghrelin, dieters struggle with the desire to eat more while attempting to continue dieting. In addition, it has been found that obese persons do not experience the normal postprandial fall in concentration of ghrelin that lean patients exhibit. Antagonism of this novel orexigenic peptide could provide an additional therapeutic target. Various antighrelin vaccines are now in clinical development.

One of the newest antiobesity therapeutic candidates is ciliary neurotrophic factor (CNTF), a trophic factor for motor neurons that was observed to cause significant weight loss in the treatment trials of patients with neurological disorders. CNTF suppresses food intake and activates leptin-like pathways in rodent models of obesity. A placebo-controlled dose-ranging trial of rh variant CNTF (rhv-CNTF, Axokine), administered as daily injections of 0.3 mcg/kg, 1 mcg/Kg, or 2 mcg/kg, demonstrated a significant weight loss in leptin-resistant obese participants with suppression of hunger signals even after the discontinuation of the medication, with the best results seen in the 1 mcg/kg group. While
the drug was well tolerated in phase 3 trials, its use was limited by the development of anti-rhvCNTF antibodies in up to 2/3 of participants. Weight loss in participants noted to develop anti-rhvCNTF antibodies was limited in comparison to other participants in the same randomization group. Currently, research is being conducted to reformulate rhv-CNTF to an oral formulation, which is preferable to its current injectable form.

**Summary**

Recognition of the increased prevalence and significance of obesity has created a new focus on the pathogenesis and prevention of this complex disorder. Although findings from biomolecular and clinical research initiatives mounted in the last few years have dramatically advanced knowledge of the underlying mechanisms that contribute to appetite regulation and energy homeostasis, prevention and treatment of obesity in the United States currently remains an elusive goal. Awareness of the multifactorial nature of obesity mandates a multidisciplinary approach. Diet, exercise and, possibly the use of ongoing pharmacotherapies and/or bariatric surgery may be required, and chronic vigilance will be critical to the goals of both weight regulation and weight stabilization. Clearly, meaningful permanent solutions to this ubiquitous medical and societal problem dictate long-term interventions and an ongoing dialogue between patients and physicians that will require the skills and dedication of both groups.

*Note: References for this chapter can be found here: www.cvpt3.com*
In the United States, approximately 23.6 million people or 7.8% of the population have diabetes mellitus. Individuals with diabetes mellitus have more than a two-fold chance of dying from cardiovascular disease (CVD) than those without diabetes mellitus. Additionally, over 60% of patients with type 2 diabetes mellitus die of a CVD and even more suffer from serious cardiovascular (CV) complications.

In this chapter, we will discuss the association of hyperglycemia and atherosclerotic CVD and the mechanisms of action, uses, and CV impact of the various drugs available to control glycemia in type 2 diabetes mellitus (Table 24-1). Additionally, the results of recently published clinical trials exploring the effects of glycemic control on CV outcomes will be summarized along with their implications for managing glycemia in type 2 diabetes mellitus.

**Hyperglycemia and Cardiovascular Disease Risk**

Observational studies suggest a correlation between glycemia, as measured by glycated hemoglobin, and CVD. A meta-analysis of 13 observational studies that dealt with the relationship of glycemic control and CVD in adults with diabetes mellitus suggests that for each percentage point increase in glycated hemoglobin, the increase in relative risk for any CVD event is 1.18. A population-based study done in Norwalk, United Kingdom, showed that the risk of CVD increased continuously with the rise of glycated hemoglobin. The lowest risk was seen in individuals with glycated hemoglobin < 5%; the greatest risk was seen in those with glycated hemoglobin > 7%. A prospective study examining the relationship of glycated hemoglobin and coronary heart disease in people with and without diabetes mellitus concluded that glycated hemoglobin was an independent risk factor for the development of CVD. In adults with diabetes mellitus, those in the highest quintile of glycated hemoglobin (≥ 8.2%) had an adjusted relative risk of 2.37 of developing CVD as compared to those in the lowest quintile. In adults without diabetes mellitus, those in the highest quintile of glycated hemoglobin (≥ 5.2%) had an adjusted relative risk of CVD of 1.41. These studies suggest that the risk of CVD increases continuously as glycated hemoglobin increases from levels that are in the low-normal range to those clearly in the diabetic range.

A study examining the relationship of glycated hemoglobin and carotid intima-media thickness found a probable direct and independent relationship between these two variables. A recent study explored the relationship between glycated hemoglobin and the severity of coronary artery disease (CAD) in patients with diabetes mellitus. Those patients with more advanced CAD (as evaluated by cardiac catheterization) had on average statistically significantly higher levels of glycated hemoglobin. Those patients without significant narrowing of any coronary artery had average glycated hemoglobin of 6.66%; those with significant narrowing of 1, 2, and 3 or 4 coronary arteries had average glycated hemoglobin of 8.00%, 8.83%, and 10.40% respectively. This study suggests not only that there is a correlation between glycated hemoglobin and the presence of CAD, but that there also is a correlation between glycated hemoglobin and the severity of CAD.
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name (Brand Name)</th>
<th>Daily Dose Range (mg)</th>
<th>Dose Frequency</th>
<th>General Adverse Effects</th>
<th>Cardiovascular Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
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<tr>
<td></td>
<td>Class Effect</td>
<td></td>
<td></td>
<td>Hypoglycemia, weight gain</td>
<td>Controversial ↑ mortality after MI*</td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ risk MI</td>
<td>NR</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td></td>
<td></td>
<td></td>
<td>Prolonged hypoglycemia</td>
<td>↓ risk MI</td>
<td>NR</td>
</tr>
<tr>
<td>Glyburide (Micronase, DiaBeta)</td>
<td>1.25-20</td>
<td>QD-BID</td>
<td></td>
<td></td>
<td>↓ risk MI</td>
<td></td>
</tr>
<tr>
<td>Glyburide micronized (Glynase, Pres Tab)</td>
<td>0.75-12</td>
<td>QD-BID</td>
<td></td>
<td></td>
<td>↓ risk MI</td>
<td></td>
</tr>
<tr>
<td>Glipizide (Glucotrol)</td>
<td>2.5-40</td>
<td>QD-BID</td>
<td></td>
<td></td>
<td>↓ risk MI</td>
<td></td>
</tr>
<tr>
<td>Glipizide sustained (Glucotrol XL)</td>
<td>2.5-20</td>
<td>QD</td>
<td></td>
<td></td>
<td>↓ risk MI</td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>1-8</td>
<td>QD</td>
<td></td>
<td></td>
<td></td>
<td>No impact on M-KATP channels</td>
</tr>
<tr>
<td>Gliclazide (Diamicron, Canada)</td>
<td>80-320</td>
<td>QD-BID</td>
<td></td>
<td></td>
<td></td>
<td>No impact on M-KATP channels ⊗ US</td>
</tr>
<tr>
<td>Gliclazide sustained (Diamicron MR, Canada)</td>
<td>30-120</td>
<td>QD</td>
<td></td>
<td></td>
<td></td>
<td>No impact on M-KATP channels ⊗ US</td>
</tr>
<tr>
<td><strong>Other Insulin Secretagogues</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td>1.5-12</td>
<td>TID AC</td>
<td></td>
<td>Minor weight gain, minor hypoglycemia</td>
<td>Favorable impact on surrogate CV disease markers</td>
<td></td>
</tr>
<tr>
<td>Nateglinide (Starlix)</td>
<td>180-360</td>
<td>TID AC</td>
<td></td>
<td></td>
<td>Unknown impact on M-KATP channels</td>
<td></td>
</tr>
<tr>
<td><strong>Alpha-Glucosidase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose (Precose)</td>
<td>75-300</td>
<td>TID AC</td>
<td></td>
<td>Flatulence, abdominal cramps, diarrhea</td>
<td></td>
<td>? Slowed progression of carotid intima-media thickness, unclear impact on morbidity &amp; mortality</td>
</tr>
<tr>
<td>Miglitol (Glyset)</td>
<td>75-300</td>
<td>TID AC</td>
<td></td>
<td></td>
<td></td>
<td>⊗ US</td>
</tr>
<tr>
<td>Voglibose</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Biguanides</td>
<td>Class Effects</td>
<td>Nausea, abdominal cramps, diarrhea</td>
<td>Phenformin</td>
<td>Lactic acidosis</td>
<td>(W) US</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Metformin (Glucophage)</td>
<td>500-2550</td>
<td>QD-TID</td>
<td>Controversial ↑ lactic acidosis*</td>
<td>↓ LDL-C, triglycerides, improved endothelial function, possible improved CV outcomes</td>
<td>Wgt N/L</td>
<td></td>
</tr>
<tr>
<td>Metformin sustained (Glucophage XR, Glu- metza, Fortamet)</td>
<td>500-2000</td>
<td>QD-BID</td>
<td>Controversial ↑ lactic acidosis*</td>
<td>↓ LDL-C, triglycerides, improved endothelial function, possible improved CV outcomes</td>
<td>Wgt N/L</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Class Effects</td>
<td>Fluid retention, weight gain, possible osteoporosis</td>
<td>Troglitazone (Rezulin)</td>
<td>Acute liver failure</td>
<td>(W) US</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>2-8</td>
<td>QD-BID</td>
<td>↑ CAD*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>15-45</td>
<td>QD</td>
<td>Improved lipid profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-IV Inhibitors</td>
<td>Class Effects</td>
<td>Wgt N, ▲ stimulation of β cell proliferation</td>
<td>Sitagliptin (Januvia)</td>
<td>100</td>
<td>QD</td>
<td>Urticaria (rare), angioedema (rare)</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza)</td>
<td>5</td>
<td>QD</td>
<td>Urticaria (rare), angioedema (rare)</td>
<td>Dose ↓ w/CRF</td>
<td></td>
<td></td>
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<tr>
<td>Vildagliptin (Galvus)</td>
<td></td>
<td>□ US</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>Class Effects</td>
<td>Reduced ischemia-reperfusion</td>
<td>Exenatide (Byetta)</td>
<td>10, 20 μg</td>
<td>BID SC</td>
<td>Nausea, rare vomiting, rare pancreatitis</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>1.2, 1.8 mg daily</td>
<td>SC</td>
<td>Nausea, vomiting, rare pancreatitis</td>
<td>Fewer cardiovascular events</td>
<td>Wgt L</td>
<td></td>
</tr>
<tr>
<td>Dopaminergics</td>
<td>Class Effects</td>
<td>Hypoglycemia, weight gain</td>
<td>Bromocriptine (Cycloset)</td>
<td>0.8 mg</td>
<td>up to 6 tabs once daily</td>
<td>Nausea, fatigue, vomiting, somnolence</td>
</tr>
<tr>
<td>Insulin</td>
<td>Class Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: ▲ increase; ▼ decreased; * see text; □ US not available in the United States; (W) US withdrawn from the United States market; AC before meals; SC subcutaneous injection; QD once daily; BID twice daily; TID thrice daily; CHF congestive heart failure; CRF chronic renal failure; LDL-C low-density lipoprotein cholesterol; MI myocardial infarction; M-KATP myocardial K+ adenosine triphosphate; NR not recommended; Wgt N/L weight neutral/loss

Adapted with permission from Weiss IA, Valiquette G, Schwarz MD. Impact of glycemic treatment choices on cardiovascular complications in type 2 diabetes. *Cardiol in Rev.* 2009;17:165.
Effects of Hypoglycemic Agents on Cardiovascular Outcomes

Sulfonylureas

Sulfonylureas are the oldest oral hypoglycemic drugs available. The hypoglycemic effect of some sulfonamides was noted in 1942 when some patients treated with a derivative of sulfanilamide for typhoid fever developed hypoglycemia. The sulfonylureas’ mechanism of action is thought to be secondary to inhibition of an ATP-dependent potassium channel causing beta-cell membrane depolarization and leading to insulin release. The first-generation sulfonylureas (chlorpropamide, acetohexamide, tolazamide, and tolbutamide) have been largely replaced by the second-generation sulfonylureas, glyburide, glipizide, glimepiride, and gliclazide (not available in the United States). Glyburide and glimepiride have a longer duration of action than glipizide. In addition to differences in duration of action, the sulfonylureas have somewhat different metabolic effects, with glipizide treatment causing higher postprandial insulin concentrations and glyburide treatment causing higher basal insulin concentrations. Treatment with glipizide has been found to lower glycated hemoglobin by 1.5% to 1.8%. The main adverse effect of sulfonylureas is hypoglycemia; serious hypoglycemia is more likely with long-acting sulfonylureas and in elderly patients.

The safety of using sulfonylureas was questioned 40 years ago when the University Group Diabetes Program published their study in which patients with type 2 diabetes mellitus were randomized to treatment with tolbutamide, insulin, or the placebo. They found that patients taking tolbutamide had an increase in CV mortality compared to those on the placebo or insulin. In a retrospective study, Garratt et al compared hospital mortality after balloon angioplasty for myocardial infarction (MI) in diabetic patients who were taking sulfonylureas compared to diabetic patients who were not. Those patients who had been taking sulfonylureas had a hospital mortality of 24%, while those not taking sulfonylureas had a mortality of 11%. In another retrospective study, Huizar et al found that a higher proportion of diabetic patients with acute MI who had been taking sulfonylurea therapy did not meet electrocardiographic criteria for thrombolytic therapy compared to diabetic patients with acute MI who had not been taking sulfonylureas (53% versus 29%). The authors concluded that because sulfonylurea therapy decreased the ST-elevations in this group of patients, there was inappropriate withholding of thrombolytic therapy.

A more recent study looked retrospectively at CV mortality in a large group of Canadian patients. Patients treated with a first generation sulfonylurea had a mortality of 67.6 deaths per 1000 person-years; those treated with glyburide had a mortality of 61.4 deaths per 1000 person-years; and those treated with metformin had a mortality of 39.6 deaths per 1000 person-years. Additionally, patients on high doses of sulfonylureas had higher mortality than those on lower doses.

The mechanism of the possible detrimental effect of sulfonylureas in diabetic patients with CAD may be through the drugs preventing the opening of myocardial K+-ATP channels, thereby increasing the effects of ischemia on the myocardium. Inhibiting these channels prevents ischemic preconditioning, a mechanism that protects the heart from ischemic injury. The sulfonylureas chlorpropamide, tolbutamide, glyburide, and glipizide all seem to have this deleterious effect on cardiac K+-ATP channels, while gliclazide and glimepiride seem to have actions restricted to pancreatic K+-ATP channels. Additionally, it has been shown that, in animals, the nonglucose secretagogue nateglinide does not have a significant effect on cardiac K+-ATP channels. For these reasons, it has been suggested that glimepiride, gliclazide, or nateglinide are the drugs of choice if sulfonylureas or other secretagogues must be used to treat hyperglycemia. Another mechanism that has been proposed is inhibition of the fibrinolytic system through increased production of plasminogen activator inhibitor-1.

Other trials have failed to show an association between sulfonylurea use and an increase in CV mortality. The United Kingdom Prospective Diabetes Study (UKPDS) followed diabetic patients treated primarily with a sulfonylurea, insulin, or diet. After 10 years, the patients treated with a sulfonylurea did not have increased CV mortality. However, it should be noted that these patients did not have pre-existing CVD and were under age 66 at the time of entry into the study. A recent meta-analysis studied CV outcomes in trials of oral diabetes mellitus medications. The pooled data of the trials studying the effects of sulfonylureas did not show a significant effect of the sulfonylureas on CV mortality.

Other Insulin Secretagogues

Meglitinide analogs include repaglinide and mitiglinide (an experimental drug). Although nateglinide, chemically, is not a meglitinide, it is pharmacologically similar to the meglitinides. Repaglinide and nateglinide are approved by the FDA for use as monotherapy or as combination therapy with metformin or a thiazolidinedione.

Although these drugs are insulin secretagogues, just like sulfonylureas, they do differ in several important aspects. Whereas sulfonylureas stimulate both basal and glucose-mediated insulin secretion, insulin secretagogues increase first-phase insulin secretions only, and stimulation of insulin secretion is glucose-dependent.
They interact with the same sulfonylurea-receptor K+--ATP channel as sulfonylureas but at a different site on the receptor. They also have increased binding affinity for β-islet pancreatic cells' sulfonylurea receptors and a reduced affinity for myocyte and cardiomyocyte sulfonylurea receptors, compared to classical sulfonylureas, suggesting that they may have a reduced influence on CVD risk factors than sulfonylureas themselves. However, it is not clear if this advantage extends to repaglinide or only to nateglinide, where it has clearly been demonstrated.

There are no data available on the impact of meglitinide analog therapy on CV risk factors; however, several early studies suggested that meglitinide analogs have a favorable impact on surrogate markers for CVD, possibly more so than sulfonylureas. The results of the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study showed that nateglinide used for 5 years did not reduce the incidence of diabetes mellitus or the coprimary composite CV outcomes in subjects with impaired glucose tolerance and either CVD or CV risk factors.

**Alpha-Glucosidase Inhibitors**

Two α-glucosidase inhibitors, acarbose and miglitol, currently are in clinical use in the United States. Voglibose is another α-glucosidase inhibitor available in some markets, and emiglitate is currently being evaluated in clinical trials. α-Glucosidase inhibitors reduce postprandial hyperglycemia and glycated hemoglobin by reducing and delaying carbohydrate absorption. α-Glucosidase inhibitors generally result in a glycated hemoglobin reduction of 0.5% to 1% and are less potent than other oral antidiabetic agents.

Most clinical studies of α-glucosidase inhibitors have been conducted on acarbose. Acarbose has been shown to reduce or delay the development of type 2 diabetes mellitus in glucose intolerant patients and to slow the progression of carotid intima-media thickness in participants with impaired glucose tolerance. However, several meta-analyses have challenged these findings and have failed to show an impact of acarbose on morbidity and mortality in type 2 diabetes mellitus. The impact of acarbose on the morbidity and mortality of diabetes mellitus remains controversial and the role of α-glucosidase inhibitors in the management of type 2 diabetes mellitus, particularly in patients with type 2 diabetes mellitus at stages beyond impaired glucose tolerance, remains unclear.

**Metformin (Biguanides)**

Metformin is considered to be the drug of first choice for most patients with newly diagnosed type 2 diabetes mellitus. It increases insulin sensitivity primarily by decreasing hepatic glucose output, and to a lesser extent, by increasing glucose utilization in peripheral tissues. The hepatic effect is mainly through a decrease in glucose neogenesis with a lesser effect on glycogenolysis. The mechanism of increased glucose utilization in peripheral tissues has been attributed to an increase in nonoxidative glucose disposal in skeletal muscle.

Metformin has multiple effects beyond its effects on glycemic control. Since insulin resistance is strongly associated with the pathogenesis of atherosclerosis and metformin decreases insulin resistance, metformin has the theoretic potential to slow the development of atherosclerosis. Metformin has a favorable effect on lipids, with treatment resulting in decreases in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, but no significant change in high-density lipoprotein (HDL) cholesterol. It has been shown to improve endothelial function in patients with type 2 diabetes mellitus (but without other risk factors associated with the metabolic syndrome), probably by decreasing insulin resistance. Additionally, metformin has been found to improve vascular function in nondiabetic women with chest pain and normal coronary arteries.

Unlike sulfonylureas, metformin is associated with weight stabilization or even weight loss. Typically, there is an average 1.5% reduction of glycated hemoglobin with metformin monotherapy. Garber et al found a dose-response relationship of metformin and the reduction of hemoglobin A1c; there was a 0.6% reduction of glycated hemoglobin with a 500 mg daily dose and a 2.0% reduction with a 2,000 mg daily dose.

Metformin is contraindicated in certain clinical situations because of the possibility of developing lactic acidosis, which includes in patients with renal failure, heart failure, significant liver disease, and alcohol abuse. The contraindications for metformin use in patients with heart failure and renal failure have recently been questioned. Some observational studies have not shown an increased morbidity and mortality in patients with heart failure treated with metformin. In a study by Masoudi et al, older patients with heart failure treated with metformin did not have increased mortality and might have had better outcomes than those patients not treated with metformin. Another retrospective study compared the morbidity and mortality of diabetic patients with heart failure who were treated from 1991 to 1996 with sulfonylurea alone, metformin alone, or combination therapy. The mortality in the sulfonylurea group was 52%, the metformin group was 33%, and the combination group was 31%. Because of these studies, some investigators suggest that the use of metformin in patients with well-compensated stable heart failure should be reevaluated. Nonetheless, other experts believe that
metformin should remain contraindicated in patients with heart failure until there are controlled clinical trials showing the safety and benefits of metformin in this group of patients.50

Similarly, the contraindication of metformin use in renal failure is somewhat controversial. Population-based studies have shown that this contraindication to metfor-

min use is often disregarded.33 Despite this practice, lactic acidosis is extremely rare in diabetic patients treated with metformin and occurs as frequently as in diabetic patients not treated with metformin.52 In a 4-year prospective study,53 patients with type 2 diabetes mellitus and mild chronic renal insufficiency who were taking metfor-

min were randomized to discontinue metformin or con-

tinue taking it. There was no difference in CV morbidity, CV mortality, or total mortality between the 2 groups.

There is increasing evidence that treatment with metfor-

min may be associated with improved CV outcomes. In the study UKPDS study,21 patients with newly diagnosed type 2 diabetes mellitus were treated intensively with in-

sulin or sulfonylureas (alone or in combination with in-

sulin or metformin) or conventionally, mainly with diet. Overall, when the different drugs used in the intensively treated group were compared, there was no difference in CV outcomes. However, in a related study of overweight diabetic patients,14 treatment with metformin alone was associated with a 36% decrease in all-cause mortality and a 39% decrease in MI compared to treatment with diet alone. Population-based observational studies suggest that metformin therapy is associated with improved CV outcomes,55,56 although studies differ as to CV outcomes when metformin is combined with a sulfonylurea.

A study using the Saskatchewan Health database56 concluded that metformin treatment alone or in com-

bination with a sulfonylurea was associated with a de-

creased all-cause and CV mortality, while a study using a Scottish55 database concluded that CV outcomes were better in patients treated with metformin alone com-

pared to those treated with combination therapy with a sulfonylurea or sulfonylurea alone. Recently, Selvin et al52 compiled a meta-analysis of the results of 40 random-

ized controlled trials that studied CV risk of oral agents, including second-generation sulfonylureas, metformin, thiazolidinediones, and meglitinides. Metformin was the only drug that was associated with a decrease in CV mortality. CV morbidity and all-cause mortality was less in the metformin group, but here the difference was not statistically significant.

**Thiazolidinediones**

The 2 thiazolidinediones available are rosiglitazone and pioglitazone. Their mechanism of action has been ex-

tensively reviewed elsewhere.57-60 They increase insulin

sensitivity by binding to the nuclear transcription factor peroxisome-proliferator-activated receptor gamma (PPAR-γ) and act directly primarily on adipose cells but also on muscle and indirectly on liver cells to increase glucose utilization and decrease glucose production. Thiazolidinediones have multiple direct effects through PPAR-γ expression at adipose tissue, including increasing fatty acid uptake and storage, increasing adiponectin secretion, and increasing glucose uptake. They promote an increase in glucose uptake at the skeletal muscle, and at the vascular wall, they decrease inflammation partly through a decrease in intercellular adhesion molecule-1 and vascular-cell adhesion molecule-1. They improve endothelial function through upregulation of endothelial nitric oxide synthase (eNOS) expression. Animal models have shown that the thiazolidinediones decrease beta-
cell apoptosis and prevent islet-cell amyloidosis. There is in vitro evidence that pioglitazone may act as a partial PPAR-a agonist. PPAR-a expression in the liver is associated with beneficial effects on lipid metabolism and at the vascular wall with a decrease in the inflammatory pro-

cess. Both drugs reduce glycated hemoglobin by 1-1.5%.

PPAR-γ may have an important effect on body fat distribution. Visceral adipose tissue is felt to be more metabolically harmful than subcutaneous adipose tissue. When patients with type 2 diabetes mellitus are treated with a thiazolidinedione, they tend to accumulate subcutaneous fat, but visceral fat decreases or remains un-

changed.61 This effect may help explain the beneficial effects of thiazolidinediones despite weight gain. The thi-

azolidinediones have been found to have a favorable effect on nonalcoholic fatty liver disease, a disorder frequently found in patients with type 2 diabetes mellitus.62,63

Troglitazone, the first thiazolidinedione used clini-

cally, was found to have significant liver toxicity, but rosiglitzzone and pioglitazone have not been associated with significant liver abnormalities. Nevertheless, it is recom-

mended that liver enzymes be periodically monitored.57,64 The thiazolidinediones are associated with weight gain of an average of 3 to 5 kilograms.57 This weight gain is sec-
nondary to increased subcutaneous fat or fluid retention or both.

There is increasing evidence that the thiazolidinedio-

nes have an adverse effect on skeletal mineralization. In an animal model,55 mice treated with rosiglitazone de-

veloped an increase in marrow adipocytes, a decrease in the ratio of osteoblast to osteoclast activity, and a re-
duction in bone formation. The authors suggested that PPAR-γ activation may have a negative effect on bone mass. Observational studies have found the association of thiazolidinedione treatment and decreased bone mineral density in diabetic women but not men,65 and in a dif-

ferent study, in diabetic men.67 A 14-week trial of rosiglitzzone in healthy postmenopausal women showed that
rosiglitazone inhibited bone formation. Because of these findings, thiazolidinediones should be avoided in patients with osteoporosis or a history of a fragility fracture.

Thiazolidinediones have been found to contribute to fluid retention and heart failure (HF). Four to six percent of diabetic patients treated with thiazolidinediones develop peripheral edema, and a higher percentage of patients who are treated with insulin and thiazolidinediones develop this complication.48 In a murine model it was found that pioglitazone directly stimulated sodium transport in the collecting duct through PPAR-γ expression.69 Sodium retention is felt to be the major cause of fluid retention in thiazolidinedione-treated patients.

In 2003, Delea et al67 reported a retrospective study of patients with diabetes mellitus treated with thiazolidinediones between 1995 and 2001. Patients treated with thiazolidinediones were, in general, younger than controls but were more likely to have CAD. After adjusting for multiple variables, patients treated with thiazolidinedione were more likely to develop congestive heart failure (CHF), with 8.2% of them developing HF at 40 months compared to 5.3% of control patients. Inzucchi et al11 retrospectively studied Medicare beneficiaries with diabetes mellitus who were discharged from the hospital after an acute MI. At 1-year follow-up, patients treated with a thiazolidinedione had a higher rate of readmission for HF but did not have an increase in mortality. In 2007, an interim analysis of the Rosiglitazone Evaluated for Cardiovascular Outcomes (RECORD)72 trial was published. In this prospective study, after a mean follow-up of 3.75 years, patients treated with rosiglitazone had more than twice the risk of HF than the control group, although there was no increase in mortality. In a more recent analysis after 5.5 years of treatment, the increased risk of HF persisted without an unfavorable effect on mortality.73 However, the FDA has required that the package insert for rosiglitazone include a boxed warning that the drug may increase the risk of myocardial ischemic events.

Several recent meta-analyses have reported on the association of thiazolidinedione use with the development of CHF. Lago et al74 reported on a meta-analysis of 7 randomized controlled trials of patients with pre-diabetes and diabetes mellitus treated with rosiglitazone or pioglitazone. The event rate of CHF was significantly higher (2.3%) in the thiazolidinedione-treated patients than in the patients not on thiazolidinediones (1.4%). However, there was no difference in CV death rates. Singh et al75 reported on a meta-analysis of 3 prospective studies and 4 observational studies all examining the association of thiazolidinediones with the development of CHF. They concluded that patients treated with thiazolidinediones had a significantly higher risk of developing CHF. HF was seen with both high and low doses of thiazolidinediones, was not limited to the elderly, and was seen in some patients who did not have a prior history of CHF. In a separate meta-analysis, Lincoff et al reported that pioglitazone was found to raise the rate of CHF but not the rate of CHF mortality.76

Despite the evidence that thiazolidinediones appear to contribute to the development of CHF, there is no conclusive evidence that they increase mortality in patients with pre-existing CHF. A recent study77 looked at the effects of rosiglitazone on patients with diabetes mellitus and pre-existing New York Heart Association (NYHA) functional class I or II CHF. At the end of one year, left ventricular ejection fraction was the same in rosiglitazone-treated and control patients. The patients treated with rosiglitazone had more events relating to worsening edema and had a greater increase in medication to treat CHF, but these patients did not have an increase in mortality, in CV hospitalizations, or in definite worsening of CHF.

The authors concluded that patients with NYHA functional class I or II CHF who are treated with rosiglitazone need to be monitored on a regular basis to avoid clinical deterioration. An observational study59 reported on the 1-year post-discharge mortality rates of elderly diabetic patients who had been hospitalized for CHF and treated with thiazolidinediones or metformin. The data from the study suggested that the patients treated with a thiazolidinedione or metformin had improved survival compared to those patients who were not treated with an insulin-sensitizing drug. The 1-year mortality rates were 30.1% lower in the thiazolidinedione-treated group and 24.0% lower in the metformin-treated group.

Because of some reports of thiazolidinedione-related morbidity and death and concerns over the risk of HF, the US Food and Drug Administration78(FDA) announced in August 2007 that the manufacturers of pioglitazone and rosiglitazone must include a boxed warning in their drug information emphasizing that these drugs may cause or worsen HF in some patients. These drugs are contraindicated in patients with NYHA functional class III or IV CHF.

There is much controversy regarding the association of thiazolidinedione use and MI. In 2007, in a meta-analysis79 of 42 trials that used rosiglitazone to treat type 2 diabetes mellitus, Nissen and Wolski concluded that there was an increased risk for MI and death in patients taking rosiglitazone (odds ratio 1.43 for MI and 1.64 for death from cardiovascular cause). The same data were re-evaluated by Diamond et al,60 but they did not find an increase in MI or death in these patients; they attributed the discordant conclusions to different statistical analytical methods. In the same year, Singh et al55 reported on a meta-analysis of 4 randomized controlled trials where rosiglitazone was used to treat type 2 diabetes mellitus. They concluded that rosiglitazone significantly increased the risk of MI and HF without increasing the risk of CV
mortality. In a retrospective review\textsuperscript{41} of elderly patients with type 2 diabetes mellitus in the Ontario, Canada database, patients receiving thiazolidinedione monotherapy were at increased risk for MI, but those who took thiazolidinediones in combination with other oral agents did not have this increased risk. The association of MI and thiazolidinedione was limited to rosiglitazone.

Because the safety of using rosiglitazone was in question, the investigators of the RECORD trial,\textsuperscript{72} a large randomized trial to evaluate the effects of rosiglitazone in patients with type 2 diabetes mellitus, released an interim analysis. After a mean follow-up of 3.25 years, there were no significant differences between the rosiglitazone group and the control group regarding MI and death from CV causes or all causes.

At this time, rosiglitazone’s safety with regard to MI is uncertain. Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial\textsuperscript{82,83} were recently reported. In this trial, an intense insulin-providing strategy was compared to an intense insulin-sensitizing strategy with regard to CV outcomes. The major drugs used in the insulin-sensitizing group were metformin and thiazolidinediones, with the most common agent in this class being rosiglitazone. There were no significant differences in the rates of death between the 2 treatment groups (Figure 24-1). In the most updated analysis of the RECORD trial, there was no additional data to suggest a significant increase in the risk of MI compared with the control group.\textsuperscript{71}

However, additional safety concerns regarding rosiglitazone have surfaced with some authorities calling for its removal from the market.\textsuperscript{83a} In a more recent meta-analysis, Nissen and Wolski concluded again that rosiglitazone continued to demonstrate an increased risk for MI, although not for CV or all-cause mortality.\textsuperscript{83b} In a retrospective observational study of Medicare beneficiaries, when compared to pioglitazone, rosiglitazone was associated with an increased risk of stroke, heart failure and all-cause mortality.\textsuperscript{83b} Therefore the FDA has severely restricted the use of rosiglitazone in the U.S. and the drug has been taken off the market in Europe.

The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in diabetes mellitus patients with Cardiovascular Disease (APPROACH) trial\textsuperscript{84} will look at the effect of rosiglitazone on the percentage change in coronary artery atheroma volume in patients with type 2 diabetes mellitus and CAD, and an ongoing double-blind trial is comparing pioglitazone to rosiglitazone regarding efficacy and safety, although recruitment may be stopped.

Unlike rosiglitazone, pioglitazone has been associated with favorable CV outcomes in some studies.\textsuperscript{85,86} The possibly different effects of these 2 drugs may be in part secondary to their different effects on serum lipids. Pioglitazone seems to have a more beneficial effect on both LDL and triglyceride levels.\textsuperscript{87} In a prospective study of patients with type 2 diabetes mellitus and dyslipidemia, Goldberg et al\textsuperscript{87} found that triglycerides decreased by an average of 51.8 mg/dl in patients treated with pioglitazone but increased by an average of 13.1 mg/dl in patients treated with rosiglitazone. Patients on pioglitazone had a greater increase in HDL cholesterol and less increase in LDL cholesterol. LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone, while LDL particle size was increased more with pioglitazone.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) study\textsuperscript{88,89} was a prospective, randomized, controlled trial designed to evaluate the CV effects of pioglitazone in patients with type 2 diabetes mellitus and macrovascular disease. The study was stopped at a mean follow-up of 34.5 months because of a significant decrease in secondary endpoints, including all-cause mortality, nonfatal MI, and nonfatal stroke in patients taking pioglitazone. There was a trend but no significant risk reduction in the primary composite endpoint of macrovascular events. In a subgroup analysis of patients who had a previous MI, treatment with pioglitazone was associated with a 28% risk reduction of fatal and nonfatal MI, a 37% risk reduction of acute coronary syndrome, and a 19% risk reduction in the cardiac composite endpoint of nonfatal MI, coronary revascularization, and acute coronary syndrome.\textsuperscript{89} HF requiring

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure24-1.png}
\caption{Rates of survival and freedom from major cardiovascular events.}
\end{figure}

hospitalization was higher in the pioglitazone group, but fatal HF was not increased.

This study has been criticized because it was stopped prematurely. Since the progression of CVD takes place over many years, the full effect of pioglitazone on macrovascular disease and HF may not have been evaluated. However, a meta-analysis of 16 randomized controlled trials (including the PROACTIVE study) investigating the CV effects of pioglitazone in patients with type 2 diabetes mellitus concluded that pioglitazone is associated with a significantly lower risk of death, MI, and stroke.

Takagi et al. looked at the effect of pioglitazone on neointimal tissue proliferation in patients with type 2 diabetes mellitus after coronary stent implantation. In this randomized trial, 23 of 44 patients were treated with pioglitazone. After 6 months, angiographic restenosis and target lesion revascularization were less frequent (but not statistically significant) in the pioglitazone group. However, the neointimal index, as determined by intravascular ultrasound, was significantly lower in the pioglitazone group. The much larger Progression of Coronary Atherosclerosis in Patients with Type 2 Diabetes (PERISCOPE) trial enrolled 543 patients with type 2 diabetes mellitus who were undergoing cardiac catheterization and coronary artery ultrasound and randomized them to receive pioglitazone or glimepiride. After 18 months, progression of atherosclerosis, as measured by change in percentage of atheroma volume from baseline, was significantly less in the pioglitazone group. The authors concluded that pioglitazone is associated with a significantly lower risk of death, MI, and stroke.

Nishio et al. evaluated pioglitazone’s effect and mechanism of action in preventing in-stent restenosis. In this randomized trial, 26 of 54 diabetic patients who underwent coronary artery stenting were treated with pioglitazone. In the pioglitazone group, insulin resistance, endothelial nitric oxide synthase, and leptin were significantly less at 6 months than at baseline. Lipids were not different between the 2 groups. Additionally, follow-up late luminal loss and in-stent restenosis were significantly less in the pioglitazone group. The authors concluded that the beneficial effect of pioglitazone on CAD may be partly mediated by leptin’s effect on decreasing insulin resistance, thereby improving endothelial function.

At this time, in each individual patient, the potential benefits of pioglitazone as they relate to the development and progression of atherosclerosis must be weighed against its demonstrated increased risks for the development of HF and skeletal demineralization. Pioglitazone should be the preferred thiazolidinedione for use in type 2 diabetes mellitus.

**Dipeptidyl Peptidase Type IV Inhibitors**

The “incretin effect” refers to the increment in insulin secretion and circulating levels seen after the oral administration of glucose when compared with the same dose of glucose administered intravenously. This increment in insulin secretion is now known to be mediated by 2 gastrointestinal hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinogetic polypeptide (GIP). GLP-1 is the principal incretin in humans; it regulates glucose homeostasis by inhibiting glucagon secretion, stimulating insulin secretion and synthesis, delaying gastric emptying, and inhibiting appetite.

Both hormones have a circulating half-life of only a few minutes and are inactivated by their main and ubiquitous degrading enzyme, dipeptidyl peptidase type IV (DPP-IV) inhibitors. Two different approaches have been used to increase their effect for therapeutic purposes; one is to use a peptidase resistant analog, exenatide (discussed below), and the other is to inhibit the peptidase, thus increasing the half-life of the peptides.

DPP-IV inhibitors are a new class of drugs developed as oral hypoglycemic agents for patients with type 2 diabetes. Sitagliptin was approved by the FDA in the United States in October 2006; saxagliptin was approved in July 2009. Vildagliptin is available in Europe but has not yet been approved by the FDA in the United States. Another DPP-IV inhibitor, alogliptin, is in clinical trials.

Sitagliptin, when used as monotherapy, decreases glycated hemoglobin by 0.8% to 1.5%, depending on the baseline glycated hemoglobin. Both sitagliptin and saxagliptin may be used in combination with metformin, a sulfonylurea, or a thiazolidinedione. The stimulation of insulin secretion is glucose-dependent, and the DPP-IV inhibitors do not cause hypoglycemia. There have been rare reports of pancreatitis associated with sitagliptin; however, a causal relationship has not been established. Doses of saxagliptin above that recommended for clinical use are associated with a decreased absolute lymphocyte count of unclear clinical significance.

Vildagliptin, at clinically relevant doses, also reduces fasting and peak postprandial glucose concentrations in type 2 diabetic participants. Despite this, insulin and C-peptide levels are unchanged by vildagliptin, compared to the placebo. However, postprandial glucagon levels are significantly lower and GLP-1 levels are significantly higher after vildagliptin administration. Although GLP-1 infusions are known to delay gastric emptying, vildagliptin administration had no such effect.

A reduced insulin response to ingested nutrients is one of the earliest defects noted in patients with impaired glucose tolerance and type 2 diabetes mellitus. DPP-IV inhibitors have been shown to reverse this defect and have been proposed to treat early glucose intolerance and possibly delay or prevent the onset of diabetes mellitus. Indeed, both GLP-1 and GIP have been shown to reduce β-cell apoptosis and stimulate β-cell proliferation. However, more data on the long-term safety of DPP-IV
inhibitors are required before they can be used for this purpose. There are no data yet on the CV impact of DPP-IV inhibitors.99

Glucagon-like Peptide-1 Agonists

Degradation-resistant GLP-1 analogs have generated considerable interest because of the major role played by incretins in the homeostasis of glucose and carbohydrate metabolism and the fact that one of the early defects in type 2 diabetes mellitus and in glucose intolerance is the attenuation or loss of the incretin effect.94

The first such analog is exenatide, a 39 amino-acid peptide with an approximately 50% sequence analogy to GLP-1, isolated from the toxic saliva of the Gila monster lizard (Heloderma suspectum). Exenatide is used as a subcutaneous injection of 5 or 10 μg twice daily. Although it was approved by the FDA in April 2005 only as adjunctive therapy to other oral antidiabetic agents, it can also be used alone. It generally provides a decrease in the glycated hemoglobin of about 1% and, contrary to insulin and sulfonylureas, is associated with a modest weight loss.100 The most common adverse effect of exenatide is nausea or, more rarely, vomiting and diarrhea. Recently, a rare association with pancreatitis has been reported; although most affected patients had other risk factors for pancreatitis, a few patients did develop a recurrence of pancreatitis on rechallenge with the drug.96c,101 A long-acting exenatide preparation that could be used as a weekly injection is in development,101-103 and a recent study showed its benefit and safety when combined with metformin; however, it is unclear when and if it will be approved.102a

Liraglutide is another GLP-1 analog that was recently approved by the FDA for marketing as a once-daily subcutaneous injection for treatment of patients with type 2 diabetes mellitus.105 It was found to be more effective than exenatide in reducing hemoglobin A1C in patients not controlled on oral antidiabetic drugs.102a Liraglutide is used in dosages of 1.2 or 1.8 mg injection daily, and is not recommended as first-line therapy in type 2 diabetes mellitus. It is not approved for use with insulin. Liraglutide has caused thyroid c-cell carcinomas in rodents and, similar to exenatide, can cause pancreatitis.

A new generation of GLP-2 receptor agonists, now under investigation, include taspoglutide and albiglutide.

There are no data on the CV impact of GLP-1 receptor agonists. However, exenatide has been shown to improve CVD surrogate marker,103,104 and a computer modeling tool predicts reduced morbidity and mortality from the use of exenatide when compared to glargine insulin.105 GLP-1 and analogs have also been shown to reduce myocardial ischemia-reperfusion injury in an in vitro isolated rat heart model.106

Insulin

Insulin infusions have been used to treat hyperglycemia in patients with and without diabetes mellitus in the setting of MI, coronary bypass surgery, and sepsis.107-109 Although insulin infusions are clearly beneficial when compared to no glycemic control intervention, the ideal glycemic target is still under discussion.110,111

In type 2 diabetes mellitus, there is progressive β-cell failure. With longstanding disease, the majority of patients are not adequately controlled on combinations of oral hypoglycemic agents; insulin must be added to the regimen. At first, basal insulin is usually added, either as NPH insulin or as the insulin analogs, glargine or detemir. NPH insulin is associated with more hypoglycemia than glargine or detemir.112 The addition of insulin is usually associated with weight gain. Recent studies suggest that detemir insulin is associated with less weight gain as compared to NPH insulin.113,114 With the addition of basal insulin, there is often postprandial hyperglycemia, which is more severe in patients with more severe β-cell failure. Holman et al115 compared the efficacy of 3 insulin regimens—premixed NPH/aspart insulin twice daily, preprandial aspart insulin 3 times daily, and detemir insulin once or twice daily. Patients who were treated with premixed NPH/aspart or preprandial aspart insulin had better glycemic control but had more hypoglycemic reactions and more significant weight gain.

In patients with poor glycemic control on oral hypoglycemic agents, an alternative to adding insulin is adding exenatide. Heine et al116 compared the effects of the addition of glargine insulin and exenatide in poorly controlled patients with type 2 diabetes mellitus who were treated with oral hypoglycemic agents. At 26 weeks, fasting glucose was lower in the glargine group and postprandial glucose was lower in the exenatide group. The glargine group gained an average of 1.8 kg while the exenatide group lost an average of 2.3 kg. Therefore, in obese patients with poorly controlled diabetes mellitus on oral hypoglycemic agents, exenatide or liraglutide may be the additional drug of first choice in this subset of patients.

Diabetes Mellitus and Cardiovascular Disease: Recent Clinical Studies

The diabetic population has significant mortality from CVD, and much of its medical care hinges on CVD prevention.117 A focus of treatment in patients with diabetes mellitus is achieving glycemic control, which until now has involved maintaining glycated hemoglobin at or below 6.5% or 7%, depending on which guidelines are followed.118-120 Since past epidemiologic studies have shown a relationship between glycated hemoglobin levels and
CV events in patients with type 2 diabetes mellitus, it has been hypothesized that tight glucose control in patients with type 2 diabetes mellitus would result in more favorable CV outcomes.

Much of our knowledge of the effects of control of type 2 diabetes mellitus and its complications has come from the UKPDS. In this 10-year study, 3,867 patients (mean age 54 years) with newly diagnosed type 2 diabetes mellitus were randomized to intensive therapy with insulin or sulfonylureas (alone or in combination with insulin or metformin) or conventional treatment. The glycated hemoglobin levels were 7.0% and 7.9% for the intensively and conventionally treated groups respectively. At the end of the study there was a significant reduction in microvascular complications, but not in macrovascular disease. The intensively treated group had a lower rate of MIs, but this just missed statistical significance ($P = .052$).

Recent large randomized clinical trials were designed to determine if intensive glycemic control actually decreases CV events in patients with type 2 diabetes mellitus. The results from Action to Control Cardiovascular Risk in Diabetes (ACCORD),$^{121,122}$ the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),$^{123}$ and the Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes (VADT)$^{124}$ trials were reported in 2008 and 2009. Each trial was performed in type 2 diabetic participants, and atherosclerotic disease events were primary or key outcomes.

The (ACCORD)$^{123}$ trial tested the hypothesis that intensive glucose-lowering (with HgbA1c target of < 6%) would reduce the incidence of atherosclerotic disease events and death compared with standard treatment with a glycated hemoglobin target of 7.0% to 7.9%. This trial included 10,251 patients (mean age 62 years, duration of diabetes mellitus 10 years) with type 2 diabetes mellitus at high risk of CV events. Baseline glycated hemoglobin was 8.1% and was maintained during the study at 6.4% for the intensive group and 7.5% for the standard treatment arm. This study was terminated early at 3.5 years because more people had died in the intensive treatment group than in the standard treatment group. At the end of the study, there was no significant difference in major CV events, including death, between the 2 groups.

These 3 trials using different methods studied somewhat similar patients (those with type 2 diabetes mellitus of about 10 years duration and increased risk for CV events) and came to somewhat similar conclusions. None of the trials demonstrated decreased CV events with intensive glycemic control, and 1 trial was stopped early because of increased deaths.

In these trials, there was an increase in hypoglycemia in the intensively treated groups. Hypoglycemia, even if “asymptomatic,” can be associated with cardiac ischemia.$^{125}$ Unrecognized hypoglycemia can contribute to adverse CV outcomes and is more frequent with insulin use and when insulin is combined with multiple oral hypoglycemic agents. In the intensively versus conventionally treated patients, insulin was used in 77% versus 55% of the ACCORD patients, 41% versus 24% of the ADVANCE patients, and 90% versus 74% of the VADT patients. Additionally, in the ACCORD and VADT trials, rosiglitazone was used in a high percentage of the intensively treated patients but no correlation has been made between rosiglitazone use and adverse CV events in these studies. Further analysis of subgroups of patients and combinations of medications needs to be done to separate the factors that influence the relationship between interventions to achieve glycemic control and CV outcomes.$^{126}$

The duration of these trials, 3.5 to 5.6 years, is relatively short compared to the natural history of the development of atherosclerosis, which is known to span decades. It may be that if these trials had been extended in time, different results would have been obtained.

In 2008, a 10-year follow-up report of patients who had been part of the UKPDS was published.$^{127}$ At the start of the trial, these patients had been newly diagnosed diabetics. In 1998 at the end of the UKPDS study, there was a not-statistically significant trend toward fewer MIs in the intensively treated group ($P = .052$). One year after
the end of the randomized study, there was no longer any difference in the glycated hemoglobin among the study groups. However, at 10 years after the end of the study, the patients who had been intensively treated had a significantly lower rate of MI and all-cause mortality. Thus, the adverse effects of hyperglycemia on CV outcomes may be delayed for many years, even decades.

In the ACCORD, ADVANCE, and VADT trials, adverse CV outcomes in both the intensively and conventionally treated groups were lower than had been expected. Overall, better outcomes were probably secondary to treatment of multiple risk factors in many of the patients. The metabolic abnormalities in type 2 diabetes mellitus not only lead to hyperglycemia but also create endothelial dysfunction, dyslipidemia, hypertension, and increased platelet activity and coagulability. In the Steno-2 study, it was found that a multifactorial intervention including glycemia control, renin-angiotensin system blockers, aspirin and lipid-lowering agents lowered the risk of death, death from CV causes, and CV events in type 2 diabetic patients with microalbuminuria. In patients with longstanding diabetes mellitus, and especially in elderly patients, treating these multiple risk factors may be more beneficial than tight glycemic control to prevent adverse CV events.

Recommendations

Results of the 10-year follow-up of the UKPDS suggest that tight control of younger, newly diagnosed patients with type 2 diabetes mellitus may have CV benefits even decades later. There is an emerging notion that tight glycemic control may be beneficial in primary prevention of CVD in younger diabetics but may become deleterious in older patients with established or subclinical CVD. In younger patients with type 2 diabetes mellitus, especially if they have no evidence of macrovascular disease, it seems reasonable to strive to control diabetes mellitus tightly and to bring the glycated hemoglobin to or below 6.5%. In older patients with established diabetes mellitus, especially if they have macrovascular disease, the goals need to be individualized. While tight control may lessen the risk of microvascular disease, it may increase the risk of hypoglycemia and possibly of adverse CV events. In these patients, a prudent glycated hemoglobin goal could be ≥ 7%, depending on the patient’s age, overall prognosis, and risk of hypoglycemia. However, a glycated hemoglobin goal of < 7% seems reasonable if it can be achieved without the use of multiple hypoglycemic agents and the risk of hypoglycemia. In the meantime, interventions such as smoking cessation, blood pressure control, moderate exercise, proper diet, aspirin, renin-angiotensin system blockers, and lipid-lowering agents should be stressed as essential parts of the care of patients with type 2 diabetes mellitus.

Note: References for this chapter can be found here: www.cvpcf3.com
Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) constitutes idiopathic disease or PAH due to secondary causes that is pathologically divided into 3 groups: plexogenic arteriopathy, veno-occlusive disease, and capillary hemangiomatosis.1 All 3 conditions can also be complicated by thrombosis in situ.2,3 Plexogenic arteriopathy is the most common form and is characterized by abnormalities in the intima and media of precapillary vessels, which can range from mild neointimal proliferation to intimal fibrosis, plexiform lesions, and necrotizing arteritis.4,4a Pulmonary veno-occlusive disease is less common and is characterized by fibrosis of the endovascular walls of small- and medium-sized veins.2 The least common form, pulmonary capillary hemangiomatosis, is characterized by proliferation of the capillary network, leading to changes in the arterial bed.2,4,5

Although the mechanisms behind the disease are not completely elucidated, it does appear that there are definite features of the disease process.6-7 There is an imbalance of endothelial mediators of vascular tone characterized by an unfavorable balance between thromboxane A and prostacyclin, and abnormal nitric oxide (NO) production, predisposing the vasculature to thrombosis and constriction (Figure 25-1).7,4 There is also an increase in the production of endothelin by the pulmonary vasculature,8 a decrease in endothelial clearance, and an increase in circulating endothelin levels in patients with PAH,10 which causes further vasoconstriction. In addition, plasma serotonin concentrations are raised in PAH patients.11 Transgenic mice that overexpress the serotonin transporter develop PAH along with downregulation of the potassium channel Kv1.5, resulting in vasoconstriction.12

It also seems that there is a cycle involving vascular injury from an unknown cause(s) in susceptible individuals,4 which leads to smooth muscle invasion of the endothelium and a further disruption of the normal balance of vascular tone and coagulation mediators, further predisposing the endothelium to thrombosis and obstruction.1 A defect in potassium channels in the smooth muscle cells of the pulmonary artery may add to vasoconstriction. Intracellular calcium is an important regulator of smooth muscle contraction and proliferation, and the voltage-gated potassium channels that determine cytoplasmic concentrations of free calcium, KV1.5 and Kv2.1, are downregulated in human pulmonary artery smooth muscle cells of patients with PAH.13

The estimated annual incidence of PAH is 15 cases per million people per year, and the mean age at diagnosis is 36 years.8 The disease has a poor prognosis.13 The results of a national registry of patients with pulmonary hypertension (PH) published in 199114 found that patients had a mean survival of 2.8 years after diagnostic catheterization was performed. In this study, the survival rate at 1 year was 68%; at 3 years, 48%; and at 5 years, 34%. In this registry, 39% of the patients had been diagnosed with primary pulmonary hypertension (PPH) before being entered into the registry, but there was no significant difference between their survival rates and the survival rates of those who had not been previously diagnosed.

Traditionally, this disease has been treated with strong arterial vasodilators, such as calcium-channel blockers,15,16 anticoagulants,17 and supplemental oxygen when needed.18 Nitrates have also been used as a treatment, and rarely, cardiac glycosides and diuretics are used, but only with extreme caution.19,20 Orally active endothelin antagonists such as bosentan and ambrisentan, as well as phosphodiesterase (PDE) inhibitors such as sildenafil and tadalafil, have been approved for clinical use in patients with PAH. There are always a number of patients who fail to respond to medical treatment. Heart and lung
transplantation\textsuperscript{20} and lung transplantation\textsuperscript{21,22} have been employed successfully in patients with PAH along with atrial septostomy.\textsuperscript{23}

There are well-defined goals for screening responsiveness to drug therapy in PPH. Not all patients respond to medication, and some have an unfavorable response. The current consensus definition of vasoactive responsiveness is a decrease in mean pulmonary artery pressure (mPAP) of 10 mmHg to an absolute mPAP of ≤ 40 mmHg with unchanged or increased cardiac output.\textsuperscript{24} An unfavorable response would be the development of symptomatic systemic hypotension or an observed decrease in cardiac output. A nonresponder to therapy would be a person who did not show any significant change in PAP without the development of adverse effects.

Prostacyclins

Prostaglandin and prostacyclin (PGI\textsubscript{2}) were discovered in 1933, when von Euler identified a lipophilic substance in seminal fluid of sheep and humans. erroneously thinking that this substance was produced predominantly in the prostate, he called it prostaglandin.\textsuperscript{25} Many years later, Moncada et al\textsuperscript{26} isolated and synthesized PGI\textsubscript{2} and that same year Whittaker et al\textsuperscript{27} described its chemical structure. Prostacyclin is now commercially available for intravenous administration as epoprostenol, and many stable analogues, including some for oral and inhalational use, are available or being investigated.

Prostacyclin is found in all tissues and body fluids and is the major metabolite of arachidonic acid in the vasculature.\textsuperscript{28} Arachidonic acid is metabolized by cyclooxygenase to PGG\textsubscript{2} and then by PG hydroperoxidase into PGH\textsubscript{1\small 2}. These compounds are converted into prostacyclin by PGI\textsubscript{2} synthetase (Figure 25-2).\textsuperscript{26,27,29} Prostacyclin is produced predominantly in the endothelium and also by smooth muscle.\textsuperscript{27,28,30,31} It is one of the most potent vasodilators known and affects both the pulmonary and the systemic circulation.\textsuperscript{32} Increases in intracellular cyclic adenosine monophosphate (cAMP) of vascular smooth muscle results in relaxation of the blood vessels. Prostacyclin has also been noted to prevent smooth muscle proliferation. Platelet aggregation and adhesion are inhibited by the increase of intracellular cAMP induced by PGI\textsubscript{2}.\textsuperscript{33,34}

An interesting note is that platelet aggregation is inhibited before adhesion.\textsuperscript{35}

Epoprostenol

Epoprostenol was the first synthetic prostacyclin to become commercially available and is currently approved for use in patients with World Health Organization (WHO) Group I PAH. The drug has been shown to prolong survival in patients with WHO class III and IV symptoms secondary to PAH. It has the same structure as prostacyclin and is a very unstable molecule; its in vitro half-life at physiologic pH is approximately 6 minute and is noted to be longer in alkaline solutions.\textsuperscript{36} Epoprostenol is also degraded by light. The product must be freeze-dried and stored at temperatures between 15°C and 25°C. The drug must be reconstituted just prior to administration in a glycine buffer with a pH of 10.5 and must be protected from exposure to light during reconstitution and infusion. At room temperature, a single infusion should be completed within 8 hours after the medication is reconstituted. Epoprostenol must be administered intravenously, since it is degraded by the gastrointestinal tract before it can be absorbed.

Epoprostenol’s in vivo half-life in humans is not measurable. In animal models, the half-life of epoprostenol is 2.7 minutes. It is hydrolyzed to 6-ketoprostaglandin F\textsubscript{1\small a} in vitro,\textsuperscript{27} but in vivo, PGI\textsubscript{2} undergoes catalyzed oxidation to 15-keto-PGI\textsubscript{2}.\textsuperscript{37} It has been noted that apolipoprotein (apo A-I), a molecule associated with high-density lipoproteins (HDL), can prolong the half-life of prostacyclin.\textsuperscript{37}

Clinical Use of Epoprostenol

Acute hemodynamic testing with epoprostenol is performed with initial infusion rates at a dose ranging from 1 to 2 ng/kg/minute with increases in the infusion rate at 5- to 15-minute increments of 1 to 2 ng/kg/minute. Further up-titration is maintained until the appearance of adverse effects or the desired long-term infusion dose is obtained.\textsuperscript{39-44} The manufacturer of the drug recommends initiating the infusion with epoprostenol at 2 ng/kg/minute and increasing it at increments of 2 ng/kg/minute.
every 15 minutes. The drug is titrated until the appearance of adverse effects, including systemic hypotension, or until the desired long-term infusion dose is reached. The infusion rate can be lowered to a dose at which there are no adverse effects, and if severe systemic hypotension develops, the infusion can be stopped, with the patient returning to baseline hemodynamic status within a few minutes due to the short half-life.45 With long-term infusion, initiation infusion rates start at 2 ng/kg/minute and are uptitrated every few days until either a clinical effect is observed or until significant adverse effects prevent further increases. Adverse effects usually improve over time allowing for further uptitration. Many clinicians use the appearance of some of the adverse effects as an indication of therapeutic effect and resolution of these adverse effects as an indication that uptitration may be warranted. Epoprostenol dosing can be down titrated while preserving its therapeutic activity, especially if a high cardiac output state is observed.46

Several adverse effects can occur, most commonly flushing, headache, nausea and vomiting, anxiety, systemic hypotension, and jaw pain on initiation of mastication. Other less common adverse effects are chest pain, dizziness, bradycardia, abdominal pain, sweating, dyspepsia, hyperesthesia, paresthesia, tachycardia, headache, diarrhea, and flu-like symptoms. These unwanted effects can easily be reversed by lowering the dose or discontinuing the medication.45

Most problems with long-term administration of the drug relate to the need for continuous intravenous delivery. These conditions include sepsis, line occlusion secondary to thrombosis, and pump failure—problems that can result in fatalities. Long-term studies have shown that most patients are able to reconstitute and properly administer their medication safely at home.39-44

Epoprostenol also seems to be an ideal screening agent for identifying responsiveness to medical therapy in patients with PPH.19 Advantages of this medication are its easy titratability, its potency, and its short half-life.17 Other medications used for screening responsiveness to therapy in patients with PPH are acetylcholine,47 adenosine,48 nitrous oxide (NO),49 and sublingual nifedipine.50 Epoprostenol is more potent than acetylcholine, giving it an advantage in this respect.51 Adenosine causes a decrease in pulmonary pressure, but it is suggested that this result is secondary to its actions on cardiac output and not because of its effects on the pulmonary vasculature.52,53 NO seems to be comparable to epoprostenol in many of its hemodynamic actions. It has a short half-life and causes a decrease in pulmonary vascular resistance (PVR). In a comparative study, Jolliet et al compared the effects of sequentially administered NO, PGI₂, and nifedipine in 10 patients with precapillary pulmonary hypertension for screening patient responsiveness to vasodilators.54 They concluded that NO inhalation had a predictive ability at least as good as or perhaps better than PGI₂ without the associated decrease in systemic vascular resistance (SVR), mean systemic arterial pressure (mSAP), and consequent increase in heart rate and cardiac index. NO also does not cause systemic hypotension. NO, when available, is probably an easier and at least equally efficacious method to assess vasoreactivity and responsiveness in the treatment of PAH.55 Sublingual nifedipine has effects on the pulmonary and systemic circulations similar to those of epoprostenol. However, the longer half-life of nifedipine limits its use.50

If the patient has a favorable drop in PVR with epoprostenol without experiencing systemic hypotension, it is a good indication that the patient will have a favorable response to longer-acting vasodilators such as nifedipine. The American College of Chest Physicians has defined a positive vasoreactive test as a fall to an mPAP of 40 mmHg or a fall by 10 mmHg without a significant change of the cardiac output.56

Figure 25-2. Formation of prostacyclin from arachidonic acid. PGH = prostaglandin endoperoxide; PGI₂ = prostacyclin; TXA = thromboxane.

The other use for prostacyclin is in severely ill PAH patients who do not seem to respond to other medical therapy. Recent studies have shown that long-term infusion of epoprostenol can improve survival in patients with PAH.

In 1990, Rubin et al. published the result of a small randomized trial looking at the effect of epoprostenol in patients with PPH who had not responded to traditional therapy or had adverse reactions to therapy. They studied 24 participants with PPH with New York Heart Association (NYHA) class III and IV heart failure for 8 weeks and found that participants who received epoprostenol improved symptomatically and had improved hemodynamic function. Acutely, epoprostenol caused no change in mPAP, decreased PVR by 27% to 32%, decreased systemic blood pressure, and increased cardiac output by 40%. At 2 months, there were no statistically significant changes in the hemodynamics of either group as compared with the beginning of therapy; however, there was a decrease in PVR from 21.6 to 13.9 Woods units in the epoprostenol group, which approached statistical significance. Perhaps more interesting is that all the epoprostenol participants had an improvement in their NYHA functional class, compared with 2 participants receiving conventional therapy. Both groups also had improvement in the distance walked during a 6-minute walk test, with the epoprostenol group showing a larger increase in distance walked.

Seventeen of these participants were followed from 37 to 69 months in an open, uncontrolled trial. When compared with historical controls, this group showed a decrease in mortality, with a 3-year survival rate of 63.3%, compared with 40.6% in the control group (Figure 25-3). These participants also had an improvement of approximately 100 m in a 6-minute walk test after 6 and 18 months of treatment with epoprostenol, and they showed some improvement in their hemodynamic variables over 12 months (Table 25-1).

Barst et al. published the results of the largest epoprostenol trial in participants with PPH. In this study, 81 participants were randomized to receive epoprostenol or standard therapy for 12 weeks. There was a dramatic improvement in exercise capacity and a decrease in mortality with epoprostenol. Participants who received epoprostenol were able to walk farther during a 6-minute walk test after 12 weeks of epoprostenol infusion. The control group showed a 29-m decrease in the distance walked in 6 minutes. Functional class improved in 40% of the epoprostenol group. While 48% did not have any change in functional class, 13% worsened. In the control group, 3% improved in functional class, whereas 87% remained unchanged and 10% worsened. It should be noted that only survivors who did not undergo transplant were included in these results and there were no deaths in the epoprostenol group compared with 8 among the control group. Cardiac parameters also improved with epoprostenol treatment (Table 25-2). Participants treated with epoprostenol also reported improvement using the Nottingham Health Profile.

Hinderliter et al. later expanded on this trial by describing the echocardiographic changes associated with long-term epoprostenol therapy. The echocardiographic results showed that participants treated with continuous infusion of epoprostenol for 12 weeks had a lower maximal tricuspid regurgitant jet velocity, less right ventricular dilatation, an improved curvature of the intraventricular septum (during diastole and systole), and also a trend toward less tricuspid regurgitation when compared with participants randomized to conventional therapy. These findings are consistent with epoprostenol's ability to impact on right ventricular remodeling.

Shapiro et al. studied the long-term effects of continuous epoprostenol therapy (> 330 days in 18 participants and 90 to 190 days in 25 participants). They demonstrated...
Table 25-1. Hemodynamic Effects of Continuous Epoprostenol Infusion in Patients with Primary Pulmonary Hypertension after 6 Months and 12 Months of Follow-Up (Mean ± SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n = 18)</th>
<th>6 Months (n = 16)</th>
<th>12 Months (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>11 ± 7</td>
<td>7 ± 5</td>
<td>8 ± 6</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>61 ± 15</td>
<td>55 ± 11</td>
<td>54 ± 16</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>91 ± 13</td>
<td>90 ± 14</td>
<td>84 ± 11</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>1.9 ± 0.6</td>
<td>2.3 ± 0.6</td>
<td>2.5 ± 0.8</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>81 ± 13</td>
<td>81 ± 13</td>
<td>89 ± 13</td>
</tr>
<tr>
<td>Mixed venous saturation (%)</td>
<td>59 ± 12</td>
<td>67 ± 7</td>
<td>64 ± 12</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>93 ± 6</td>
<td>93 ± 6</td>
<td>92 ± 10</td>
</tr>
<tr>
<td>Stroke volume (mL per beat)</td>
<td>41 ± 18</td>
<td>53 ± 18</td>
<td>51 ± 23</td>
</tr>
<tr>
<td>Total pulmonary resistance (U)</td>
<td>22 ± 11</td>
<td>15 ± 6</td>
<td>14 ± 6</td>
</tr>
<tr>
<td>Total systemic resistance (U)</td>
<td>31 ± 11</td>
<td>25 ± 11</td>
<td>22 ± 10</td>
</tr>
</tbody>
</table>


Table 25-2. Hemodynamic Effects of Epoprostenol (E) and Conventional Therapy (CT) in Patients with Primary Pulmonary Hypertension after 12 Weeks of Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change from Baseline*</th>
<th>Difference Between Treatments</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP (mmHg)</td>
<td>−4.8 ± 1.3</td>
<td>−6.7</td>
<td>−10.7 to −2.6</td>
</tr>
<tr>
<td>mRAP (mmHg)</td>
<td>−2.2 ± 1.1</td>
<td>−2.3</td>
<td>−5.2 to 0.7</td>
</tr>
<tr>
<td>mSAP (mmHg)</td>
<td>−4.8 ± 1.2</td>
<td>−3.9</td>
<td>−9.6 to 1.7</td>
</tr>
<tr>
<td>mPCWP (mmHg)</td>
<td>0.4 ± 1.2</td>
<td>1.4</td>
<td>−2.5 to 5.3</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>0.3 ± 0.1</td>
<td>0.5</td>
<td>0.2 to 0.9</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>−0.9 ± 2.5</td>
<td>0.9</td>
<td>−5.2 to 7.2</td>
</tr>
<tr>
<td>SAO₂ Sat (%)</td>
<td>2.0 ± 1.6</td>
<td>2.6</td>
<td>−1.8 to 7.1</td>
</tr>
<tr>
<td>Mixed Venous O₂ Sat (%)</td>
<td>1.2 ± 1.8</td>
<td>3.8</td>
<td>−1.6 to 9.2</td>
</tr>
<tr>
<td>Stroke volume (mL/beat)</td>
<td>6.6 ± 2.2</td>
<td>10.1</td>
<td>2.5 to 17.8</td>
</tr>
<tr>
<td>PVR (mmHg/L/min)</td>
<td>−3.4 ± 0.7</td>
<td>−7.6</td>
<td>−9.5 to −2.8</td>
</tr>
<tr>
<td>SVR (mmHg/L/min)</td>
<td>−4.00 ± 1.0</td>
<td>−6.1</td>
<td></td>
</tr>
</tbody>
</table>

mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; mSAP = systemic artery pressure; mPCWP = mean pulmonary capillary wedge pressure; SAO₂ Sat = systemic arterial oxygen saturation; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; * ± values are the mean (± SE) changes from baseline. 95% confidence intervals (CI) are for comparisons between treatment groups. A CI that does not contain 0 indicates statistical significance.

improved survival over 1, 2, and 3 years of 80% \( (n = 36) \), 75% \( (n = 17) \), and 49% \( (n = 6) \), respectively, compared with the historical control participants at 10, 20, and 30 months of 88% \( (n = 31) \), 56% \( (n = 27) \), and 47% \( (n = 17) \), respectively. They also described a method for noninvasive long-term follow-up of participants with PPH.

The effects of prostacyclin treatment in PAH may in fact go beyond those of immediate vasodilation. After establishing baseline hemodynamic variables in 27 participants with severe PPH, McLaughlin et al\(^4\) evaluated patient response to the administration of adenosine, a vasodilator, and long-term therapy with epoprostenol. When comparing the hemodynamic responses to the 2 treatments, epoprostenol therapy caused a long-term reduction in PVR that exceeded the short-term reduction achieved with adenosine. In this study, long-term epoprostenol therapy reduced PVR in participants who showed no short-term response to adenosine.

Continuous prostacyclin therapy can also reduce endothelial cell injury, an etiologic factor in the development of PAH. Prostacyclin infusion in patients favorably reduces the plasma levels of P-selectin while increasing thrombomodulin levels, markers of endothelial injury, and altered hemostasis.\(^6\) The drug can also improve the balance between endothelin clearance and release, an abnormality seen in patients with PPH.\(^9\)

Although epoprostenol does not constitute a cure for PAH, it provides a substantial improvement as a palliative treatment for the disease.\(^5\) Higenbottam et al\(^6\) have studied participants with PPH in England since the early 1980s, looking at the effect of epoprostenol use on heart and lung transplantation. His group studied 44 participants, 25 of whom received epoprostenol, and measured the time to transplantation and its success. In this study, they noted that epoprostenol doubled the time on the waiting list for transplant or until death. They also noted that epoprostenol was the 1 factor that influenced longevity the most. However, it should be noted that a total of only 10 participants were transplanted, and that 7 of these participants received epoprostenol.\(^4\)

**Iloprost**

Iloprost is a more stable analogue of epoprostenol and has a similar structure, with some minor modifications. It has similar effects on platelet aggregability\(^6,13\) and vasodilation.\(^6,8\) Iloprost is 2 to 7 times more potent as an inhibitor of platelet aggregation than as a vasodilator.\(^6,66\) Because of its structural modifications, iloprost has a half-life of 13 min\(^6\) and is not degraded by light. It is metabolized by beta-oxidation.\(^8\) Drug elimination is substantially reduced in patients with renal failure\(^8\) and severe hepatic disease.\(^7\) This drug is reconstituted in a solution with physiologic pH and has been administered intravenously, by inhalation, and orally. When taken orally, less than 20% of the medication reaches the systemic circulation.\(^4\)

When administered acutely, iloprost is similar to epoprostenol in its effects in patients with PPH. Scott et al\(^1\) noted that there were no significant differences between these drugs and their effects on heart rate, cardiac index, PVR, PAP, and SVR. A long-term study with iloprost has also been done in participants with PH secondary to systemic sclerosis.\(^7\) In this study, aerosolized iloprost caused marked pulmonary vasodilation, with maintenance of gas exchange and SAP. Iloprost therapy may be life-saving in decompensated right heart failure from PH secondary to lung fibrosis. This is especially true for patients who cannot tolerate systemic vasodilator therapy because of the associated shunting and drop in SAP.

A long-term study was performed with iloprost in participants with PH secondary to systemic sclerosis and primary antiphospholipid syndrome.\(^7\) In this study, there was improvement in participants’ NYHA class and some improvement in PVR. However, this study included only 5 participants. Nonetheless, it did show that iloprost could be administered safely for long periods in patients with PH.\(^7\) Aerosolization of prostacyclin or iloprost has been shown to cause selective pulmonary vasodilation, an increase in cardiac output, and improved venous and arterial oxygenation in patients with severe PPH.\(^7,4-7,66\) Iloprost inhalation has also been shown to cause a rapid decrease in levels of atrial natriuretic peptide and cyclic GMP in parallel with pulmonary vasodilation and hemodynamic improvement.\(^5\)

In 2000, Hoeper et al demonstrated that aerosolized iloprost might be a potential alternative for the treatment of PPH.\(^7,6\) While continuous intravenous infusion of epoprostenol is an effective treatment for PPH, this approach requires the insertion of a permanent central venous catheter, with the associated risk of serious complications. These investigators evaluated 24 participants with PPH who received aerosolized iloprost for at least 1 year. These participants had significant increases in walking distance and cardiac output, while mPAP and PVR showed statistically significant declines. Olschewski et al found similar results regarding the efficacy of inhaled iloprost to treat PPH.\(^7,6\) The addition of oral sildenafil to an inhaled iloprost regimen has also been shown to provide greater benefit than iloprost alone.\(^6,8\)

Although inhaled iloprost appears to benefit patients with mild to moderate forms of PPH, it was unclear if those benefits extend to treating patients with severe forms of PAH. Schenk et al posed that while iloprost demonstrated short-term hemodynamic benefits, it could not be used as an alternative chronic treatment in patients with severe PH.\(^8\) In a small, uncontrolled trial, aerosolized iloprost reduced PAP and increased cardiac output...
by significant amounts. The effect of iloprost lasted for 20 minutes and was similar as different doses of intravenous epoprostenol. However, a persistent treatment change to inhaled iloprost could not be achieved because all patients developed signs of right heart failure. After termination of iloprost inhalation, a return to standard epoprostenol therapy led to a restoration of clinical and hemodynamic benefit.

Other studies have also demonstrated the limitation of inhaled iloprost in treating severe forms of PAH. In 2002, Olschewski et al studied a large population of participants with severe PAH and NYHA functional class III and IV heart failure. The primary endpoint of the study was an improvement of 6-minute walk distance by 10% and 1 functional class improvement by 12 weeks. Of the 203 participants studied receiving 2.5 or 5.0 µg of inhaled iloprost 6 or 9 times a day, 16.8% of the iloprost participants versus 4.9% of participants receiving the placebo (P = .007) reached the combined clinical endpoint. Secondary endpoints, which included 6-minute walk test distance, NYHA class, Mahler dyspnea index, and quality of life measurements were statistically better in those patients receiving iloprost therapy, showing that inhaled iloprost was an appropriate treatment option for patients with severe PAH.

Treprostinil

Treprostinil (UT-15, formerly known as 15AU81) is a stable prostacyclin analogue with a pharmacologic profile similar to that of epoprostenol, and it has a significantly longer half-life. Treprostinil is administered subcutaneously in patients with PAH and has been found to improve exercise tolerance. In 470 participants with NYHA functional class II, II, or IV symptoms and mPAP ≥ 25 mmHg, participating in a 12-week trial with PAH, the difference in mean distance walked was 16 m (P = .006). Secondary endpoints also revealed improvement in hemodynamic parameters including a reduction in mean right atrial pressure (mRAP), mPAP, cardiac index, PVR, and mixed venous saturation. Quality of life measures by their physical dimension score at 12 weeks (P = .64) and Borg dyspnea score were also improved (P < .0001). Although this distance is less than that seen in the epoprostenol studies, the discrepancy is explained by the inclusion of healthier participants at the time of randomization.

Based on this experience, the FDA has approved treprostinil for use in PH. The FDA has also recently approved inhaled treprostinil for clinical use in PAH. Channick et al studied the safety and efficacy of inhaled treprostinil added on the therapy in participants treated with the oral endothelin receptor antagonist bosentan. Of the 11 participants studied, inhaled treprostinil was found to be safe and effective. Six-minute walk test distance improved at 12 weeks by 67 m (P = .01) at 1 hour post inhalation and 49 m from baseline (P = .009) during the trough period before inhalation. In 9 of the 11 participants, NYHA functional class improved from III to II.

The TRIUMPH-1 trial evaluated 235 participants with NYHA class III or IV PAH who were also receiving oral therapy with either endothelin receptor antagonists or phosphodiesterase (PDE) inhibitors to receive inhaled treprostinil. After 12 weeks, a 20 m improvement in 6-minute walk distance was noted (P = .0006) and trough 6-minute walk distance improved by 14 m (P = .01).

Other Prostacyclins

Cicaprost and beraprost are 2 stable prostacyclin analogues that can be used in oral form. In a study of PPH participants, Beraprost was shown to enhance survival. In another study, beraprost was shown to improve exercise capacity and symptoms in participants with PAH, in particular, those with PPH. Beraprost has also been shown to enhance pulmonary vasodilation in children with PH when used simultaneously with inhaled NO. This combination may offer an alternative mode of treatment for patients with postoperative PH and PAH who do not respond to inhaled NO alone or conventional therapy.

A pilot study by Okano et al evaluated the efficacy of beraprost sodium in 12 participants with severe PPH unresponsive to calcium-channel blockers and inhaled NO. An acute response was evaluated after 1 dose of beraprost sodium (2 µg/kg) in 6 participants. Chronic response with a daily dose of 80 to 180 µg in 10 participants over an average of 2 months was assessed. Only one patient responded acutely, 3 showed no response, while 8 showed improvement in functional class and were still alive with the same dose of beraprost sodium during a mean of 5 months of follow-up. One patient died suddenly at 18 months. Beraprost sodium may be the first treatment option in patients with severe symptoms of PPH before resorting to intravenous PGI2 with its inherent risks and increased medical costs. However, before such treatment can be recommended, further multicenter clinical trials are needed to investigate the long-term effects of the drug.

Nagaya et al showed the possible benefits of beraprost in improving mean survival for participants with mild forms of PPH as compared to participants receiving conventional therapy (ie, with anticoagulants and calcium-channel blockers). Kaplan-Meier survival curves demonstrated that the 1-, 2-, and 3-year survival rates for the beraprost group were 96%, 86%, and 76%, respectively, as compared with 77%, 47%, and 44%, respectively, in the conventional treatment group (P < .05). However, the study was limited because it was retrospective and it studied participants with mainly mild PPH who naturally
might have longer survival rates than those with severe PPH.

**Endothelin Inhibitors**

Endothelin is a naturally occurring polypeptide substance with potent vasoconstrictor actions. Endotensin or endothelial contracting factor was discovered in 1985 by Hickey et al.94 who reported finding a potent, stable vasoconstricting substance produced by cultured endothelial cells. Subsequently, Yanagisawa et al.95 isolated and purified the substance from the supernatant of cultured porcine aortic and endothelial cells and then went on to prepare its cDNA. This substance was subsequently renamed endothelin.

Endothelins are the most potent vasoconstrictors known to date. Their chemical structure is closely related to that of certain neurotoxins (sarafotoxins) produced by scorpions and the burrowing asp (*Atractaspis engaddensis*).96 Endothelins have now been isolated in various cell lines from multiple organisms. They are considered autocoids/cytokines97 given their wide distribution, their expression during ontogeny and adult life, their primary role as intracellular factors, and the complexity of their biologic effects.

**Structure**

Endothelin is a polypeptide consisting of 21 amino acids. There are 3 closely related isoforms: endothelin-1, 2, and 3 (ET1, ET2, and ET3, respectively) that differ in a few of the amino acid constituents (Figure 25-4). The endothelin molecules have several conserved amino acids, including the last six-carboxyl (C)-terminal amino acids and 4 cysteine residues that form 2 intrachain disulfide bonds between residues 1 to 15 and 3 to 11. These residues might have biologic implications particularly in relation to three-dimensional structure and function. The main differences in the endothelin isopeptides reside in their N-terminal segments. ET1, the peptide originally identified by Yanagisawa and the major isofrom generated in blood vessels, is the most potent vasoconstrictor and appears to be of greatest significance in cardiovascular regulation.98,99

**Endothelin Receptors**

The receptors for endothelin have been isolated and their genes cloned.100-102 The receptors are classified on the basis of their affinity for the various endothelin isoforms (Table 25-3). So far, 2 receptors, ETA and ETB, are well characterized. The ETA receptor has 10 times more binding affinity for ET1 than ET3. The ETB receptor has nearly identical affinity for all 3 isopeptides. In humans, ETA and ETB receptors exhibit significant sequence similarity, having about 63% amino acid identity and a high degree of sequence conservation across mammalian species (about 90%).103 Functional data point to the presence of possible subtypes of the endothelin receptors on the basis of responses to various agonists and antagonists; but to date, molecular studies have not been able to support this subclassification.104,105

The endothelin receptors belong to the rhodopsin superfamily, which contains other members including the beta1-adrenergic, beta2-adrenergic, serotonin1, serotonin2, and vasopressin1 and vasopressin2 receptors. Members of this family are characterized by the presence of 7 hydrophobic transmembrane segments in the receptor that span the membrane, with their action mediated
Prostacyclins, Endothelin Inhibitors, and Phosphodiesterase-5 Inhibitors

by G proteins. The receptors appear to be glycoproteins, with the sugar moiety being a possible constituent for ligand interaction. The ETA receptors probably recognize the tertiary structure of both the N- and C-terminal segments, while the ETB receptors recognize predominantly the C-terminal parts, explaining the differences in affinities of the 2 receptors for the isoforms.

The differential distribution of the endothelin receptors in various tissues is responsible for the multiplicity of actions attributed to endothelin. The mRNA for the ETA receptor is expressed in the heart, aorta, and blood vessels of the brain but not in the endothelial cells, suggesting that vascular expression of this receptor occurs selectively in vascular smooth muscle cells. The ETA receptors can be upregulated by hypoxia, vasoconstriction, angiotensin II, and estrogens, whereas ETB receptors can be upregulated by C-type natriuretic factor and angiotensin II.

### Table 25-3. Endothelin Receptors and Their Antagonists

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>ETA</th>
<th>ETB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinity</td>
<td>ET1 &gt; ET2 &gt;&gt; ET3</td>
<td>ET1 = ET2 = ET3</td>
</tr>
<tr>
<td>Location</td>
<td>VSMC</td>
<td>EC, VSMC</td>
</tr>
<tr>
<td>Action</td>
<td>Vasoconstriction</td>
<td>Vasodilation, vasoconstriction</td>
</tr>
<tr>
<td>Upregulators</td>
<td>Hypoxia, cAMP</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Downregulators</td>
<td>Endothelins, angiotensin II</td>
<td>cAMP</td>
</tr>
<tr>
<td>Selective agonist</td>
<td>—</td>
<td>Endothelin-3</td>
</tr>
<tr>
<td>Selective antagonist</td>
<td>BQ-123</td>
<td>BQ-788</td>
</tr>
</tbody>
</table>

VSMC = vascular smooth muscle cells; EC = endothelial cells; ET = endothelin; cAMP = cyclic adenosine monophosphate

sodium-hydrogen antiporter. This increased intracellular pH can enhance the sensitivity of the myofilaments to calcium, thereby augmenting contraction even without changing the calcium concentration.120,121 It has also been noted that the increase in intracellular pH can, by itself, stimulate hypertrophic and mitogenic responses in different cells.122,123

The binding of endothelin to its receptor might also alter ion-channel permeability (such as the voltage-dependent L-type calcium channels via G proteins) and cause activation of other secondary messengers (eg, production of prostanoids by activating phospholipase A) or release of NO.124-127 NO has been shown to antagonize some of the effects of endothelin on vascular smooth muscle contraction, perhaps by decreasing release of endothelin from endothelial cells.128 In addition, experiments have revealed a competitive inhibition of ET1 binding to its receptors in cardiac membranes of rats by potassium channel–opening agents. These agents exert cardioprotective action seen in rats with experimentally induced myocardial infarction by suppressing cardiac arrhythmias that may be due, in part, to inhibition of the proarrhythmic effects of cardiac endothelin. It has been suggested that ET1 may close adenosine 5’-triphosphate (ATP)-sensitive potassium channels,129,131 thereby preventing efflux of potassium from the cell. Retention of potassium in these cells leads to depolarization of membranes and contraction of muscle.

**Endothelin Antagonists**

Much of our knowledge about the role of endothelin in various pathophysiologic states, as well as the effects of exogenous endothelin, has come from the research with endothelin antagonists.132,133 Several antagonists to endothelin have been discovered in recent years (Table 25-4). The original receptor antagonist was isolated from the cultured broth of *Streptomyces misakiensis*, but this had low potency in binding and functional assays. In the subsequent years, there has been the development of an array of peptide and endothelin-receptor antagonists. While some of the agents are receptor-specific for either the ETA or ETB subtypes, others are nonspecific. However, these compounds are hydrolyzed by peptidase in the systemic circulation and the gastrointestinal tract.134 Recently, research has been focused on the development of orally active nonpeptide antagonists. There are also other classes of drugs (Table 25-5) that either interfere with endothelin release or modify its metabolism.

**Use in Pulmonary Hypertension**

Since PH is characterized by endothelial injury, smooth muscle proliferation, and pulmonary vasoconstriction, ET1 has been implicated in the pathophysiology of both primary and secondary PH in view of its vasoconstrictor and mitogenic properties (Figure 25-1). The plasma concentration as well as the immunoreactivity and expression of m-RNA for ET1 in the endothelial cells of hypertrophied pulmonary vessels are increased in both primary and secondary PH.9,135,136 In the rat model of PH induced by exposure to a hypoxic environment, pulmonary ET1- and ETA- and ETB-receptor gene expression is upregulated.137 The clearance of ET1 was thought to be decreased in participants with PPH as compared to controls.138 However, a study in which blood was sampled directly from the pulmonary artery has suggested an absence of a transpulmonary gradient for ET1. In addition, experiments have revealed a competitive inhibition of ET1 binding to its receptors in cardiac membranes of rats by potassium channel–opening agents. These agents exert cardioprotective action seen in rats with experimentally induced myocardial infarction by suppressing cardiac arrhythmias that may be due, in part, to inhibition of the proarrhythmic effects of cardiac endothelin. It has been suggested that ET1 may close adenosine 5’-triphosphate (ATP)-sensitive potassium channels, thereby preventing efflux of potassium from the cell. Retention of potassium in these cells leads to depolarization of membranes and contraction of muscle.

**Figure 25-5. Intracellular signal transduction pathways activated by endothelins (ETs).** Activated endothelin receptor stimulates phospholipase C (PLC) and phospholipase A2 (PLA2). Activated endothelin receptor also stimulates voltage-dependent calcium channels (VDC) and probably receptor-operated calcium channel (ROC). Inositol triphosphate (IP3) elicits release of calcium ion from caffeine-sensitive calcium store. Protein kinase C (PKC) activated by diacylglycerol (DG) sensitizes contractile apparatus. Elevated intracellular free calcium ion induces contraction. Cyclooxygenase products [prostacyclin (PGI2), prostaglandin E (PGE2 thromboxane A2 (TXA2)) modify the contraction. IP2 = inositol biphosphate.

been shown to prevent both hypoxia-induced PH and pulmonary artery remodeling. In another study in rats, combined treatment with an oral ETA antagonist and an oral prostacyclin analog was more effective in ameliorating PH and right ventricular hypertrophy than either drug alone. The selective ETA antagonist LU 135252 and nonselective antagonist BSF 420627 were both shown to reduce monocrotaline-induced PH in rats. Clinical studies using endothelin antagonists in participants with PH have been carried out and some are ongoing. It was shown that short-term ETA-receptor antagonism significantly improves hemodynamics in participants with severe chronic PAH.

The FDA has approved bosentan (Tracleer) as the first oral drug for the treatment of PH. The efficacy of bosentan was based on 2 placebo-controlled studies in participants with symptomatic, severe (WHO class III-IV) PPH or PH due to scleroderma or other connective tissue diseases or autoimmune diseases. Bosentan was added to current therapy that included vasodilators, anticoagulants, diuretics, digoxin, or supplemental oxygen. The drug was shown to improve exercise ability and decrease the rate of clinical worsening. The starting dose was 62.5 mg twice daily for 4 weeks and then increased to 125 mg twice daily. Higher doses are not recommended due to the potential for liver toxicity. Dose adjustment is not required in patients with renal impairment. The Bosentan Trial of Endothelin Antagonist Therapy (Breathe-1) enrolled 213 participants with PAH, in functional class III and IV, in a double-blind, randomized fashion to receive either the placebo or 62.5 mg of bosentan twice a day for 4 weeks followed by either 125 mg or 250 mg twice a day for at least 12 weeks.

The primary endpoint of degree change in exercise capacity was met at 16 weeks resulting in an improvement in 6-minute walk test distance of 44 m. Bosentan improved the secondary endpoint of Borg dyspnea score by -0.6. The other secondary endpoints of WHO functional class resulted in a 16% improvement at 16 weeks, and time to clinical worsening favored bosentan treatment compared to the placebo group (P = .002). In order to determine if bosentan is beneficial to patients without advanced disease, patients in functional class II were enrolled in the EARLY study. One hundred sixty eight patients were randomized to the placebo with functional class II disease and with a 6-minute walk test distance of < 80% predicted or < 500 m, a Borg dyspnea index ≥2, and a PVR ≥320 dyne/sec/cm$^5$ or greater.

The study revealed a treatment effect of -22.6% improvement in PVR compared to the placebo (P < .0001). Improvement in mean 6-minute walk test distance did not reach statistical significance.

The second oral endothelin receptor antagonist approved by the FDA for PAH, ambrisentan (Letairis), is a more selective ET-A receptor antagonist with a 100:1 selectivity to the receptor compared to 20:1 for bosentan. It is The Ambrisentan in Pulmonary Arterial Hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy study 1 (ARIES-1) enrolled 202 patients with PAH to the placebo versus 5 or 10 mg ambrisentan. This 12-week study primary endpoint of 6-minute walk test distance was achieved with a mean placebo corrected improvement of 31 m (P = .08) for the
5 mg dose and 51 m ($P < .001$) for the 10 mg dose. WHO functional class improved by 3% and 16.4% respectively compared to the placebo ($P = .036$). Borg dyspnea score improved by -0.6 in the combined treatment groups ($P = .017$). Brain natriuretic peptide levels in the placebo groups increased by 9% at 12 weeks but were decreased by 30% and 45% respectively with the 5 mg and 10 mg treatment doses ($P < .003$).

The ARIES-2 trial ran concurrent to the ARIES-1 trial evaluating 2.5 and 5 mg dosing of ambrisentan. The primary endpoint was 6-minute walk test distance at 12 weeks with a placebo-corrected improvement in distance by 32 m ($P = .022$) and 59 m ($P < .001$) for the 2.5 mg and 5 mg doses respectively. Time to clinical worsening was improved at 12 weeks ($P < .001$), quality of life as assessed by the Short Form-36 score improved ($P = .005$), Borg dyspnea score for the combined treatment group improved by -1.1 ($P = .019$), and brain natriuretic peptide levels were improved by 29% and 30% respectively, with a 13% increase in the placebo group ($P < .003$). Even though ambrisentan is in the same pharmacologic class, the elevations of transaminases seen with bosentan are not seen with ambrisentan. Nevertheless, the FDA requires monthly monitoring of transaminase levels in treated patients. Both bosentan and ambrisentan are not available in pharmacies; they are dispensed via a direct distribution program by the manufacturers through special pharmacies.

Sitaxsentan has the highest selectivity for the ET-A receptor with a 6,500:1 affinity. The Sitaxsentan to Relieve Impaired Exercise Trial-1 (STRIDE-1) measured peak VO$_2$ as the primary endpoint at 12 weeks. Sitaxsentan given either 100 mg or 300 mg orally once daily for 12 weeks was compared with the placebo in 178 participants. Results from the study did reveal a statistical improvement in this parameter compared with the placebo by a 3.1% increase ($P < .01$) in the 300 mg group but did not prove statistically significant in 100 mg group. In addition, other cardiopulmonary endpoints in either group, including $O_2$ at anaerobic threshold or $V_{\text{E}}/V_{\text{CO}_2}$ score at anaerobic threshold, were met. Secondary endpoints of 6-minute walk test distance were statistically improved for both treatment groups by 35 m and 33 m respectively (each $P < .01$). Functional class and hemodynamic parameters, including cardiac index and PVR, improved compared with the placebo (each $P < .02$ at both doses). Unfortunately, the 300 mg dose revealed significant elevations in transaminases in 10% of participants compared with 3% in the 100 mg group and 0% in placebo-treated participants.

Due to these findings, the STRIDE-2 study compared 50 mg and 100 mg dosing versus the placebo in 247 participants followed for 18 weeks. An open-label arm was also included for observation of participants treated with bosentan. The primary endpoint of 6 minute walk test distance was met with a placebo-corrected distance improvement of 24.2 m ($P = .07$); 31.4 m ($P = .03$); and 29.5 m ($P = .05$) for the 50 mg, 100 mg, and open-label treatment groups respectively. WHO functional class also improved in the sitaxsentan group compared with the placebo in the 100 mg group only. Because of recent findings of fatal hepatotoxicity, the drug has been withdrawn.

**Adverse Effects**

Bosentan was the first dual ETA/B receptor antagonist to undergo phase 2/3 testing for indications that require long-term administration, such as systemic hypertension and heart failure. In these studies, a number of cases of asymptomatic transaminase elevation were observed to occur—a process that appeared to be dose-dependent. These findings suggested that bosentan administration could cause liver injury. No liver biopsies were performed in these participants, and the transaminase elevations resolved shortly after the discontinuation of bosentan. Subsequent studies have shown that bosentan induces liver injury through inhibition of the canalicular bile salt export pump, and that the cholestatic potency of bosentan is increased by the concomitant administration of glyburide, a known inhibitor of the bile salt export pump. Inhibition of this pump causes intracellular accumulation of cytoxic bile salts and bile salt–induced liver cell damage.

Additionally, the ENABLE trials showed an increased rate of fluid retention in participants receiving bosentan for the treatment of heart failure. Post marketing experience with ambrisentan suggests significant fluid retention with patients receiving therapy; however, the incidence of transaminase abnormalities with ambrisentan compared to bosentan appears to be significantly lower.

**Phosphodiesterase 5 Inhibitors**

Sildenafil is currently approved for the treatment of WHO class II and III patients. The Sildenafil Use in Pulmonary Arterial Hypertension trial (SUPER-1) showed improvement in 6 minute walk test distances in the 20, 40, and 80 mg three times daily dosing of sildenafil compared with the placebo as early as 4 weeks and extending to 12 weeks. No significant improvements were noted beyond the 20 mg dose in the short-term trial. Therefore, it is recommended that only the lower dose be used in clinical practice. An uncontrolled extension trial showed Kaplan Meier survival to be 94% at 1 year. Recently the drug was shown to be of benefit in patients with advanced idiopathic pulmonary fibrosis.

Tadalafil is the second PDE inhibitor that has recently been approved by the FDA. The results of the Pulmo-
Combination Therapies

Given the multiple pathophysiologic targets in PAH, combining therapies that target different disease pathways (Figure 25-1) is logical and may improve patient outcomes. Several randomized trials and case series support the use of combination therapy. However, additional studies are needed before definitive combination strategies are defined.

Emerging Therapies

None of the available treatments for PAH have major effects on survival. Among the new agents that promise treatment of PAH are rho-kinase inhibitors and soluble guanylate cyclase stimulators (eg, cinaciguat). Although these new classes of agents have beneficial effects, they are not selective in their actions on the pulmonary beds and can produce systemic hypotension. It is hoped that new methods of administration, such as the delivery of nanoparticles by inhalation, will allow for more selective treatment for the pulmonary vascular beds.

Vasoactive intestinal peptide (VIP) is an endogenous polypeptide that is part of the glucagon-secretion neurohormonal axis. VIP is a potent systemic and pulmonary vascular dilator, in addition to its ability to control salt and water balance. Immunohistochemistry and radioimmunoassay of lung tissue in patients with PAH reveal low levels of VIP. Aviptadil is being investigated as an inhalation agent in patients with PAH.

Various treatments to enhance NO production or delivery are under investigation, as well as innovative anti-inflammatory approaches.

See also Chapter 37, Cardiovascular Drugs in Development.

Conclusion

Epoprostenol is now available in the United States and is approved for use in patients with PPH. Although this agent has been used with limited success in other areas, there is a great amount of work to be done with its more stable analogues. Inhaled Iloprost is currently available for the treatment of PAH as is treprostinil, a prostacyclin analogue approved for intravenous, inhaled and subcutaneous use in PAH. Perhaps one of these other agents will provide an oral therapy for PPH, a valuable treatment for severe congestive heart failure, a palliative treatment for inoperable peripheral vascular disease or intractable Raynaud’s phenomenon, or as a useful adjunct to standard therapy of acute myocardial infarction.

Endothelin, a potent vasoconstrictor and mitogenic agent, plays a role in multiple disease entities involving various organ systems in both experimental animals and human beings. In the few years since endothelin’s discovery, much progress has been made in the development of specific receptor antagonists. Endothelin antagonists have helped to elucidate the role of endothelin in normal physiologic processes and in the pathogenesis of several cardiovascular conditions. Bosentan and ambrisentan are now approved for use in PH. Efforts are now underway to customize more specific antagonists and, by utilizing the known structure of endothelin, to modify key amino acids and thus create novel agents.

Another innovative approach is to control endothelin action by interfering with the endothelin-converting enzyme essential for the production of the active compounds. There are still ongoing questions regarding the efficacy and safety of selective versus nonselective receptor blockers. Hepatotoxicity has been observed with some compounds. Additional research should help resolve
safety issues so as to ultimately optimize the clinical benefits of endothelin antagonism.

It has also been shown that endothelial NO synthase levels and NO metabolites are diminished in the pulmonary arteries of patients with PAH. The use of PDE-5 inhibitors as monotherapy or in combination with other classes of agents has provided symptomatic benefit in patients.

An evidence-based treatment paradigm for patients with PAH is shown in Figure 25-6.

Note: References for this chapter can be found here: www.cvpt3.com
Dopamine, the endogenous precursor of both norepinephrine and epinephrine, is used predominantly in intensive care unit settings as an intravenous pharmacotherapy for patients with ventricular dysfunction and various forms of shock. Dopamine acts at low doses by stimulating specific peripheral dopaminergic receptors, which are classified into 2 major subtypes (Figure 26-1): (1) DA1 receptors, which, when stimulated, mediate arterial vasodilation in the coronary, renal, cerebral, and mesenteric arteries as well as natriuresis and diuresis; and (2) DA2 receptors, which are located in presynaptic areas and, when stimulated, mediate the inhibition of norepinephrine release. At increasingly higher doses, dopamine, in addition, selectively activates the beta1-adrenergic receptors, leading to both a positive inotropic and a chronotropic effect on the heart (see Chapter 13, Inotropic Agents). Next, the alpha1- and alpha2-adrenergic receptors are activated, leading to an increase in systemic vascular resistance and blood pressure due to vasoconstriction (Table 26-1).

For a number of years, there has been interest in developing new pharmacologic agents that share some of the qualities of dopamine but have their own unique advantages. Each is an agonist at one or both of the peripheral dopaminergic receptors (Table 26-2).

Fenoldopam is an intravenous dopamine agonist that has specificity for the D1 receptor and had been used in the treatment of congestive heart failure (CHF); it is approved for use in hypertensive emergencies. The pharmacologic action of fenoldopam is to dilate selected arteries, and it has the advantage of maintaining renal perfusion, despite reducing blood pressure. Problems with the drug’s oral bioavailability have limited its use to parenteral treatment of severe hypertension.

In this chapter, the clinical pharmacology of the dopaminergic agonists are reviewed, and the peripheral dopaminergic receptors are discussed.

Dopaminergic Receptors

Molecular pharmacologists have divided the dopaminergic receptors into various subtypes. The peripheral dopaminergic receptors, D1 and D2, have been the target...
of various cardiovascular pharmacotherapies that do not cross the blood–brain barrier and therefore do not affect the central nervous system’s dopaminergic receptors. A number of distinct dopamine receptors in the central nervous system have been found. They have been broken down into 2 groups: D₁-like and D₂-like. The D₁-like group includes the specific receptors D₁α, D₁β, and D₂. These are G protein–linked receptors that stimulate adenylate cyclase, causing an increase in intracellular cAMP. The D₂-like group includes D₂, D₃, and D₄. These are also G protein–linked receptors, but they inhibit adenylate cyclase and thus also the formation of cAMP.

The D₃- and D₄-like receptors are all distinct; however, they are currently grouped on the basis of their similarities. The peripheral dopamine receptors have a different nomenclature and are classified into 2 distinct families—D₁ and D₂ receptors. Studies have found the D₁ receptors to be similar to the D₁-like central receptors and the D₂ receptors to be similar to the D₂-like central receptors. However, additional study is required before a firm conclusion can be made regarding the significance of these similarities. The remainder of this chapter concentrates solely on the peripheral dopamine receptors and their activation.
DA1 receptors are located postsynaptically on the smooth muscle of the renal, coronary, cerebral, and mesenteric arteries (Table 26-3). Their activation results in vasodilation through an increase in cyclic adenosine monophosphate (cAMP)–dependent protein kinase A activity. This causes relaxation of smooth muscle.1,5 This vasodilatory effect tends to be strongest in the renal arteries, where blood flow can be increased up to 35% in normal arteries and up to 77% in patients with unilateral renal disease (dopamine doses were 1 mg/kg/min).7,8 Evidence points to additional DA1 receptors located in the tubule of the kidney, which seem to be directly responsible for the natriuresis that is also seen with dopamine administration.8

Although their exact role in renal tubular physiology has not been established, the DA1 receptors have been shown to regulate both the Na+/K+-ATPase pump; however, Lee has recently pointed out the difficulty of dissecting the natriuretic response due to increased blood flow from the natriuretic response secondary to Na+/K+-ATPase inhibition.8 While the exact mechanism of DA1-receptor activation in the kidney remains uncertain, natriuresis associated with dopamine infusion is quite clear. Abnormalities in the renal DA1 receptors may, in fact, contribute to the etiology of some cases of systemic hypertension.14,15 Based on the combined effects of activated DA1 receptors, research on selective DA1 agonists has focused on their use as a treatment for systemic hypertension and for hypertensive crises, particularly in patients with impaired renal function. The advantage of this pharmacologic approach over currently available antihypertensive medications would be the maintenance of renal perfusion combined with natriuretic and diuretic effects. In addition, some research on DA1 agonists has focused on the possibility of increased myocardial blood flow with this treatment.16 Since currently available vasodilators often exhibit coronary steal, a DA1 agonist might correct this problem. Finally, the potential use of DA1 agonists for CHF is attractive based on the reduction in afterload caused by their selective vasodilatory ability.

Peripheral DA2 receptors are located on presynaptic adrenergic nerve terminals and on sympathetic ganglia; when activated, they inhibit norepinephrine release.17-20 They are located on the adrenal cortex, where they inhibit angiotensin II–mediated aldosterone secretion.18,19 DA2 receptors are also located in the pituitary gland; when stimulated, they can inhibit prolactin release. The DA2 receptors in the emetic center of the medulla, when stimulated, can induce nausea and vomiting.17 DA2 receptors are thought to be present in the kidney, although their function is unknown.20 The consequence of DA2-receptor activation has been experimentally shown to be a reduction in cAMP.6 The combined effects of inhibiting both norepinephrine-induced vasoconstriction and aldosterone release with selective DA2 agonists is an attractive approach for the treatment of both hypertension and CHF. Presynaptically acting dopaminergic agents are among the few types of adrenergic drugs that have not been thoroughly researched for the treatment of hypertension.21 With respect to their use in HF, DA2 agonists would treat the associated edema by inhibiting aldosterone secretion and could reduce afterload through the inhibition of norepinephrine release.

**Dopamine-Receptor Agonists**

**Dopamine**

Dopamine, the parent agonist, is given intravenously at varying doses to achieve different hemodynamic effects.

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Table 26-3. Dopamine Receptors Outside and Inside the Blood–Brain Barrier

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Location</th>
<th>Physiologic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA1</td>
<td>Kidney</td>
<td>Renal vasodilation, diuresis, natriuresis, direct inhibition of renin secretion</td>
</tr>
<tr>
<td></td>
<td>Select arterial blood vessels</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA2</td>
<td>Peripheral adrenergic nerve terminals</td>
<td>Inhibition of norepinephrine release</td>
</tr>
<tr>
<td></td>
<td>Sympathetic ganglia</td>
<td>Inhibition of transmission</td>
</tr>
<tr>
<td></td>
<td>Adrenal cortex</td>
<td>Inhibition of aldosterone secretion</td>
</tr>
<tr>
<td></td>
<td>Pituitary gland</td>
<td>Inhibition of prolactin release</td>
</tr>
<tr>
<td></td>
<td>Area postrema of the CNS</td>
<td>Emesis</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

In the low-dose range (2 to 5 μg/kg/min), dopamine activates only D_{1a} and D_{1b} receptors.\textsuperscript{22} It is used at this dose to improve renal perfusion during acute low-cardiac-output situations such as cardiogenic, septic, and hypovolemic shock. Diuresis and natriuresis are also observed at this dose.\textsuperscript{22} At a somewhat higher dose (5 to 10 μg/kg/min), dopamine also activates \beta_1 receptors for a chronotropic and inotropic effect. Heart rate may actually increase, decrease, or stay the same, depending on the balance of \beta_1 or D_{1a} receptors found in a particular person.\textsuperscript{17}

A higher number of \beta_1 receptors causes an increase in heart rate, while a higher number of D_{1a} receptors causes a decrease in heart rate because of the inhibition of norepinephrine release. At this dose level, dopamine has been used to treat HF, often in combination with vasodilators such as nitroprusside or nitroglycerin.\textsuperscript{22} In addition, if used with dobutamine, a \beta_1 agonist, the increase in cardiac output can be magnified.\textsuperscript{17} Adverse effects with this dose of dopamine may include arrhythmia and/or tachycardia.\textsuperscript{17} At the highest levels of dopamine infusion (10 to 20 μg/kg/min), both \alpha_1 and \alpha_2 vasoconstrictive receptors are activated. Blood pressure may now increase, along with systemic vascular resistance. Because these peripheral effects occur at highly variable doses in different individuals, renal perfusion and blood pressure must be carefully watched during any dopamine infusion. In addition, potential adverse effects of dopamine may occur at these high doses and can include the occurrence of arrhythmias, myocardial ischemia, and a reduction in blood flow to the limbs.\textsuperscript{22} Although these effects are rare, high-dose dopamine must be used with caution and in closely monitored situations.

The use of low-dose dopamine as a renal protective agent during acute conditions that place patients at risk of impaired renal function is no longer standard practice. During recent years, a number of investigators questioned the use of “renal dose” dopamine, suggesting that low-dose dopamine does not have the renoprotective effects previously thought.\textsuperscript{23} In a multicenter, randomized, double-blind, placebo-controlled trial of 328 critically ill patients, Bellomo et al\textsuperscript{24} looked at the effects of low-dose dopamine on renal function. Outcome measures included an increase in serum creatinine from baseline, the need for dialysis, duration of stay in hospital and/or an intensive care unit, and death. These investigators found no significant protection from renal dysfunction conferred by dopamine. In another double-blind randomized controlled trial of 126 patients, Lassnigg et al\textsuperscript{25} looked at the renoprotective effects of low-dose dopamine after cardiac surgery. They found no significant difference in the concentration of serum creatinine or the need for dialysis between the groups that received low-dose dopamine or the placebo.

Fenoldopam

Fenoldopam is well known as a potent selective D_{1a} agonist. There is also weak evidence that fenoldopam has mild alpha-antagonist activity at the alpha_2 receptor site.\textsuperscript{4-25a} Unlike dopamine, fenoldopam has no significant effects on alpha_1 beta-adrenergic or D_{1a} receptors. It acts as a vasodilator, being up to 6 to 9 times as potent as dopamine itself, particularly in the renal bed (Figure 26-2). It is poorly soluble in lipids, thus does not penetrate the blood–brain barrier and has no central nervous system effects. Fenoldopam is available in an oral formulation; however, its bioavailability is inconsistent (10% to 35%) and poor when it is taken with food. Metabolism is rapid (half-life of about 10 minutes); thus, frequent administration is required for sustained effect.\textsuperscript{26-28} For these reasons, fenoldopam is only used via the intravenous route and has been investigated primarily in the treatment of both hypertensive emergencies and urgencies.

Hypertensive emergency is a condition that affects 2.4% to 5.2% of hypertensive patients in the United States.\textsuperscript{29,29a} This condition—defined as a diastolic blood
pressure > 115 mm Hg and/or end-organ damage such as encephalopathy, intracranial hemorrhage, pulmonary edema, dissecting aortic aneurysm, or acute myocardial infarction—requires immediate care. Historically, sodium nitroprusside has been the preferred agent to treat these patients. It is a potent venous and arterial dilator, with a rapid onset of action, a short half-life, a low incidence of tolerance, and a high predictability of response. However, sodium nitroprusside has some disadvantages, including thiocyanate toxicity, a possible adverse effect on renal function, and a possible coronary steal due to its potent vasodilation of both arteries and veins. Alternative intravenous agents have also been used to treat hypertensive emergency, including labetalol, esmolol, clevidipine, nicardipine, and nitroglycerin. Intravenous fenoldopam therapy offers an alternative with potentially fewer adverse events.25-40 At doses that reduce the blood pressure into target ranges, little overshoot hypotension is observed.

Fenoldopam has been investigated and its effects reported on in the literature for more than 25 years. Among the reported clinical trials, there are data from over 1,000 patients who have been treated with fenoldopam for hypertension. Some of these studies have been noncomparative. Of those that are comparative, most compare fenoldopam to sodium nitroprusside. Investigations of fenoldopam in hypertensive adults have demonstrated a clear dose-response relationship in lowering both systolic and diastolic blood pressure, along with a dose-related reflex tachycardia.25,37-40 At doses that reduce the blood pressure into target ranges, little overshoot hypotension is observed.

Investigators from the Fenoldopam Study Group40 enrolled 107 patients in a randomized double-blind study evaluating 4 different fixed doses of fenoldopam for 24 hours in patients with hypertensive emergency, defined as diastolic blood pressure > 120 mm Hg and/or target-organ damage including new renal dysfunction, hematuria, acute CHF, myocardial ischemia, or grade III-IV retinopathy. Of these patients, 94 received 0.01, 0.03, 0.1, or 0.3 μg/kg/min of fenoldopam for 24 hours. The mean time to achieve a 20-mm Hg reduction in diastolic blood pressure was 132.8 ± 15.1, 125 ± 17.0, 89.3 ± 12.6, and 55.2 ± 12.8 minutes respectively, illustrating a dose-dependent effect in lowering of blood pressure. At the highest dose (0.3 μg/kg/min), heart rate increased by an average of 11 beats per minute. It was reported that 2 patients in the study developed hypotension, although the dose in these 2 patients was not specified.

In comparison with nitroprusside, fenoldopam has been shown to have equal efficacy in reducing blood pressure and to produce fewer adverse effects. In a randomized prospective trial of fenoldopam versus sodium nitroprusside in hypertensive adults with diastolic blood pressure > 120 mm Hg, Panecek et al enrolled 183 patients. The dose of each medication was titrated to achieve a diastolic blood pressure of 95 to 110 mm Hg, or a maximum reduction of 40 mm Hg, and patients remained in the study for at least 6 hours.

Results of the study showed equivalent antihypertensive efficacy with similar adverse events. Ten patients were withdrawn from the study in the fenoldopam group, 5 for hypotension, and 5 others for flushing, hypokalemia, tachycardia, and a gastrointestinal bleed. Eleven patients were withdrawn from the nitroprusside group: 10 secondary to hypotension and one with palpitations and dizziness. In a smaller study of 33 patients, Pilmer et al found similar results: equal efficacy for the treatment of severe systemic hypertension with fenoldopam and sodium nitroprusside, with no difference in rate or severity of adverse events.25 There is a limited experience comparing the efficacy or safety of fenoldopam to agents other than nitroprusside for the treatment of hypertension.

The natriuretic and diuretic effects of fenoldopam in hypertensive patients have been studied in smaller trials, including both noncomparative and comparative studies with sodium nitroprusside. Murphy et al, in a study of 10 patients with hypertension, found that intravenous fenoldopam was associated with a 46% increase in urinary flow rate and a 202% increase in sodium excretion. GFR increased by 6%. Shusterman et al, in a study of 22 patients, 11 on fenoldopam and 11 on nitroprusside, showed, in addition to natriuresis and diuresis, a significant increase in creatinine clearance in the fenoldopam group.46 These studies point to additional effects of fenoldopam and also illustrate the advantage of fenoldopam over nitroprusside in treating hypertension in patients with chronic renal insufficiency or CHF who would benefit from natriuresis and diuresis.

The adverse-effect profile of fenoldopam is similar to that of nitroprusside, including reflex tachycardia and a more moderate risk of hypotension. Elliot et al point out that intraocular pressure increases with fenoldopam but not with nitroprusside; thus it is important to be aware that fenoldopam is contraindicated in patients with glaucoma.43,44

Fenoldopam is administered by constant intravenous infusion for up to 48 hours, beginning with a dose of 0.1 μg/kg/min. Doses are increased by 0.05 to 0.10 μg/kg/min every 10 to 20 minutes as necessary, up to 1.5 μg/kg/min.

Although most clinical experience with fenoldopam has focused on its approved use for hypertensive emergencies, the drug has been investigated for other possible indications. Fenoldopam may be useful as an adjunct to fluids in preventing radiocontrast nephropathy in patients with chronic renal insufficiency.45,46 Selective
intrarenal administration of fenoldopam may provide even greater protection against radiocontrast injury.47,48 In high-risk patients undergoing cardiac surgery or surgery for aortic dissection, the use of fenoldopam may preserve renal function.49-54

Bromocriptine and Other D₂-Selective Agonists

Selective D₂-receptor agonists represent another class of drugs that have been experimented with for the treatment of hypertension.55 Traditionally, patients with hypertension are characterized by a relative excess of plasma norepinephrine. Thus, a D₂-selective agonist would reduce plasma norepinephrine and consequently vasodilate peripheral arteries and reduce blood pressure. Included in this class of drugs are, among others, bromocriptine, carmoxirole, ropinirole, quinpirole, co-dergocrine, and cabergoline. In general, these drugs have also been investigated for use in treating Parkinson's disease and are known to cross the blood–brain barrier. As a result, while the majority of drugs in this class may have beneficial effects in hypertension, they may also be associated with severe adverse effects from the activation of central dopaminergic receptors. Quinn et al found that bromocriptine lowers blood pressure in normal and hypertensive individuals.56 However, Walden et al, using similar doses to those in the Quinn study, found that bromocriptine was not effective in lowering blood pressure in hypertensive patients.57 Lahlou et al found that bromocriptine induced tachycardia via central D₂ stimulation.58 Other studies reported associations between bromocriptine and loss of vision and between bromocriptine and angiopathy. One report found that bromocriptine, used at low dose to suppress lactation, induced myocardial infarction;60 however, other studies showed the drug was both efficacious and safe in diabetes mellitus,60 and is approved for this indication.60a-c

A number of studies found that both the D₂-receptor agonists carmoxirole and ropinirole have potent antihypertensive effects; however, inadequate numbers of studies prevent conclusions from being drawn regarding their safety and efficacy.61 These drugs also cross the blood–brain barrier to an extent. However, they can stimulate 2 central areas that lie outside the blood–brain barrier (the pituitary gland and the chemoreceptor trigger zone in the area postrema) inducing both prolactin release and nausea and vomiting.

In summary, D₂ selective agonists represent a class of drugs that have potential as antihypertensive agents. Since these agents can cross the blood–brain barrier, peripheral D₂ agonists that do not affect the central nervous system need to be developed.

Conclusion

Nonselective and selective dopaminergic agonists are available for the treatment of hypertensive emergencies and CHF. In addition to intravenous dopamine, a nonselective agonist used for treatment of ventricular dysfunction and for the preservation of renal blood flow in low-output states, newer agents have and continue to be evaluated in clinical trials.

Fenoldopam is a selective D₁ agonist that is used to treat patients with hypertensive emergency. Because of bioavailability problems with the oral formulation, only the intravenous form is in use. Fenoldopam was FDA-approved for the treatment of hypertensive emergencies and has demonstrated efficacy for these conditions.

Note: References for this chapter can be found here: www.cvpct3.com
In 1981, de Bold and colleagues\(^1\) infused a homogenized rat extract that triggered a potent natriuresis, diuresis and a small kaliuresis, thus supporting prior theories suggesting that the heart is more than merely a mechanical pump.\(^2\) This result paved the way for the notion that the heart is also an endocrine organ. Subsequent fractionation and bioassay of rat atrial homogenates confirmed that this natriuretic bioactivity resides in the atrial granules.\(^3\)

On the heels of these original observations, several groups isolated atrial natriuretic peptide in a pure form and determined its amino acid sequence. Shortly thereafter, a series of related peptides were isolated, further suggesting the endocrine capabilities of the heart. In 1988 Sudoh and associates discovered a peptide in porcine brain with structural homology and biological properties similar to those of atrial natriuretic peptide.\(^4\) Although subsequent studies showed it to be secreted predominantly by ventricular tissue in the heart,\(^5\) the peptide retained the name brain natriuretic peptide (BNP).

Soon after the discovery of BNP, C-type natriuretic peptide also was isolated from porcine brain.\(^6\) Although C-type natriuretic peptide production occurs mostly in the central nervous system and vascular endothelium, its structural homology and similarities in metabolism with the other natriuretic peptides led to its inclusion in the same family of peptide hormones. As a result of these findings, there developed an explosive interest in cardiac peptide research, which has led to the heart's being recognized as a true endocrine organ.

This chapter reviews the clinical pharmacology of nesiritide, a human form of BNP made by recombinant DNA technology, which is available for intravenous use in patients for the management of acute congestive heart failure (CHF) associated with dyspnea.

**Pharmacology of Nesiritide**

The pharmacologic effects of nesiritide are mediated via the same receptor that mediates the effects of atrial natriuretic peptide, the guanylyl cyclase A (GC-A).\(^7\) It binds to the GC-A receptors on the cell surface of vascular smooth muscle and endothelial cells. This receptor binding triggers intracellular activation of the secondary messenger cyclic guanosine monophosphate (cGMP), which in turn causes decreased intracellular concentrations of calcium, with subsequent relaxation of smooth muscle and vasodilation.\(^7\)\(^9\)

In addition, nesiritide appears to be act in 4 principal ways to oppose the activity of the renin-angiotensin-aldosterone axis: (1) it causes vasorelaxation; (2) it blocks aldosterone secretion by the adrenal cortex; (3) it inhibits kidney renin secretion; and (4) it opposes the sodium-retaining action of aldosterone. In addition, antagonism of antiuretic hormone, water intake, and salt intake mediated in the central nervous system amplify the effects of BNP in reducing plasma volume (Figure 27-1; Table 27-1).

**Natriuretic and Diuretic Effects**

BNP promotes natriuresis and diuresis via a series of mechanisms that are not mutually exclusive of each other, including an increase in glomerular filtration rate that occurs as a consequence of afferent arteriolar vasodilation and efferent arteriolar vasoconstriction and enhanced sodium delivery to the medullary collection duct; by inhibition of sodium reabsorption by medullary collecting ducts secondary to reduction in the effects of aldosterone and/or angiotensin II; by redistribution of blood flow to deeper nephrons with less sodium reabsorptive capacity; and by decreased secretion and/or effect of antidiuretic hormone.
On a more primary level, BNP may be an endogenous antagonist to angiotensin II because their binding sites overlap in the brain, kidney, and adrenal cortex. An additional intriguing action of BNP is its ability to induce natriuresis without concomitant kaliuresis. When increased potassium excretion occurs, it seems to correlate with an enhanced tubular flow rate. BNP inhibits renin release by secondary effects at the macula densa or, less likely, via a direct effect on the juxtaglomerular cells. Natriuretic peptides may also change the production of adiponectin in patients with heart failure (HF).

**Hemodynamic Effects**

The hemodynamic effects of nesiritide are characterized by venous and arterial dilation, resulting in decreased preload and afterload. A dose of 0.015 μg/kg/min causes a reduction in pulmonary capillary wedge pressure (PCWP) by an average of 6 mmHg, right atrial pressure (RAP) by an average of 3 mmHg, mean pulmonary pressure by an average of 5.5 mmHg, and systemic vascular resistance (SVR) by an average of 150 dyn.sec.cm⁻⁵. Although nesiritide has no direct positive inotropic effect, cardiac index has been shown to increase by an average of 0.2 L/min/m² secondary to a dose-dependent afterload reduction. Following discontinuation of nesiritide, PCWP returns to within 10% of baseline in 2 hours, but no rebound increase to levels above baseline state are observed.

**Pharmacokinetics**

In patients with HF, nesiritide administered intravenously demonstrated a biphasic disposition from the plasma. The mean terminal half-life of nesiritide is approximately 18 minutes and mean volume of distribution at steady state is estimated to be 0.19 L/kg. At steady state, plasma BNP levels increase from baseline endogenous levels by approximately 3-6 fold with nesiritide infusion doses ranging from 0.01 to 0.03 μg/kg/min.

Human BNP is cleared mainly via binding to cell surface clearance receptors with subsequent cellular internalization and lysosomal proteolysis. Some are also cleared by proteolytic cleavage of the peptide by endoproteases or by renal filtration. The average total body clearance is approximately 9.2 ml/min/kg. Clearance of nesiritide is not affected by age, gender, race/ethnicity, baseline endogenous BNP level, severity of HF, or concomitant administration of angiotensin-converting enzyme inhibitors.

Attempts have been made to use orally active neutral endopeptidase inhibitors to potentiate the effects of natriuretic peptides in the treatment of hypertension and HF. In addition, orally active dual inhibitors have been developed for the same indications. Development of these drugs was slowed because of toxicity (increased risk of angioedema) and lack of additional efficacy compared to angiotensin-converting enzyme inhibitors used alone.

**Pharmacodynamics**

With the recommended dose of nesiritide of 2 μg/kg as an intravenous bolus followed by a 0.01 μg/kg/min infusion, 60% of the 3-hour effect (dose of nesiritide is titrated every 3 hours, see Dosing and Administration later in this chapter), PCWP reduction is achieved within 15 minutes and reaches 95% of the 3-hour effect within an hour. Approximately 70% of the 3-hour effect on systolic blood pressure reduction is reached within 15 minutes. The pharmacodynamic half-life of the onset and offset of the hemodynamic effect of nesiritide is longer than what the pharmacokinetic half-life would predict.

**Clinical Trials in Heart Failure**

Decompensated HF represents an interaction of hormonal and anatomical responses including the overactivation of the sympathetic nervous system (elevation of epinephrine and norepinephrine levels and downregulation of beta receptors), leading to vasoconstriction, a decrease in myocardial contractility, and overactivation of the renin-angiotensin-aldosterone system, leading to vasoconstriction and retention of salt and water. Elevation of circulating BNP is another biologic marker of acute HF decompensation.

In HF, the increase in cardiac volume and pressure overload stimulates the production of natriuretic peptides to enhance diuresis and to produce vasodilation.
Natriuretic Peptides: Nesiritide

Table 27-1. Reported Effects of Natriuretic Peptides in Humans

<table>
<thead>
<tr>
<th>Effect Type</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular effects</td>
<td>Increase in lipolysis, Effects on blood pressure/volume regulatory regions in the brain</td>
</tr>
<tr>
<td>Vasodilation</td>
<td></td>
</tr>
<tr>
<td>Hemoconcentration</td>
<td></td>
</tr>
<tr>
<td>Hormonal effects</td>
<td>Decrease in plasma renin activity, Decrease in aldosterone, cortisol, ACTH, TSH, and prolactin, Inhibition of vasopressin secretion and/or effects, Induction of pancreatic secretion, Modulation of insulin secretion and/or metabolism, May be endogenous antagonist to angiotensin II, Enhance production of adiponectin</td>
</tr>
<tr>
<td>Renal effects</td>
<td>Natriuresis, diuresis with no concomitant kaliuresis, Increase in glomerular filtration rate, Decrease in effective renal plasma flow, Increase in filtration fraction, Increase in renovascular resistance, Increase in urinary volume and electrolytes</td>
</tr>
<tr>
<td>Central nervous system effects</td>
<td>Modulation of sympathetic activity, Increase in heart rate</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; TSH = thyroid stimulating hormone


to help reduce ventricular preload and afterload. Unlike the sympathetic nervous system and renin-angiotensin-aldosterone system, which continue to activate even in chronic and severe HF, the natriuretic peptide system may be overwhelmed in CHF, leading to a state of relative deficiency.

Colucci and colleagues studied the clinical efficacy and compared the effects of nesiritide to conventional treatment in patients who were admitted with decompensated HF. Patients hospitalized were enrolled to either the efficacy trial or the comparative trial. In the efficacy trial, 127 participants were randomized into either 6-hour infusions of the placebo or 1 of 2 doses of nesiritide (0.015 or 0.03 mg/kg/min) preceded by bolus doses of 0.3 and 0.6 mg/kg, respectively. Subsequently, the blind was broken and participants were maintained on open-label treatment for up to 7 days. The majority of participants had New York Heart Association (NYHA) class III or IV HF and mean left ventricular ejection fraction of 22%, a mean of PCWP of 28 mmHg, and a cardiac index of 1.9 L/min/m². Nesiritide caused dose-dependent reduction in PCWP (6 to 9.6 mmHg) and resulted in a 60% and 67% improvement in global clinical status as compared with 14% of those receiving the placebo (P < .001). It also reduced dyspnea in approximately 55% of participants compared with 12% in those receiving the placebo (P < .001). Hypotension resulted in discontinuation of the study drug in only one participant who was receiving the 0.03 µg/kg/min dose.

In the comparative trial, 305 participants were randomized to open-label treatment with standard care intravenous agents or double-blind treatment with 1 of 2 dose levels of nesiritide (0.015 µg/kg/min infusion preceded by a 0.3 µg/kg bolus or 0.03 µg/kg/min infusion preceded by a 0.6 µg/kg bolus). The duration of therapy was based on usual clinical criteria and ranged up to 7 days. The majority of participants in the trial were in NYHA class III or IV HF.

Among the 102 participants randomized to standard therapy, 57% were treated with dobutamine, 19% with...
milrinone, 18% with nitroglycerin, 6% with dopamine, and 1% with amrinone. Endpoints such as global clinical status and dyspnea were assessed as in the efficacy trials. They were similar to those observed with standard intravenous therapy. The most common adverse event with nesiritide was hypotension, which was symptomatic in 11% and 17% of participants treated with the 0.015 μg/kg/min and 0.03 μg/kg/min dose respectively, as compared to 4% in participants receiving standard therapy. Other adverse events were similar in frequency in the nesiritide and standard treatment groups, except for the frequency of nonsustained ventricular tachycardia, which decreased with the 0.03 μg/kg/min dose of nesiritide (1% in the 0.03 μg/kg/min versus 10% in 0.015 μg/kg/min dose group versus 8% in standard treatment group, P < 0.02).11

The Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial was a multicenter, randomized, double-blind, placebo-controlled study looking at the hemodynamic and clinical effects of nesiritide compared with nitroglycerin therapy for symptomatic decompensated HF.12 Four hundred and ninety-eight participants with dyspnea at rest from HF were randomized to an adjustable dose of nitroglycerin, placebo, fixed-dose nesiritide, or adjustable dose nesiritide. At the end of this period, the placebo group was crossed over to a prespecified treatment with either nitroglycerin or fixed-dose nesiritide. Duration of treatment after crossover was at the discretion of the investigators. Participants receiving adjustable-dose nesiritide continued on this same regimen. For 3 hours, nesiritide was administered as 2 μg/kg intravenous bolus followed by an infusion of 0.01 μg/kg/min in both the fixed dose and the adjustable dose group. After the first 3 hours, the adjustable dose group could have the nesiritide dose increased by administering a 1 μg/kg intravenous bolus followed by an increase of 0.005 μg/kg/min over the previous infusion rate. The maximum allowable infusion rate was 0.03 μg/kg/min. The primary endpoints were change in PCWP and dyspnea at the end of the 3 hours.

Both nesiritide treatment groups (ie, fixed dose and adjusted dose) were pooled for study analysis. Nesiritide significantly decreased PCWP compared to either the placebo (P < .001) or nitroglycerin (P < .027) added to standard care at the 3-hour time point. The most common adverse event was headache, which occurred less often in nesiritide-treated participants (8%) than in the nitroglycerin-treated participants (20%, P = .003). Symptomatic hypotension was similar in frequency in both groups (5%).12

The Prospective, Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) trial examined the proarrhythmic effects of nesiritide and dobutamine.17,18 Two hundreds and forty-six participants with NYHA class III or IV HF were randomized to 1 or 2 doses of nesiritide (0.015 or 0.03 μg/kg/min) or dobutamine (minimum dose of 5 μg/kg/min) and underwent Holter monitoring for 24 hours before and during treatment. Compared with either dose of nesiritide, dobutamine was associated with significant increases in premature ventricular beats (average change in hourly total premature ventricular beats compared to baseline: with dobutamine + 69; with nesiritide 0.015 μg/kg/min -13; and with nesiritide 0.03 μg/kg/min -5, [P < .002]).

A post-hoc analysis combining the long-term mortality results from the comparative trial by Colucci and the PRECEDENT trials (reflecting a total of 507 participants) demonstrated that compared to treatment with dobutamine, nesiritide 0.015 μg/kg/min was associated with a reduction in cumulative 6-month mortality by 37% (15.8% versus 25%, P = .03).19 This observed mortality difference could not be explained by differences in baseline demographics, severity or etiology of CHF, or other comorbid conditions. However, further trials are required to confirm this effect19a and to establish the most optimal dose to maximize the effect.

In addition, anecdotal reports have appeared suggesting that nesiritide has a demonstrable efficacy in the HF patient with mild to moderate renal insufficiency. Interestingly, nesiritide also appears to preserve renal function in some acutely decompensated HF patients (if hypotension does not intervene) who might otherwise experience a significant decline in renal function coincident to the process of diuresis.

A pharmacoeconomic study has also demonstrated an advantage of nesiritide over dobutamine in the treatment of decompensated CHF.20

The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, a phase 3 study, evaluated the efficacy and safety of nesiritide in over 7,000 participants with acute decompensated HF.21-22a Participants hospitalized for HF were randomized to receive intravenous nesiritide or matching placebo for 24 hours to 7 days. The drug was shown to be safe regarding renal function, but it did not affect acute dyspnea, mortality, and rehospitalization.

In addition, studies are in progress evaluating nesiritide in participants with pulmonary hypertension, including those with lung transplants, in participants with acute myocardial infarction to preserve left ventricular function, in children recovering from Fontan surgery for single ventricle heart defects and based on animal data.22b

**Safety and Drug Interactions**

The safety profile of nesiritide was obtained by compiling data from the different randomized clinical trials within the dose range of 0.01 to 0.03 μg/kg/min.11,12,17,19 The stud-
ied participant population is representative of a compromised CHF population, including comorbidities such as significant atrial and ventricular arrhythmias, diabetes mellitus, hypertension, significant renal insufficiency, and acute coronary syndromes. The most common adverse effect of nesiritide was dose-related hypotension (11% to 35%), and approximately 50% of participants were symptomatic. The incidence of other adverse effects was similar to the control groups. Nesiritide may affect renal function in participants with severe HF whose renal function may depend on the activity of the renin-angiotensin-aldosterone system. When nesiritide was initiated at doses higher than 0.01 μg/kg/min in the VMAC study, there was an increased rate of elevated serum creatinine over baseline compared to standard therapies. Higher doses have been associated with increased rates of hypotension and worsening renal function.

No trials specifically examining potential drug interactions with nesiritide were conducted. There were also no long-term studies performed evaluating the carcinogenic potential of nesiritide.

**Dosing and Administration**

The recommended dose of nesiritide is an intravenous bolus of 2 μg/kg followed by a continuous infusion at a dose of 0.01 μg/kg/min. To prevent excessive hypotension or worsening of renal function, nesiritide should not be initiated at a dose that is above the recommended dose. The dose of nesiritide can be adjusted 0.005 μg/kg/min (preceded by a bolus of 1 μg/kg) every 3 hours up to a maximum of 0.03 μg/kg/min. There is limited experience with administering nesiritide for longer than 72 hours. However, in the VMAC study, duration of treatment was not specified. The longest infusion reported was 161 days in a NYHA class IV patient who was poorly responsive to other intravenous therapies while awaiting a cardiac transplant. The patient responded well clinically and tolerated therapy for 161 days. Tolerance or tachyphylaxis was not observed.

Nesiritide is not recommended for use in patients with a systolic blood pressure < 90 mmHg or in those patients suspected of having a low cardiac-filling pressure. If there is any uncertainty regarding volume status, an initial infusion rate of 0.005 μg/kg/min without a bolus is recommended. If symptomatic hypotension occurs, the infusion rate should be immediately decreased or discontinued. In patients with the cardiorenal syndrome, there is no evidence that nesiritide will improve renal function or enhance diuresis.

In patients awaiting cardiac transplantation with secondary pulmonary hypertension, a continuous infusion of nesiritide has been used alone or in combination to lower pulmonary artery pressure. It is recommended that nesiritide be discontinued several hours before induction of cardiac anesthesia to avoid the development of catecholamine-refractory vasoplegia following cardiopulmonary bypass.

In past years, there were preliminary data to suggest a benefit from outpatient use of nesiritide in patients with chronic decompensated CHF. However, more recent data show no benefit from outpatient nesiritide use. Although nesiritide therapy may be initiated in the emergency department, it is most commonly used in patients who remain symptomatic despite parenteral diuretic therapy.

Nesiritide is physically and chemically incompatible with injectable formulations of heparin, insulin, ethacrylate sodium, bumetanide, enalaprilat, hydralazine, and furosemide. These drugs should not be co-administered with nesiritide through the same IV catheter. Injectable drugs that contain sodium metabisulfite as a preservative are also incompatible with nesiritide.

**Conclusion**

Two decades of active natriuretic peptide research have produced tremendous insights into the molecular biology, physiology, and pathophysiology of these hormones and have established the principle that the heart is a pump and a true endocrine organ. In addition, several approaches toward the pharmacologic manipulation of natriuretic peptides in vivo have been developed. The natriuretic peptides play a fundamental role in the regulation of vascular hemodynamics. They play a crucial role in maintaining vascular fluid homeostasis and act to counterbalance the renin-angiotensin-aldosterone system. In these roles, these peptides are part of the human body’s natural system of checks and balances. They perform important protective functions in many acute situations and have proved useful in altering hemodynamics in many studies on CHF.

Nesiritide mimics the actions of endogenous natriuretic peptides. Clinical studies using the intravenous infusion of nesiritide in more than 1,700 participants with acute decompensated HF have demonstrated that it exerts dose-related vasodilation that is rapid in onset and sustained for the duration of infusion. Nesiritide reduces PCWP and improves the symptom of dyspnea. These effects compared favorably to nitroglycerin, dobutamine, and other standard treatment for decompensated HF. It decreases preload and afterload and suppresses the renin-angiotensin-aldosterone axis and the release of norepinephrine. Nesiritide also promotes diuresis and seems to have no proarrhythmic property. However, it may induce renal dysfunction because of excessive hypotension and/
or diuresis, and the drug must be monitored closely. Nesiritide is a valuable therapeutic option in the treatment of patients hospitalized for decompensated HF.

The results of a recent, placebo-controlled study demonstrated that nesiritide use in acute CHF did not affect mortality; however, there was no significant kidney function impairment. Hypotension was more prevalent with nesiritide than with placebo.22a

A prominent use of natriuretic peptides may be as markers for disease.34-52a Routine immunoassay of BNP may provide a preliminary test of ventricular function or other abnormalities and may permit physicians to more carefully select patients for further investigation and treatment. Despite its utility as a biomarker, a recent study using BNP-guided therapy to treat CHF did not show an advantage over symptom-guided treatment.53

The natriuretic peptide field is still in its infancy, and further investigation of the natriuretic peptide family promises to add new insights into their mechanism of action and improved potential clinical uses in the future.

Note: References for this chapter can be found here: www.cvpct3.com
In the early 1900s, Cajal first described the nerve connections between the hypothalamus and the neurohypophysis. Subsequently, it was discovered that the cell bodies of the hypothalamo-hypophysial nerve fibers were found in the anterior hypothalamus, while the nerve axons terminated in capillary beds located in the neurohypophysis. Antidiuretic hormone (ADH), which is the same as arginine vasopressin (AVP), and the closely related oxytocin are synthesized in the supraoptic nuclei of the hypothalamus, and to a lesser extent in the paraventricular nucleus (Figure 28-1). These hormones are transported from the anterior hypothalamus to the neurohypophysis where they are stored and later released.

Vasopressin was first isolated by du Vigneaud and Turner in 1951 and was found to be a nonpeptide with a 6-member disulfide ring and a 3-member tail with an amidoated terminal carboxyl group. AVP has been shown to have a wide variety of physiologic activities (Table 28-1), the most important of which are its antidiuretic and vasoconstrictive actions, which act to maintain homeostasis of body fluid levels while maintaining blood pressure. The most important for vasopressin secretion are elevated plasma osmolality and reduced circulating blood volume. The plasma AVP levels of normally hydrated humans after an overnight fast are in the range of 2-4 pg/ml. A level of approximately 50 pg/ml must be reached before a significant increase in mean arterial pressure is noted in normal conscious human beings. Vasopressin levels are greatly increased in clinical situations associated with reduced circulating blood volume, as seen in patients with dehydration and hemorrhage. The highest AVP levels have been found in patients following traumatic surgical procedures and hypotensive hemorrhage.

If AVP secretion or binding are functioning in an abnormal fashion, a marked distortion of fluid balance results, which may lead to disease states such as the syndrome of inappropriate antidiuretic hormone (SIADH) or diabetes insipidus, conditions usually not associated with systemic hypertension or hypotension. AVP blood levels can also be elevated in other pathophysiologic states associated with increased body fluid volumes, such as hepatic cirrhosis and congestive heart failure (CHF). Recently, great attention has focused on the role of AVP in the homeostasis of the cardiovascular system and in cardiovascular pathophysiology and therapy. As a therapy, it is now considered an alternative to epinephrine for use in patients undergoing cardiopulmonary resuscitation and in patients with septic shock. Its maintenance in blood pressure regulation, its effect on heart rate and cardiac output, its role as one of the neurohormones activated in CHF and its observed direct effects on vascular smooth muscle cell and myocyte cell hypertrophy will be discussed in this chapter. A new class of agents, the vasopressin receptor antagonists, will also be discussed, some of which are now approved for use in patients with hyponatremia. These agents may have potential in treating patients with...
HF who are volume-overloaded and for other disease entities such as cirrhosis, where hyponatremia and volume overload are significant clinical problems.

### Vasopressin Analogues

Vasopressin analogues were first synthesized in the 1960s for the purpose of creating peptides that were more resistant to degradation while retaining potency. Several analogues were produced, the first of which was desmopressin, a V₂ receptor agonist that mimics vasopressin’s antidiuretic effect (Figure 28-2). Desmopressin is the treatment of choice for neurogenic forms of diabetes insipidus, and has also been used as a hemostatic agent because it heightens platelet aggregation and because of its ability to transiently raise plasma levels of endogenous factor VIII and von Willebrand factor. It has, therefore, become an attractive alternative to the large numbers of blood transfusions required by patients with hemophilia A, von Willebrand’s disease, uremia, cirrhosis, and other diseases with associated platelet dysfunction.

Terlipressin, a V₁ receptor agonist (causing vasoconstriction) is used in the emergency treatment of bleeding from esophageal varices (Figure 28-2) and as an alternative to epinephrine in patients with cardiopulmonary arrest.

### Vasopressin Receptors

All AVP receptors are G protein-coupled receptors with a structure composed of a single polypeptide chain with 7 transmembrane domains. Two AVP receptor subtypes,
V₁ and V₂ were initially characterized. A third “pituitary specific” receptor has been designated V₁b or V₃; therefore, the V₁ receptor is now referred to as the V₁a receptor.

The V₁a receptor has classically been associated with AVP’s vasoconstrictor effect; however, the V₁a receptor has been found to mediate a multitude of other diverse physiologic actions (Table 28-2). The cDNA for the V₁a receptor encodes a protein having 394 amino acids with a molecular weight of 44.2 kd. The activation pathway following V₁a receptor stimulation can be seen in Figure 28-3. V₁a receptor stimulation shares the same intracellular activation pathway as that of the angiotensin II receptor, consisting of phospholipase C activation, mobilization of intracellular Ca²⁺, and stimulation of protein kinase C. Mitogenic and hypertrophic effects of vasopressin, mediated via the V₁a receptor, have been observed in both smooth muscle and myocyte cell cultures. Tahara et al demonstrated that AVP, when added to growth-arrested vascular smooth muscle cells, induced hyperplasia and hypertrophy. The addition of a nonspecific vasopressin antagonist to these cell cultures inhibited AVP-induced increases in intracellular free calcium and the activation of mitogen-activated protein kinase, while preventing the AVP-induced hyperplasia and hypertrophy. These investigators also observed that vasopressin increased the secretion of vascular endothelial growth factor (VEGF) from human vascular smooth muscle cells. Given VEGF’s known mitogenic capability, it has been suggested that vasopressin might act as a paracrine hormone that could strongly influence the permeability and growth of the overlying vascular endothelium. Additionally, neonatal rat cardiomyocytes have a single population of high affinity binding sites with the V₁a receptor subtype profile. When the receptor was blocked, AVP-induced increases

### Table 28-2. Location and Effects of Vasopressin Receptor Stimulation

<table>
<thead>
<tr>
<th>Location/Receptors</th>
<th>Location/Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V₁a Receptors</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatocytes</td>
<td>Stimulates glycogenolysis</td>
</tr>
<tr>
<td>Glomerular mesangial cells</td>
<td>?</td>
</tr>
<tr>
<td>Platelets</td>
<td>Promotes aggregation</td>
</tr>
<tr>
<td>Vascular smooth muscle cells</td>
<td>Induces vasoconstriction</td>
</tr>
<tr>
<td>Adrenals</td>
<td>Stimulates aldosterone secretion</td>
</tr>
<tr>
<td>Myometrium</td>
<td>Increases contractility</td>
</tr>
<tr>
<td>Endometrium</td>
<td>Mediates uterine substance release</td>
</tr>
<tr>
<td><strong>V₂ Receptors</strong></td>
<td></td>
</tr>
<tr>
<td>Renal distal tubules</td>
<td>Increases free water reabsorption</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>Increases free water reabsorption</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>?</td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>Induces vasodilation</td>
</tr>
<tr>
<td><strong>V₃ Receptors</strong></td>
<td></td>
</tr>
<tr>
<td>Adenohypophyseal cells</td>
<td>Potentiation of corticotropin-releasing hormone stimulation</td>
</tr>
<tr>
<td>Kidney, thymus, heart, lung, spleen, uterus, breast</td>
<td>?</td>
</tr>
</tbody>
</table>


in cytosolic calcium, the activation of MAP kinase, and AVP-induced protein synthesis were inhibited. This has suggested that the antagonism of V1a might be beneficial in preventing the development of cardiomyocyte hypertrophy or mediate its regression. In summary, these observations suggest that vasopressin via the V1a receptor might play a role in the regulation of vascular and cardiac function.

The V2 receptor mediates the antidiuretic effects of AVP in the kidney. The receptor has also been identified in the seminal vesicles of humans where its role is uncertain. The V2 receptor has also been implicated in vascular smooth muscle relaxation, allowing for the possibility that AVP could have variable effects on the vasculature that complicates the investigations into AVP’s role in the pathophysiology of hypertension and CHF (Table 28-2). The V2 receptor has been cloned and found to encode a protein of 370 amino acids with a weight of 40.5 kd. Signal transduction of the V2 receptor differs from that of the V1a receptor, working via adenylate cyclase and cAMP.

The V3 receptor or V1 receptor has been found to have more homology with the oxytocin receptor than the V1a receptor. Using DNA nucleotide sequences, deKeyzer et al constructed a phylogenetic tree of AVP receptors that revealed that the V1 receptor did not diverge from the V1a receptor as previously thought but from an earlier ancestor of the human oxytocin receptor.

The molecular cloning of the V1 receptor was found to yield cDNA that encodes a 421 amino acid protein. The mRNA of this receptor is also found in many other tissues, including kidney, thymus, heart, lung, spleen, uterus, and breast, indicating a possible role for the V3 receptor in the regulation of cellular functions in these organs (Table 28-2). The signaling properties of the V3 receptor have been shown to be identical to V1a receptor, and the activation of the V3 receptor plays a major role in the regulation of adrenocorticotropic hormone (ACTH) secretion involved in the physiologic response to stress.

Chan et al reported the unexpected discovery of a potentially novel vasopressin receptor during an attempt to synthesize new V1 receptor selective antagonists. They synthesized 4 new peptide analogues of vasopressin that caused a significant depressor response when administered in vivo to rats. This effect was resistant to V1a and V2 selective antagonists. The peptides did not show any V1a or V2 agonist or antagonist activity.

After hormone binding, the AVP receptor-ligand complex is endocytosed and delivered to endosomes. The endosomes are then either joined to lysosomes for degradation or to the plasma membrane for recycling. This endocytosis has been observed for both the V1a and V2 receptors in vascular smooth muscle, liver, bladder, and kidney cells. Endocytosis is, therefore, thought to play a role in the desensitization of tissues to vasopressin and to modulate the overall extent of the cellular response to AVP.

Other Physiologic Effects Of Vasopressin

Effects on the Autonomic Nervous System

The interaction of AVP with the sympathetic and parasympathetic systems is not well understood, with much species variation. It is generally thought that circulating AVP in the central nervous system lowers sympathetic activity while enhancing efferent vagal tone. AVP has been shown to decrease heart rate and renal sympathetic nerve activity, via stimulation of the V1a receptor. AVP may mediate its effect on the sympathetic nervous system via augmented baroreflex activity or centrally in the central nervous system, or more specifically the area postrema. Lesions produced in the area postrema of rabbits have resulted in reduced effects of AVP in decreasing both renal sympathetic nerve activity and heart rate. These effects are mostly likely mediated via V1a receptor stimulation.

It has also been postulated that the effects of AVP are due to direct suppression of sympathetic tone in the central nervous system or suppression of ganglionic transmission. Vasopressin has been implicated as a neurotransmitter in the paraventricular nucleus pathway, affecting cardiovascular function through both pressor actions and sympathetic response.

Effects on the Baroreflex

When arterial pressure falls, there is decreased activity of afferent nerves from the carotid sinus and aortic arch (baroreceptors) that project to the dorsomedial regions of nucleus tractus solitarii via cranial nerves IX and X. Through a series of complex interactions within the brain, the sympathetic nervous system is then activated, leading to increases in peripheral resistance and cardiac output and, therefore, a rise in blood pressure.

Studies have indicated that baroreceptors may play a permissive role in the sympathoinhibitory effects of AVP. Normal baroreceptor activity would, therefore, allow AVP to exert its inhibitory influence with chronic elevations in salt intake, allowing for vasodilation, thereby accommodating the increased volume load and allowing natriuresis.

AVP elicits a greater decrease in heart rate for a given increase in arterial pressure than other vasoconstrictors when administered to several species, an action thought to be due to the baroreflex mechanisms. In rabbits, vasopressin decreased heart rate due to a shift in the baroreflex curve to a lower pressure with no increase in its...
Vasopressin and Vasopressin Receptor Antagonists

Cardiac Arrest

Epinephrine is the vasopressor of choice in the ACLS guidelines. Vasopressin, however, may be a viable option in patients unresponsive to standard treatment. Vasopressin is recommended as a means to support blood pressure and/or to obtain the return of spontaneous circulation in patients refractory to epinephrine. Following ventricular fibrillation arrest, higher serum concentrations of vasopressin have been associated with successful resuscitation, while higher serum concentrations of catecholamines have been associated with a lower chance of survival.

Epinephrine has some disadvantages in cardiac arrest treatment, including increased myocardial oxygen consumption, risk of ventricular arrhythmias, ventilation-
perfusion defects, and reduced cerebral blood flow. These effects may be due to increased myocardial oxygen consumption and lactate production induced by beta-adrenergic receptor activation in myocardial and skeletal muscle. Vasopressin increases oxygen delivery to the heart and increases cardiac contractility in nitric oxide-mediated pathway, minimizing these consequences.

Vasopressin has been linked with greater increases in arterial tone and ACTH release, particularly during hypoxia and acidosis. Vasopressin may be beneficial in prolonged or refractory cardiac arrest in which the precipitating acidosis renders catecholamines ineffective in eliciting a pressor response. Vasopressin-mediated vasoconstriction in cerebral vasculature may help maintain cerebral oxygen delivery and allow survival with fully intact neurologic activity. Vasopressin's duration of action is longer than epinephrine (50 to 100 minutes versus 5 minutes).

In a small study of participants with out-of-hospital ventricular fibrillation, a significantly larger number initially treated with IV vasopressin 40 U were resuscitated and survived 24 hours versus participants treated with 1 mg IV epinephrine. There was no difference in survival to hospital discharge.

There is preliminary evidence that vasopressin is effective in enhancing the probability of return to spontaneous circulation in patients with ventricular fibrillation. The ACLS guidelines recommend a 40 U bolus of IV vasopressin followed by 300 J to 360 J direct current cardioversion to restore spontaneous circulation in patients with ventricular fibrillation arrest refractory to epinephrine.

Studies have not evaluated whether the combination of vasopressin and epinephrine would be better than epinephrine alone, with no additional benefit coming from the combination.

**Vasodilatory Shock**

Vasopressin-induced vasoconstriction raises systolic blood pressure by increasing systemic vascular resistance in vasodilatory shock due to sepsis or cardiopulmonary bypass. Low levels of vasopressin were found in patients during septic shock possibly due to a defect in the baroreflex-mediated secretion of vasopressin or a depletion of vasopressin stores during failed attempts to correct hypotension. Supplemental vasopressin may correct this.

Vasopressin may be better than catecholamine pressors in these cases since vascular smooth muscle is poorly responsive to alpha-adrenergic agonists in septic shock due to an acidic state. An increase in urine output often follows vasopressin treatment. Stimulation of vasopressin receptors in efferent arterioles causes constriction of glomerular efferent arterioles. The constriction maintains glomerular filtration rate despite reduced renal blood flow. In contrast, stimulation of catecholamine receptors in afferent arterioles rarely increases urine output even with increased blood pressure.

In a randomized, placebo-controlled trial, Argenziano studied vasopressin in 10 vasodilatory shock participants post left ventricular assist device. Intravenous vasopressin 0.1 U/min led to a significant increase in mean arterial blood pressure from 57 to 84 mmHg, allowing norepinephrine to be discontinued.

Several preliminary studies have been published using vasopressin to treat vasodilatory septic shock. In participants poorly responsive to catecholamines, low-dose vasopressin infusions at 0.04 U/min for 16 hours increased mean arterial pressure, systemic vascular resistance and urine output in participants with vasodilatory shock and limited responsiveness to catecholamines. Vasopressin allows down-titration and cessation of catecholamine pressors often within 24 hours. Vasopressin doses can be titrated down to 0.01 U/min over 2 to 11 days before discontinuation. When dose reduction results in blood pressure decrease, arterial pressure can be restored with increasing vasopressin doses.

Although current guidelines do not suggest the substitution of AVP for norepinephrine or dopamine as a first-line agent for vasodilatory shock, it should be considered as adjunctive hemodynamic therapy under special circumstances. According to the Vasopressin and Septic Shock Trial in participants requiring between 5 and 15 mcg/min norepinephrine infusion after adequate fluid resuscitation, and in participants at risk for renal failure (defined by increase in serum creatinine 1.5 × baseline, decrease in glomerular filtration rate by 25%, or urine output <0.5 mL/kg/hr for 6 hrs), it is recommended that AVP be administered between 0.01 and 0.03 U/min.

**Therapeutic Monitoring**

Since patients receiving vasopressin are hemodynamically unstable, it is important to monitor cardiovascular adverse effects. Vasopressin causes transient, reversible reductions in cardiac output and heart rate. Coronary vasoconstriction also decreases coronary blood flow and offsets changes in vagal and sympathetic tone. Patients should be monitored for bradycardia, arrhythmia, myocardial, and/or mesenteric ischemia. Vasopressin may exacerbate regional ischemia by reduction of collateral-dependent myocardial perfusion. An increased rate of right heart failure in left ventricular assist device patients has been observed.

**Adverse Events**

Data are lacking on adverse events after resuscitation in terms of impaired vital organ function. Due to the presence of vasopressin receptors in various tissues, there is
the potential for reduced regional blood circulation in pulmonary, coronary, and splanchnic blood vessels. Vasopressin has not been associated with ischemic bowel or increased liver insufficiency. There is the potential for increase in pulmonary arterial pressure and hypertension, although these adverse effects also have not been observed.

**Vasopressin Antagonists for Heart Failure and Hyponatremia**

With a better understanding of the role of AVP in human physiology, numerous AVP antagonists have been studied for the treatment of disease states associated with elevated levels of AVP. Initially, all AVP antagonists were peptides having little oral bioavailability. OPC 21268 was one of the first orally effective, V$_1$a selective, nonpeptide AVP antagonists developed. It blocks AVP-induced vasoconstriction. At the same time, OPC 31260 (a predominant V$_2$ antagonist) was synthesized. It induces a strong aquaretic effect in humans. In healthy male volunteers, it increased urine volume, plasma sodium, and plasma AVP in a dose-dependent manner without altering blood pressure or heart rate. Since then, many other vasopressin antagonists have been studied in vitro and in animal models to better understand the potential clinical use of these drugs. In this section, we will focus on their use for treatment of CHF.

**Vasopressin and CHF**

Much of the pathophysiology, morbidity, and mortality seen in CHF are mediated by neurohormonal changes. These neurohormones have been studied and include the activation of the renin-angiotensin-aldosterone system (RAAS), AVP, and the sympathetic nervous system. The activation of these systems leads to vasoconstriction and salt and water retention. The water retaining effect of ADH is exacerbated by the RAAS and norepinephrine that limit water excretion by lowering glomerular filtrate rate and increasing proximal water and sodium reabsorption. The severity of the defect in water excretion and the associated reduction in plasma sodium concentration parallel the severity of CHF.

Elevated AVP levels have been recorded in CHF. Data from the Studies of Left Ventricular dysfunction (SOLVD) showed that participants with HF had significantly higher levels of AVP compared with control groups. Also observed in participants with CHF is that participants with hyponatremia are more likely to have elevated AVP levels than participants without hyponatremia. The Survival and Ventricular Enlargement (SAVE) trial showed that high AVP levels are associated with worsened 1-year cardiovascular morbidity. Activation of the carotid sinus and aortic arch baroreceptors by the low cardiac output in HF leads to enhanced release of ADH and secondary water retention. Secretion of AVP, normally controlled via hypothalamic osmoreceptors, is overridden in CHF by nonosmolar stimuli, leading to dilutional hypo-osmolality. An impaired baroreflex could lead to maintenance of high AVP levels in CHF, despite constantly declining osmolality. It has been shown that in participants without CHF, increased baroreflex activity suppresses AVP levels that have been increased by osmotic stimulation. Besides its effects on fluid balance, AVP infusion is found to cause a decrease in heart rate, cardiac output, and a dose-dependent increase in total peripheral resistance in young male patients who have been pretreated with ACE inhibition (to prevent fluctuations in angiotensin II). AVP has also been shown to lead to coronary vasoconstriction. Angiotensin II may also increase AVP levels.

**Vasopressin Antagonists in CHF**

Beta-adrenergic receptor blockers, ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists have proven mortality benefit in the treatment of HF. On the other hand, diuretics are the mainstay of treatment for acute and chronic volume overload in HF but do not improve survival. In fact, they are associated with numerous adverse effects that include hypotension, electrolyte abnormalities, worsening renal function, and activation of the RAAS. Hyponatremia in the setting of HF is, in general, an indicator of poor prognosis. Mild hyponatremia is encountered frequently in patients hospitalized for worsening HF. Low admission plasma sodium concentration seems to be an independent predictor of increased mortality after discharge and of rehospitalization. Vasopressin receptor antagonists have been investigated as agents that can, via V$_2$ inhibition, increase free water excretion, facilitate diuresis, and prevent correct hyponatremia without activation of the RAAS. Vasopressin receptor antagonists, via V$_1$ inhibition, can also promote vasodilation and afterload reduction. Over the past several years, vasopressin antagonists (vaptans) have been developed and have been studied in patients with HF.

**Tolvaptan**

Tolvaptan (OPC 41061) is an orally active AVP antagonist without intrinsic agonist properties. It is selective to the V$_2$ receptors (29:1) found in the collecting tubules. When studied in single- and multiple-dosing studies in rats, tolvaptan produced a consistent, dose-dependent (1 mg and 10 mg) aquaretic effect. In comparison trials, tolvaptan and furosemide both produced an increase in urine volume; however, tolvaptan produced electrolyte-free water clearance while furosemide caused a decrease
in serum sodium. Furosemide also significantly activated the RAAS, whereas tolvaptan did not. Combination therapy showed an additive effect on urinary volume and free water excretion. In hospitalized patients with hyponatremia, tolvaptan appeared to be more effective than fluid restriction.

The effect of tolvaptan in patients with HF and clinical evidence of volume overload was evaluated in an early randomized, double-blind study of 254 participants who were randomized to the placebo or 1 of 3 different oral doses of tolvaptan (30, 45, or 60 mg daily) for 25 days in addition to standard HF therapy. Results showed a significant decrease in body weight at day one and correction of hyponatremia at 25 days in participants receiving tolvaptan. Participants treated with tolvaptan had greater urine volume, greater net fluid losses, and decreases in urine osmolality. They had small but significant improvement in serum sodium, but the effect gradually decreased over 25 days. The main adverse effects were dry mouth, thirst, and polyuria. Quality of life assessment showed no difference between the study drug and the placebo.

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in CHF (ACTIV in CHF) trial was a randomized, multicenter, double-blind, parallel-group, dose-ranging, placebo-controlled, phase 2 feasibility trial involving 319 participants hospitalized with decompensated HF, left ventricular ejection fraction (LVEF) < 40%, and systemic congestion. The participants were randomized to tolvaptan therapy (30, 60, or 90 mg orally daily) versus the placebo in a 1:1:1:1 ratio for 60 days. The primary endpoints were change in body weight at 24 hours and death or worsening of HF at 60 days.

A significant reduction in body weight was seen with a mean weight loss of 1.6 kg after 1 day and 2.8 kg by hospital discharge. At discharge, fewer tolvaptan-treated participants complained of dyspnea. After 60 days, there was no significant difference in the primary endpoints of death, hospitalization, and worsening HF. However, a trend toward decreased mortality was observed in the tolvaptan group ($P = .18$). The most frequent adverse effect with tolvaptan was thirst. Tolvaptan was not associated with any increased incidence of hypotension, tachycardia, hypokalemia, or worsening renal function.

The Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST) was a prospective, international, multicenter, randomized, double-blind, placebo-controlled study that enrolled 4,133 participants hospitalized with acutely decompensated HF and documented LVEF ≤ 40%. Participants were treated with standard optimal therapy and randomized within 48 hours of hospitalization to receive tolvaptan (30 mg daily) or the placebo until the end of the long-term outcome study. The EVEREST clinical status trials assessed the short-term effect of tolvaptan, showing a statistically significant improvement on the primary endpoint: the composite of participant-assessed global clinical status and body weight change at day 7 or at discharge. The degree of weight loss at day one (1.7-1.8 versus 1.0 kg with the placebo plus standard treatment) and at day 7 or at discharge (3.3-3.8 versus 2.7-2.8 kg with the placebo plus standard treatment) were statistically in favor of tolvaptan. A higher percentage of participants treated with tolvaptan reported an improvement in dyspnea at day one (72% to 77% versus 65% to 71% with the placebo). However, this study did not show improvement in the global clinical status with tolvaptan.

The EVEREST outcome trial included all participants from the short-term trials and demonstrated no difference in the primary endpoints at a median follow up of 10 months: all-cause mortality ($P = .68$) or in a combined endpoint of cardiovascular death or HF hospitalization ($P = .55$). In a prespecified analysis of noninferiority to the placebo, tolvaptan was determined to be noninferior to the placebo for both of the primary endpoints. Tolvaptan reduced body weight throughout the study (including 56 weeks of treatment). Among participants with a baseline plasma sodium concentration < 134 mEq/L, tolvaptan produced a greater increase in plasma sodium at 7 days or time of discharge if earlier (5.5 versus 1.9 mEq/L with the placebo, $P < .0001$) and up to 56 weeks of follow-up ($P < .05$). However, the difference tended to become smaller over time.

In summary, tolvaptan showed symptomatic improvement in the short-term study and a good safety profile in the long-term follow up. The adverse events of thirst and dry mouth leading to drug discontinuation occurred in 6.5% of participants receiving tolvaptan and 5.5% of participants receiving the placebo. Hypernatremia occurred in 1.7% of tolvaptan participants and 0.5% of the placebo participants. The Effects of Tolvaptan on Hemodynamic Parameters in Subjects with Heart Failure (ECLIPSE) trial enrolled 181 participants with symptomatic HF (New York Heart Association [NYHA] class III and IV and LVEF ≤ 40%) and randomized them to double-blind treatment with tolvaptan at a single oral dose of 15, 30, or 60 mg or the placebo. The primary endpoint was pulmonary capillary wedge pressure. All 3 doses of tolvaptan significantly decreased pulmonary capillary wedge pressure compared with the placebo (-6.38 ± 0.62 mmHg with 15 mg; -5.67 ± 0.70 mmHg with 30 mg; -5.71 ± 0.65 mmHg with 60 mg; -4.16 ± 0.67 with the placebo; $P$ versus placebo < .05 for each tolvaptan group).

Secondary endpoints showed a statistically significant increase in urine volume at 3 hours. None of the other secondary outcome measures, including cardiac output,
Conivaptan

Conivaptan (YM087, Vaprisol), a nonspecific V$_1$A and V$_2$ parenteral vasopressin receptor antagonist, became the first FDA-approved AVP antagonist in 2005. Conivaptan is approved for use in both hypervolemic and euvolemic hyponatremia. It is a nonpeptide antagonist that, in various animal models, demonstrated high affinity and antagonist effects for both the V$_1$A and V$_2$ receptors (10:1 selectivity). Conivaptan has no agonist effect and does not inhibit the binding of AVP to the anterior pituitary (V$_1$B receptors). 

In a dog model, intravenous conivaptan inhibits, in a dose-dependent manner, the pressor response to exogenously administered vasopressin. In conscious rats, orally administered conivaptan also demonstrated dose-dependent inhibition of AVP-induced pressor responses but had no effect on basal blood pressure. In the same model, conivaptan caused a dose-dependent increase in urine volume and reduced urine osmolality with significantly lower electrolyte excretion when compared with furosemide. The aquaretic effect of conivaptan was sustained at 8-10 hours post dosing.

In a dog model of CHF, intravenous administration of conivaptan significantly increased left ventricular contractility and cardiac output, reduced left ventricular end-diastolic pressure and peripheral vascular resistance, and increased flow and reduced urine osmolality by markedly increasing free water clearance. In healthy, normotensive human subjects, both oral and intravenous forms of YM087 caused a marked increase (7-fold) in urine flow rate and a fall in urine osmolality (600 to < 100 mosmol/L). This aquaresis was accompanied by an increase in plasma osmolality (283 to 289 mosmol/L).

In a double-blind, randomized, placebo-controlled study of 142 participants with HF (NYHA class II and IV), participants treated with intravenous conivaptan demonstrated a significant reduction in right atrial and pulmonary capillary wedge pressures when compared to the placebo. The hemodynamic improvements were accompanied by increases in urine output without a detrimental effect on serum creatinine.

Although conivaptan is approved for the treatment of euvolemic and hypervolemic hypo-natremia, it is not approved for the treatment of CHF. Conivaptan has numerous cytochrome P450 interactions with cardiovascular medications, making it impractical for oral long-term daily use. Ongoing trials continue to evaluate conivaptan for short-term use in acute decompensated CHF.

Lixivaptan

Lixivaptan is a newer, potent, orally active, nonpeptide competitive AVP antagonist selective for the V$_2$ receptor. Forty-two participants with chronic symptomatic HF requiring diuretic therapy were enrolled in 2 centers in the United States in a randomized, double-blind, placebo-controlled, ascending, single-dose, safety, efficacy, and tolerability study. Enrolled subjects had NYHA class II or III HF, an ejection fraction ≤ 35%, serum sodium concentration between 120 and 140 mmol/L, and serum potassium concentration in the normal range. Five participants were enrolled in each dose group of lixivaptan 10, 30, 75, 150, 250, and 400 mg and paired with 2 participants who were randomized to the placebo for each group. Dose-related increases in urine volume were observed over 4 hours with lixivaptan at doses > 10 mg compared with the placebo. Urine volume increased at 24 hours from 1.8 L in the placebo group to as much as 3.9 L with lixivaptan 400 mg (P < .01). At baseline, urinary osmolality was elevated, consistent, with neurohormonal activation and water retention characteristic of participants with HF. Urine osmolality was reduced with lixivaptan in a dose-related manner compared to the placebo. No significant differences were observed in urinary electrolytes excretion, leading to no significant difference in serum concentrations of chloride, magnesium, blood.
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urea nitrogen, and potassium. The increases in urine volumes were accompanied by significant increases in soluble-free water excretion, consistent with an aquaretic effect of vasopressin antagonists. At doses > 75 mg, serum sodium was significantly increased. AVP antagonism was well tolerated in these participants without any serious adverse events. Clinical outcomes, however, were not assessed.139

The Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patients Evaluation (BALANCE) is an ongoing multicenter, international, randomized, double-blind, efficacy and safety study of the effects of titrated oral lixivaptan in participants with hyponatremia hospitalized for HF. The study will include approximately 650 participants who will receive lixivaptan or the placebo with dose titration for 60 days. The primary objective of the study is to determine whether lixivaptan can effectively and safely increase serum sodium concentration in HF participants with volume overload and hyponatremia. Secondary objectives include an assessment of all-cause mortality, cardiovascular and HF hospitalizations, and acute change in body weight.

Treatment of HF aims primarily at relief of symptoms, prevention of disease progression, and improvement in survival. The clinical trials that have evaluated the role of different vaptans in participants with HF have been encouraging because they are effective in alleviating symptoms. However, these studies have not definitively demonstrated an impact on clinical outcomes either by preventing disease progression or improving survival.

**Conclusion**

Vasopressin plays a complex role in human physiology and pathophysiology. Additional investigations are needed before vasopressin’s role in the etiology of cardiovascular disease can be entirely delineated. Its role in systemic hypertension is currently being investigated. Vasopressin does have important therapeutic effects in hemorrhagic and vasodilatory shock and for use in patients undergoing cardiopulmonary resuscitation. With an increased understanding of the role of vasopressin upregulation in certain disease states such as HF, much effort has focused on the development of vasopressin antagonists. It is expected that these aquaretic compounds will ultimately replace current generation diuretics, which often cause both hyponatremia and worsened renal function. The initial studies from animal models and early human experience demonstrate aquaretic effects, correction of hyponatremia, and the preservation of renal function. However, a recent large clinical study (EVEREST) failed to show improvement in clinical outcomes. With an increasing number of more selective orally active vasopressin antagonists (vaptans), new studies are under way to establish the role of vaptans in the treatment paradigm for HF and other entities (Table 28-3) associated with volume overload and hyponatremia.

---

**Table 28-3: Potential Uses of Vasopressin Antagonists**

<table>
<thead>
<tr>
<th>Selective V1 Receptor Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. As a vasodilator to treat congestive heart failure, especially in conjunction with ACE</td>
</tr>
<tr>
<td>inhibitors and β blockers.</td>
</tr>
<tr>
<td>2. Systemic hypertension, especially in conjunction with ACE inhibitors and β blockers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selective V2 Receptor Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Increasing free water clearance in treatment of congestive heart failure, cirrhosis of</td>
</tr>
<tr>
<td>the liver, other edematous states.</td>
</tr>
</tbody>
</table>


Note: References for this chapter can be found here: www.cvpct3.com
In 1711, invasive cardiology was born when Stephen Hales performed a cardiac catheterization on a living horse using brass pipes. Since then, many significant advances have occurred in this field. In 1977 in Zurich, Andreas Grüntzig performed the first percutaneous transluminal coronary angioplasty on a human patient, and in France in 1986, the first coronary artery stent was placed in a human by Jacques Puel and Ulrich Sigwart.

The most recent advance in this dynamic field occurred in 2003, when the first of the drug-eluting stents (DES), the sirolimus-eluting Cypher stent, was approved for use in the United States (Figure 29-1). Since then, 3 other DES have been approved for use in the United States. This chapter will describe the rationale for DES and then focus on their pharmaceutical characteristics. While not the primary purpose of this chapter, the safety and efficacy of these devices will also be discussed.

**Rationale for Drug-Eluting Stents**

Percutaneous transluminal coronary angioplasty certainly represented a significant therapeutic advance for the treatment of coronary atherosclerosis, but it was far from a cure for managing atherosclerotic lesions. The long-term success of this procedure suffered from abrupt vessel closure and a 6-month restenosis rate of about 40%. The development of coronary artery stents by Palmaz and Schatz was designed to reduce the vessel reclosure rates seen with balloon angioplasty and the efficacy of these bare-metal stents (BMS) for preventing vessel restenosis was proven in subsequent clinical trials. While 6-month restenosis rates were reduced to about 30% with coronary stenting, the exposure of the stent struts to blood constituents created a thrombogenic environment around the stent, necessitating dual antiplatelet therapy with aspirin and either ticlopidine or clopidogrel for at least several weeks and preferably for up to 1 year following coronary stent placement.

Although dual antiplatelet therapy did help with complications, restenosis remained a problem with BMS due to another phenomenon, neointimal hyperplasia, occurring as a consequence of coronary artery stent placement. This has resulted in the need for re-intervention in up to 20% of cases of BMS placement. Neointimal hyperplasia is the formation of scar tissue and represents a healing response by the vessel in response to stent placement (Figure 29-2). In response to the arterial injury that occurs with stent placement, vascular smooth muscle cells (which are normally in the resting phase of the cell cycle [Go]) begin to proliferate and migrate from the media...
Cardiovascular Pharmacotherapeutics

There are currently 4 DES available in the United States (Table 29-1). These are broadly categorized as first-generation (Cypher and Taxus) and second-generation (Endeavor and Xience V) stents. While the underlying indication for each stent is to limit smooth muscle cell proliferation, each stent has unique characteristics that should be understood when interpreting study data as well as deciding on which stent to use for a given patient. The characteristics of DES can be broadly divided into 3 categories: the drug, the platform, and the polymer. There are distinctions between the first- and second-generation DES in each of these 3 categories, which will now be discussed.

**Drugs Utilized in Drug-Eluting Stents**

The drugs that are eluted from DES all reduce neointimal growth by arresting the cycle of cell proliferation (Figure 29-3). Of the 4 drugs currently available in stents, they essentially comprise 2 classes: 1) sirolimus and its analogs (everolimus and zotarolimus) and 2) paclitaxel (Figure 29-4a, 4b).

Sirolimus (a.k.a. rapamycin) is a macrocyclic antibiotic derived from *Streptomyces hygroscopicus*. It was first discovered from a soil sample on Easter Island, otherwise known as Rapa Nui, hence the name rapamycin. While the drug does have antifungal properties, it was not pursued as an antibiotic due to its immunosuppressive properties, and it ultimately ended up being approved by the US Food and Drug Administration (FDA) in 1999 for prophylaxis of transplant rejection. Preliminary data in human and rat models demonstrated sirolimus to cause dose-dependent inhibition of arterial intimal thickening, proliferation, and migration of vascular smooth muscle cells, leading to its development as an antiproliferative agent. Sirolimus is able to readily diffuse across cell membranes and into the cytosol, where it binds with high affinity to FK-506 binding protein 12 (FKBP12). The sirolimus-FKBP12 complex inhibits the mammalian target of rapamycin which, while not well understood, is believed to relay mitogenic signals through the PI3 kinase-dependent mitogenic pathway that regulates cell growth and cell division. Activation of mammalian target of rapamycin allows for the cell cycle to progress from the G1 to the S phase, and its inhibition is believed to be the primary mechanism of action for sirolimus-eluting stents. Sirolimus has also been shown to enhance senescence/apoptosis of endothelial cells that, along with its antiproliferative properties, may delay endothelial healing.

Zotarolimus and everolimus are analogs of sirolimus, with only minor chemical modifications differentiating them (Figure 29-4a). These newer agents share the ability of sirolimus to bind to FKBP12 and inhibit smooth muscle cell proliferation. Subsequently, there is synthesis of extracellular matrix, proteoglycans, and collagen, which combine to form a neointimal mass that can ultimately impinge on the lumen diameter. This mass is hypocellular, comprised primarily of matrix proteoglycans and collagen, with lesser amounts of smooth muscle cells. Consequently, the most effective treatments would be those that alter matrix synthesis as opposed to those targeting only cell proliferation.

In recognition of the significance the neointima has as it relates to stent restenosis, the incorporation of antiproliferative drugs onto the stent itself was investigated as a means of minimizing or at least controlling the intimal overgrowth occurring in response to BMS placement. The premise was to have the drug elute from the stent itself, thereby producing a localized effect on limiting smooth muscle cell proliferation. This proved to be a very successful strategy, reducing 8-month in-segment restenosis rates from 36% to 9%. There are currently 4 DES available in the United States (Table 29-1). These are broadly categorized as first-generation (Cypher and Taxus) and second-generation (Endeavor and Xience V) stents. While the underlying indication for each stent is to limit smooth muscle cell proliferation, each stent has unique characteristics that should be understood when interpreting study data as well as deciding on which stent to use for a given patient. The characteristics of DES can be broadly divided into 3 categories: the drug, the platform, and the polymer. There are distinctions between the first- and second-generation DES in each of these 3 categories, which will now be discussed.

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**Figure 29-2. Possible mechanism of restenosis following bare-metal stent placement.** (A) Normal cross-section of arterial wall. (B) Stent placement. Placement of a stent results in damage to the endothelium, internal elastic lamina, and intimal and medial layers of the arterial wall. (C) Smooth muscle cell proliferation. In response to arterial damage, platelets are attracted to the area, and cytokines and macrophages are released. Growth factors then trigger smooth muscle cells to proliferate from the media to the intima and lumen of the vessel. (D) Neointimal formation. Vessel lumen decreases due to growth of the neointima. Neointimal growth may continue until the neointima is covered by endothelial cells. Drug-eluting stents serve to reduce neointimal proliferation and preserve lumen size, although they tend to slow re-endothelialization as well. Data from Shedden L et al.
Table 29-1. Drug-Eluting Stents Currently Available in the United States

<table>
<thead>
<tr>
<th>Drug eluted</th>
<th>First Generation Stents</th>
<th>Second Generation Stents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cypher</td>
<td>Taxus Express</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Stainless steel</td>
<td>Stainless steel</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Hydrocarbon-based elastomer (SIBBS)</td>
<td>Hydrophilic phosphorylcholine (Biolinx)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strut thickness</th>
<th>140 μm</th>
<th>132 μm</th>
<th>91 μm</th>
<th>81 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer thickness</td>
<td>14 μm</td>
<td>16 μm</td>
<td>6 μm</td>
<td>7 μm</td>
</tr>
<tr>
<td>Angiographic late loss</td>
<td>0.14 ± 0.42 mm</td>
<td>0.41 ± 0.54 mm</td>
<td>0.61 ± 0.46 mm</td>
<td>0.12 ± 0.29 mm</td>
</tr>
<tr>
<td>Binary restenosis</td>
<td>2.6%</td>
<td>10.1%</td>
<td>9.4%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

PEVA, poly(ethylene co-vinyl acetate); PBMA, poly(n-butyl methacrylate); SIBBS, poly(styrene-b-isobutylene-b-styrene)

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**Figure 29-3.** The cell cycle and the mechanism of action of paclitaxel, sirolimus, and the sirolimus analogs everolimus and zotarolimus. Data from Byrne RA et al.14

**Figure 29-4.** Chemical structures for the drugs found in first- and second-generation coronary artery stents.
Paclitaxel is a compound derived from the bark of the Pacific yew tree (Taxus brevifolia) that was discovered as part of a National Cancer Institute’s initiative many years ago to screen thousands of plant extracts for antitumor activity. After its antineoplastic mechanism of action was elucidated in 1979, it was approved for oncologic use in 1992. It is now used for treating cancers of the lung, breast, and ovaries, in addition to being embedded on the Taxus stent. Its role as both an antineoplastic and antirestenotic drug is due to its antiproliferative activity. After being readily taken up into the cytoplasm, paclitaxel serves to disrupt proper microtubule assembly. Microtubules are vital for proper development and functioning of the cytoskeleton. They are involved with cell division, motility, and maintenance of cell shape. They also play an important role in signal transduction from mitogen receptors, intracellular transport, and vesicle formation.

Paclitaxel stabilizes polymerized microtubules and promotes the assembly of unorganized and denaturalized microtubules inside the cytoplasm. The end result is more microtubules, although these microtubules are dysfunctional and abnormally stable. Consequently, these microtubules have difficulty disassembling, which is a necessary step for progression from the G2 to the M phase of the cell cycle.

The antiproliferative effect of paclitaxel is long-lasting even at low doses, which is a desirable characteristic for use in DES. The ability of paclitaxel to inhibit intimal hyperplasia, smooth muscle cell proliferation and migration, matrix formation, and endothelial cell regeneration has been well described. However, proper microtubule function is also needed for endothelial cell migration and attachment to matrix protein, which are needed for restoration of arterial endothelium. In fact, coronary artery endothelium appears to be especially sensitive to the effects of paclitaxel, which can result in slowed wound healing and re-endothelialization.

### Stent Platform

The stent design is a critical factor when dealing with device biocompatibility. The shape and size of the stent struts and the material from which the stent is made can impact in-stent restenosis rates. In fact, stent design is believed to be the second most important factor (small vessel size being the first) for affecting in-stent restenosis. Since the degree of neointimal growth is related to the amount of vessel injury, a stent design that would minimize vessel injury upon placement is preferred. The thickness of the stent struts, the ratio of metal density to total surface area, and the number of strut intersections can impact the degree of vessel injury, platelet aggregation, inflammation, and neointimal hyperplasia that occur with stent placement.

The ideal thickness of stent struts is difficult to quantify. Thicker struts have the advantages of producing more radial force and providing a more rigid scaffolding to reduce elastic recoil and maintain arterial lumen diameter following the procedure, as well as having improved visibility during the procedure itself. However, thicker struts can produce more damage to the arterial wall that, as mentioned above, can increase neointimal hyperplasia. In addition, thinner struts have shown some potential in reducing BMS restenosis. It has also been shown that neointimal overgrowth may be lessened by having fewer intersections between struts. Currently available stents have a 10% to 15% metal-to-surface area ratio, which represents an improvement over the 20% ratio seen in early stents. This reduced ratio is believed to result in lower thrombosis and restenosis rates with contemporary stents compared to their older counterparts.

The most common material used in stent production is medical grade 316L stainless steel, which has high tensile strength and corrosion resistance due to the addition of chromium. The composition of these stents is largely iron (60% to 65%) with lesser amounts of chromium (17% to 18%) and nickel (12% to 4%). However, the material is not very biocompatible, and it is also relatively radiolucent, making postdeployment visualization a challenge. Newer materials, such as cobalt-chromium alloys, allow for the development of thinner struts and improved radiopacity without sacrificing radial strength. The first-generation Cypher and Taxus stents use a stainless-steel foundation, while the second-generation Endeavor and Xience V stents employ a cobalt-chromium alloy (Table 29-1).

### Stent Polymers

DES are designed to contain a drug that is loaded onto the stent either directly or through the use of polymer coatings; they release (elute) that drug from the stent over a period of time. The amount of drug loaded onto the stent is sufficient to produce a localized effect without resulting in systemic toxicity. An ideal DES polymer should have good coating integrity throughout the manufacturing and deployment process, be compatible with drug and vessel, provide uniform drug distribution along the stent, retain the drug during stent deployment, provide controlled drug release, and have a stable shelf-life. The first-generation stents use permanent polymers that have been shown to trigger hypersensitivity reactions and inflammation. This may contribute to the increased risk of late stent thrombosis seen with these stents, as well as progressive rebound restenosis. The use of more biocompatible polymers represents a significant distinction between the first- and second-generation stents.
The Cypher stent uses 2 nonerodable polymers: polyethylene-co-vinyl acetate and poly-n-butyl methacrylate. These 2 polymers are combined with sirolimus at a concentration of 140 mcg/cm² and then coated with a drug-free poly-n-butyl methacrylate layer to control drug release. Within the first 30 days, 80% of the drug is released from the stent, with 100% being released over 4-6 weeks.48,53 The Taxus stent employs the Translute polymer, which is a matrix-controlled system made of soft elastomeric triblock co-polymer known as poly(styrene-b-isobutylene-b-styrene). Paclitaxel is placed on the surface of the poly(styrene-b-isobutylene-b-styrene) matrix in a low drug-to-polymer ratio (1 mcg/mm²) to slow the speed of drug release and to provide for a sustained-release effect. The Taxus stent displays a biphasic elution profile, with 10% eluted in the initial 10 days and the remaining 90% remaining sequestered indefinitely.48,53

The Endeavor stent contains a phosphorylcholine nonerodable polymer known as Biolinx. This polymer has 3 constituents: a hydrophobic polymer (C10) to hold onto the drug and control its release, another polymer (C19) to improve biocompatibility, and a hydrophilic polyvinyl pyrrolidinone polymer on the outermost layer of the stent to increase the initial drug burst and further improve biocompatibility.47 About 70% of the drug is eluted from this polymer over the first 30 days.48

The polymer coating in the Xience V stent contains 2 layers: a primer and drug reservoir as well as 2 polymers: an acrylic polymer and a fluoro polymer.54 Everolimus is placed on the stent at a concentration of 100 mcg/cm² with no top-coat polymer layer.55 The first day after stent implantation, 25% of the drug is released, with 75% being released in the first month and all drug released within 4 months.56

**Efficacy of Drug-Eluting Stents**

The efficacy of DES has been extensively characterized and has been the subject of many reviews and meta-analyses.56a A thorough discussion of DES efficacy is beyond the scope of this chapter, and the reader is referred to recent reviews of the topic for more details.57,57a Tables 29-2 and 29-3 provide an overview of the efficacy of the currently available DES.58,48 When determining stent efficacy, it is believed that the rate of target lesion revascularization is the most relevant endpoint as this most accurately represents the mechanism of action of these devices. When this endpoint is analyzed, one can arrive at the following conclusions regarding DES efficacy:14

1. DES are clearly more efficacious than BMS in preventing in-stent restenosis. The magnitude of reduction is about 35% to 70%.

2. The benefits of DES have been maintained as long as 4 to 5 years, showing no increased risk of death, myocardial infarction, or stent thrombosis compared to BMS.

3. There is no evidence of mortality reduction with DES.

4. The time course of thrombotic events is shifted later compared to BMS. In other words, the few cases of stent thrombosis that do occur happen > 1 year after DES placement versus < 6 months after BMS placement.

5. There is continued debate as to which DES is superior.

It should be kept in mind that the efficacy rates reported in the literature with DES are typically seen with de novo lesions in native coronary arteries between 2.5 and 3.75 mm in diameter and < 30 mm in length. Off-label uses of these stents, eg, bypass grafts, acute myocardial infarction, comprise at least 50% of all interventions and tend to involve more complicated cases and procedural complexity.14 As such, the benefits seen in rigorous clinical trials may not necessarily translate to a more complicated patient.

**Safety of Drug-Eluting Stents**

DES are a double-edged sword. The mechanism that makes them so efficacious appears to be the same mechanism by which problems arise. The most noticeable safety issue with DES is late stent thrombosis,85b which can occur years after stent placement. The mechanism for this is believed to be interference with re-endothelialization, or the formation of a healthy functioning endothelium after the stent is placed. While these stents are very effective at limiting neointimal smooth muscle cell proliferation, they are not specific for smooth muscle cells and also appear to inhibit the proliferation, migration, and differentiation of endothelial progenitor cells in vitro, which play a role in the re-endothelialization process.86,87

This concept was not fully appreciated until reports of very late (> 1 year postintervention) stent thrombosis began to surface in the literature.88 Pathology studies subsequently discovered evidence of vascular inflammation and poor endothelialization of stent struts even more than 1 year after stent placement.88 The cause of this is likely due to many factors, one of which may be an inflammatory response mounted against the polymer residue that remains in the vessel wall after drug elution.88,89 Several risk factors have been associated with an increased risk of thrombosis following DES placement. The biggest of these is premature discontinuation of dual antiplatelet therapy (ie, aspirin + thienopyridine), followed by renal failure, bifurcation interventions, diabetes mellitus, and left ventricular dysfunction.89 It has since been shown that continuation of dual antiplatelet therapy beyond 1 year results in lower rates of death and myocardial
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>DES</th>
<th>Duration</th>
<th>Efficacy (TLR/TVR)</th>
<th>Safety (Total Mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolfi et al58</td>
<td>Meta-analysis</td>
<td>2005</td>
<td>Cypher</td>
<td>6-12 mos</td>
<td>0.23 (0.15 – 0.35)</td>
<td>1.29 (0.52 - 3.18; n = 1905)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1855</td>
<td>Taxus</td>
<td></td>
<td>0.39 (0.29- 0.53)</td>
<td>0.89 (0.28-2.80; n = 1533)</td>
</tr>
<tr>
<td>Roiron et al59</td>
<td>Meta-analysis</td>
<td>8987</td>
<td>All DES</td>
<td>12 mos</td>
<td>0.36 (0.31-0.41)</td>
<td>1.02 (0.64-1.64)</td>
</tr>
<tr>
<td>Schampaert et al60</td>
<td>Meta-analysis</td>
<td>1510</td>
<td>Cypher</td>
<td>2 yrs</td>
<td>0.25 (0.18-0.35)</td>
<td>1.32 (0.62-2.78)</td>
</tr>
<tr>
<td>Nordmann et al61</td>
<td>Meta-analysis</td>
<td>3513</td>
<td>Taxus</td>
<td>3 yrs</td>
<td>Not assessed</td>
<td>1.10 (0.71-1.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1296</td>
<td>Cypher</td>
<td>4 yrs</td>
<td>Not assessed</td>
<td>1.46 (0.92-1.31)</td>
</tr>
<tr>
<td>Stettler et al62</td>
<td>Network meta-analysis</td>
<td>18,023</td>
<td>Cypher</td>
<td>Up to 4 yrs</td>
<td>0.30 (0.24-0.37)</td>
<td>1.00 (0.82-1.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Taxus</td>
<td>0.42 (0.33-0.53)</td>
<td>1.03 (0.84-1.22)</td>
</tr>
<tr>
<td>Kastrati et al63</td>
<td>Meta-analysis</td>
<td>4958</td>
<td>Cypher</td>
<td>12-59 mos</td>
<td>0.31 (0.23-0.41)</td>
<td>1.03 (0.80-1.30)</td>
</tr>
<tr>
<td>Spaulding et al64</td>
<td>Meta-analysis</td>
<td>1748</td>
<td>Cypher</td>
<td>4 yrs</td>
<td>Not assessed</td>
<td>1.24 (0.84-1.83)</td>
</tr>
<tr>
<td>Stone et al65</td>
<td>Meta-analysis</td>
<td>5321 total</td>
<td>Cypher</td>
<td>2-4 yrs</td>
<td>0.29 (0.22-0.39)</td>
<td>1.27 (0.86-1.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Taxus</td>
<td>0.38 (0.30-0.48)</td>
<td>0.94 (0.70-1.26)</td>
</tr>
<tr>
<td>Pasceri et al66</td>
<td>Meta-analysis</td>
<td>1857</td>
<td>All DES</td>
<td>8-12 mos</td>
<td>0.40 (0.30-0.54)</td>
<td>0.90 (0.53-1.51)</td>
</tr>
<tr>
<td>Boyden et al67</td>
<td>Meta-analysis in diabetics</td>
<td>1520</td>
<td>Cypher</td>
<td>6-9 mos</td>
<td>0.34 (0.26-0.45)</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Kastrati et al68</td>
<td>Meta-analysis</td>
<td>2476</td>
<td>All DES</td>
<td>12-24 mos</td>
<td>0.38 (0.29-0.50)</td>
<td>0.76 (0.53-1.10)</td>
</tr>
<tr>
<td>Kumbhani et al69</td>
<td>Meta-analysis in diabetics</td>
<td>2952</td>
<td>Cypher</td>
<td>6-12 mos</td>
<td>0.35 (0.27-0.46)</td>
<td>0.64 (0.32-1.28)</td>
</tr>
<tr>
<td>Stettler et al70</td>
<td>Network meta-analysis</td>
<td>14,799</td>
<td>Cypher</td>
<td>Up to 4 years</td>
<td>Diabetes: 0.29 (0.22-0.39)</td>
<td>Diabetes: 0.88 (0.55- 1.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Taxus</td>
<td>No diabetes: 0.29 (0.22-0.38)</td>
<td>No diabetes: 1.02 (0.77-1.29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes: 0.38 (0.28- 0.55)</td>
<td>Diabetes: 0.91 (0.60-1.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No diabetes: 0.46 (0.33-0.60)</td>
<td>No diabetes: 0.90 (0.67-1.16)</td>
</tr>
<tr>
<td>Brar et al71</td>
<td>Meta-analysis</td>
<td>7352</td>
<td>All DES</td>
<td>7-24 mos</td>
<td>0.44 (0.35-0.55)</td>
<td>0.89 (0.70-1.14)</td>
</tr>
<tr>
<td>Kirtane et al72</td>
<td>Meta-analysis</td>
<td>9470</td>
<td>All DES</td>
<td>Median 2.9 yrs</td>
<td>0.45 (0.37-0.54)</td>
<td>0.97 (0.81-1.15)</td>
</tr>
</tbody>
</table>
infarction for patients receiving DES, but not BMS. As a result, current post-stent treatment guidelines recommend a minimum of 1 year of dual antiplatelet therapy for patients receiving a DES, and up to 1 year for patients receiving a BMS.

When looking at overall mortality as a function of stent safety, we are reliant on registry data and meta-analyses. Although data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) suggested a possible increase in mortality at 3 years with DES versus BMS, most data sets do not suggest there to be an overt problem with DES compared to BMS (Tables 29-2 and 29-3). However, there are 2 patient groups in whom safety concerns have been raised regarding DES: diabetics and those with acute myocardial infarction. While there are some data to suggest poorer outcomes (ie, death or stent thrombosis) with DES in these patients, this had not been a consistent finding.

Future Directions

The field of percutaneous coronary intervention remains a moving target in terms of the dynamic changes that continue to occur in this field. Since the ideal coronary artery stent is not yet available for clinical use, nearly every aspect of stent technology is being investigated and modified in an attempt to improve deliverability, reduce restenosis, and ultimately improve clinical outcomes. New drugs continue to be developed and studied for application to coronary stents. Biolimus, another sirolimus analog, tacrolimus, novolimus, and pimecrolimus are just a few compounds that are being investigated in this regard. In addition, drug dosages and release characteristics (slow versus fast) continue to be analyzed in a continual effort to improve stents. Modifications to stent design include the use of different metal alloys to provide increased flexibility, improved radial strength and radio-opacity, and less recoil. The use of a platinum-chromium alloy represents such an effort (TAXUS Element stent) and is currently being investigated in the TAXUS PERSEUS Workhorse trial. Paclitaxel is also being investigated as an independent drug to be administered with BMS to reduce restenosis. Coroxane is a protein-engineered nanoparticle albumin bound paclitaxel that is administered intravenously just after the stenting procedure.

Perhaps the most active area of stent research involves the use of different types of polymers. Given the many issues with current stent polymers, especially those in the first-generation stents, elimination of the polymer burden altogether is an attractive option. Reservoir stents represent such an option; these stents contain no polymer at all but rather use porous stent surfaces to deliver drug. The CoStar stent is an investigational device that releases paclitaxel toward both the luminal and/or abluminal side of the vessel through a bioresorbable polymer located within the walls of the stent.

Another option is coating the stent with a proendothelial agent. As mentioned above, currently available antiproliferative agents inhibit the proliferation, migration, and differentiation of endothelial progenitor cells in vitro, which plays a role in the re-endothelialization process. In addition, a reduction in circulating CD34+ cells has been demonstrated with sirolimus stent implantation. The investigational Genous Bio-Engineered Stent is coated with a CD34-binding antibody designed to attract endothelial progenitor cells and promote reendothelialization. The use of bioabsorbable polymers is also of great interest, as this would eliminate the presence of a
Table 29-3. Select Efficacy Studies and Meta-Analyses Comparing Drug-Eluting Stents*

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sample size</th>
<th>DES</th>
<th>Duration</th>
<th>Efficacy† (TLR/TVR)</th>
<th>Safety† (Total mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kastrati et al75</td>
<td>Meta-analysis</td>
<td>3669</td>
<td>Cypher vs. Taxus</td>
<td>6-13 mos</td>
<td>0.64 (0.49-0.84)</td>
<td>0.86 (0.49-1.50)</td>
</tr>
<tr>
<td>Stettler et al76</td>
<td>Meta-analysis</td>
<td>4513</td>
<td>Cypher vs. Taxus</td>
<td>8-24 mos</td>
<td>Diabetes: 0.86 (0.40-1.86) No diabetes: 0.54 (0.30-0.99)</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Stettler et al81</td>
<td>Network meta-analysis</td>
<td>18,023 total</td>
<td>Cypher vs. Taxus</td>
<td>Up to 4 yrs</td>
<td>0.70 (0.56-0.84)</td>
<td>0.96 (0.83-1.24)</td>
</tr>
<tr>
<td>Schöning et al77</td>
<td>Meta-analysis</td>
<td>8695</td>
<td>Cypher vs. Taxus</td>
<td>9-37 mos</td>
<td>0.74 (0.63-0.87)</td>
<td>0.92 (0.74-1.13)</td>
</tr>
<tr>
<td>Gurman et al78</td>
<td>Meta-analysis</td>
<td>7455</td>
<td>Cypher vs. Taxus</td>
<td>6-12 mos</td>
<td>0.67 (0.53-0.84)</td>
<td>0.88 (0.61-1.25)</td>
</tr>
<tr>
<td>ENDEAVOR III79</td>
<td>Randomized, controlled, single-blind</td>
<td>436</td>
<td>Endeavor vs. Cypher</td>
<td>9 mos</td>
<td>1.79 (0.62 – 5.12)</td>
<td>No difference due to low event rates (p = 1.0)</td>
</tr>
<tr>
<td>SIRIUS80</td>
<td>Randomized, controlled, single-blind</td>
<td>1012</td>
<td>Cypher vs. Taxus</td>
<td>9 mos.</td>
<td>0.56 (0.34 – 0.93)</td>
<td>0.45 (0.16 – 1.31)</td>
</tr>
<tr>
<td>SORT OUT II81</td>
<td>Randomized, open label</td>
<td>2098</td>
<td>Cypher vs. Taxus</td>
<td>18 mos.</td>
<td>0.72 (0.48 – 1.07)</td>
<td>0.99 (0.64 – 1.53)</td>
</tr>
<tr>
<td>REALITY82</td>
<td>Randomized, controlled</td>
<td>1386</td>
<td>Cypher vs. Taxus</td>
<td>12 mos.</td>
<td>0.98 (0.64 – 1.49)</td>
<td>1.74 (0.77 – 3.91)</td>
</tr>
<tr>
<td>ISAR-DIABETES83</td>
<td>Randomized, controlled, single-blind</td>
<td>250, all with diabetes</td>
<td>Cypher vs. Taxus</td>
<td>9 mos.</td>
<td>1.89 (0.82 – 4.87)</td>
<td>1.5 (confidence interval not reported; p = 0.52)</td>
</tr>
<tr>
<td>ENDEAVOR IV84</td>
<td>Randomized, controlled, single-blind</td>
<td>1548</td>
<td>Endeavor vs. Taxus</td>
<td>12 mos.</td>
<td>2.6 (confidence interval not reported; p = 0.228)</td>
<td>1.0 (confidence interval not reported; p = 1.0)</td>
</tr>
<tr>
<td>SPIRIT III85</td>
<td>Randomized, controlled, single-blind</td>
<td>951</td>
<td>Xience V vs. Taxus</td>
<td>2 yrs</td>
<td>Target vessel failure (primary endpoint): 0.68 (0.48-0.98); TLR 0.60 (0.35-1.04)</td>
<td>0.77 (confidence interval not reported; p = 0.64)</td>
</tr>
<tr>
<td>SPIRIT IV85a</td>
<td>Randomized, controlled, single-blind</td>
<td>3687</td>
<td>Xience V vs Taxus</td>
<td>1 yr</td>
<td>Target vessel failure (primary endpoint): 0.62 (0.46-0.82); TLR 0.77 (confidence interval not reported; p = 0.64)</td>
<td></td>
</tr>
</tbody>
</table>
Drug-Eluting Stents

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thrombogenic foreign body in the arterial wall. They would also possess the advantage of not interfering with computed tomography or magnetic resonance imaging studies and would not present a barrier to coronary artery bypass graft surgery if that were to be needed at some point.

Several of these types of stents are in development, involving both polymeric (eg, Igaki-Tamai stent, BVS stent, Sahajanand stent, REVA stent) and metallic bio-absorbable/biodegradable stent systems (eg, magnesium alloy AMS stent; 2-3 month degradation time). The disadvantage of these stents is the relative lack of radial strength compared to BMS that can make them less effective against elastic recoil, limited stent flexibility, and low radio-opacity, which can make placement difficult. In addition, inflammatory reactions have been observed in animal models in response to stent degradation. Nonetheless, bioabsorbable stents hold great promise in overcoming many of the limitations of DES. They have good deliverability, cause little vascular trauma upon deployment, minimize the inflammation seen with DES polymers, and do not retard endothelialization. Whether or not this translates to measurable clinical benefit remains to be seen in controlled clinical trials.

In addition, DES that are polymer free are in clinical trials, as well as BMS with novel coatings which are anti-inflammatory. Also, drug-eluting balloons for use in angioplasty are being evaluated, especially for specific coronary lesions where DES cannot be delivered.

Summary

DES represent a significant advance in the treatment of coronary artery disease, adding to the benefits previously seen with BMS. DES inhibit the neointimal overgrowth that occurs in response to BMS placement. The pharmaceutical construct of DES involves embedding an antiproliferative drug onto a metal stent platform containing a polymer coat to regulate drug release. Each of the 4 DES currently available differ from each other in terms of drug, stent platform, and polymer, with the newer stents exhibiting better deliverability, less vessel trauma, and better endothelialization compared to earlier DES. As a whole, DES reduce stent restenosis rates by about 35% to 70% compared to BMS with no increased risk of major adverse cardiovascular events. The ability of the vascular endothelium to grow over the stent has represented a significant obstacle in terms of stent performance, necessitating long-term dual antiplatelet therapy to reduce the occurrence of late stent thrombosis. Newer stent designs involve better platforms to maintain scaffolding strength while improving deliverability and minimizing vessel trauma and localized inflammation. With this in mind, coronary artery stents will undoubtedly change over the next several years, likely for the better, as the pursuit of the ideal stent continues.

Note: References for this chapter can be found here:
www.cvpct3.com
Part 3

Special Topics
Alternative and Complementary Medicine for Preventing and Treating Cardiovascular Disease

William H. Frishman, MD

More and more individuals are looking outside the borders of conventional medicine for at least part of their health care needs. In the United States, more visits are being made to nonconventional healers than to physicians, at an annual cost of over $30 billion; most of this cost is out-of-pocket.

As a health care discipline, alternative medicine is defined as those medical approaches that in the past were not traditionally addressed in allopathic medical schools. Complementary medicine is a term first used in Great Britain to describe the use of alternative medicine as an adjunct to, and not primarily a replacement for, conventional medical care. In the 21st century, there is an ongoing effort to integrate complementary and alternative medicine (CAM) into conventional medicine practice (Integrative Medicine). In 1998, the National Institutes of Health, recognizing the need to vigorously evaluate CAM therapies, created the National Center for Complementary and Alternative Medicine (NCCAM), which supports ongoing scientific research and educational programs.

In recent years, multiple hospitals have formed Centers of Integrative Medicine, and many allopathic medical schools are now offering course work in CAM.

CAM therapies have been used to treat cardiovascular disorders. However, the use of CAM for treating cardiovascular disease is a highly charged subject with both critics and proponents. CAM therapies are a challenge to the scientific training of many cardiovascular physicians, with most positive observations being considered a placebo effect (see Chapter 2, The Placebo Effect in the Treatment of Cardiovascular Disease), which has been shown to be very powerful in patients with cardiovascular disease, especially in those who participate in randomized clinical trials (Table 30-1). A recent study with patient-based evaluations showed that cardiovascular patients treated by CAM doctors are more likely to be satisfied with the overall treatment outcome, possibly because of the longer and better patient-practitioner interaction. Therefore, physicians can no longer turn a deaf ear to the possibilities of CAM, and a growing number are already integrating CAM into their practices or are referring their patients to other CAM practitioners. The American College of Cardiology has been sponsoring an annual course on CAM as part of their continuing medical education efforts. In a recent workshop, the NCCAM emphasized the need for an exchange of ideas between CAM practitioners and scientists, and for collaborative research efforts.

One study used the 2002 National Health Interview Survey and analyzed data on CAM use in 10,572 respondents with cardiovascular disease. Among those with cardiovascular disease, 36% had used CAM (excluding prayer) in the previous 12 months. The most commonly used therapies were herbal products (18%) and...
mind-body therapies (17%). Among herbs, echinacea, garlic, ginseng, ginkgo biloba, and glucosamine with or without chondroitin were most commonly used. Overall, fewer respondents (10%) used CAM specifically for their cardiovascular conditions (5% for hypertension, 2% for coronary artery disease [CAD], 3% for vascular insufficiency, < 1% for heart failure [HF] or stroke). Most, however, who used CAM for their cardiovascular condition perceived the therapies to be helpful (80% for herbs).

Clearly, the use of alternative medicine is far higher than previously reported. Although most alternative therapies are relatively innocuous, some involve the use of pharmacologically active substances (eg, herbal medicine, megavitamin therapy, and some folk remedies) that could complicate existing medical therapy or even harm patients. Although an increasing number of physicians are becoming more comfortable with alternative medicine, the widespread use of nutritional supplements with potential pharmacologic activities demands that all physicians not only inquire about their patient’s use of alternative medicine but also educate themselves and their patients as to the potential harms and benefits of these remedies. The reluctance of patients to disclose their use of complementary medicines stems from fear of disapproval of these interventions by their physicians and from the belief that natural remedies are harmless. Surveys also indicate that patients fail to discuss the use of dietary supplements with their health care providers because they believe that these practitioners know little or nothing about these products and may even be biased against them.

Rather than dismissing a patient’s highly motivated intentions toward health-conscious behaviors or refusing to prescribe for them out of fear of potential drug interactions, it behooves physicians to understand the range of complementary therapies available and when they can be safely integrated into conventional medicine. Thus, they may more effectively counsel their patients in a collaborative and more effective atmosphere of open communication. Physicians’ knowledge of nutritional supplement intake is also critical to avoid potentially dangerous interactions with prescribed medication. For example, consider patients taking warfarin who are also ingesting nonprescribed natural blood thinners such as garlic, ginger, fish oil, ginkgo biloba, and even excessive amounts of vitamin E at the same time. Such a combination clearly poses potential risks for both patient and the physician.

This chapter limits its review to some of the pharmacologically active substances most commonly used or that have effects on the cardiovascular system based on the existing scientific literature. This chapter pays attention to medicinal plants, which the author accepts to be pharmacologically active substances in a diluted form, and 4 other alternative remedies (vitamins/minerals, other micronutrient supplements, homeopathic remedies, and chelation).

### Megavitamins and Other Micronutrient Substances

Vitamins and minerals are required in trace amounts for normal bodily functioning. A number of people have subscribed to the notion that “more is better.” Ingestion of micronutrient supplements (vitamins and minerals) beyond the “recommended daily allowances” (RDAs) is beneficial in certain deficiency states resulting from inadequate intake, disturbed absorption, or increased tissue requirements; however, routine dietary supplementation of micronutrients in the absence of deficiency states and beyond what one can usually obtain from consumption of a well-balanced diet has been shown to be of questionable benefit and in some cases may be harmful. Of course, there are exceptions. This section reviews those micronutrient supplements with beneficial, neutral, and harmful effects on the cardiovascular system (Table 30-2).

In 1994, the US Congress passed the Dietary Supplement Health and Education Act, which prevents the US Food and Drug Administration (FDA) from regulating vitamins, minerals, and herbal products as drugs. The law permits the continued marketing of dietary supplements sold before October 15, 1994 (defined as vitamins, minerals, botanicals, amino acids, enzymes) without the review or approval of any government agency. In June 2007, the FDA established the dietary supplement current Good Manufacturing Practice (cGMP) regulation that requires manufacturers to evaluate their products through testing identity, purity, strength, and composition. Health claims can be made on the label with FDA approval and a disclaimer saying that the product is not intended to diagnose, treat, cure, or prevent any disease.

### The Rationale for Targeted Nutritional Supplements for Cardiovascular Health

The heart, which has approximately 5,000 mitochondria per cell and functions in a high-oxygen environment, is one of the most susceptible of all organs to free-radical oxidative stress. Fortunately, it is also highly responsive to the benefits of targeted nutritional agents, such as phytonutrients, antioxidants, and nutraceuticals.

The term *nutraceutical* includes a wide variety of nonprescription nutritional supplements normally found in the body or in natural sources (such as vitamins, amino acids, and herbs). Strong scientific evidence from large and repeated clinical trials has confirmed their efficacy and safety as well as guidelines for patient selection, dosage, and potential medication interactions. Dietary phy-
Fat-soluble vitamins (K, E, D, and A) are stored to a variable extent in the body and are more likely to cause adverse reactions than water-soluble vitamins, which are readily excreted in the urine. Excessive vitamin K can cause hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency and anemia (with Heinz bodies), hyperbilirubinemia, and kernicterus in newborns; moreover, vitamin K can counter the effects of oral anticoagulants by conferring biologic activity on prothrombin and factors VII, IX, and X. In contrast, high doses of vitamin E may potentiate the effects of oral anticoagulants.

Table 30-2: Clinical Effects of Nutraceutical Supplementation* to Prevent and Treat Cardiovascular Disease

<table>
<thead>
<tr>
<th>Nutraceutical</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>No benefit, potential mortality risk with supplemental doses $\geq 400$ IU</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>No benefit proven</td>
</tr>
<tr>
<td>Thiamine</td>
<td>Useful in depletion state related to diuretics</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Reduces homocysteine levels, but no benefit proven</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>No benefit proven</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>May be effective in reducing vascular calcification</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Reduces homocysteine levels, but no benefit proven</td>
</tr>
<tr>
<td>Pyridoxine (Vitamin B3)</td>
<td>Reduces homocysteine levels, but no benefit proven</td>
</tr>
<tr>
<td>Niacin (nicotinic acid)</td>
<td>Reduces cholesterol, LDL-C, VLDL-triglycerides, raises HDL-C, mortality benefit in MI survivors</td>
</tr>
<tr>
<td>Carotenoids</td>
<td>No benefit proven, possible increased mortality risk</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>No benefit proven</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Small amounts ($\leq 1$ oz/day in males, $\leq 0.5$ oz/day females) may reduce risk of both cardiovascular and cerebrovascular diseases</td>
</tr>
<tr>
<td>Magnesium</td>
<td>May have benefits in reducing blood pressure, may be protective during acute MI</td>
</tr>
<tr>
<td>Chromium</td>
<td>Mild cholesterol-lowering effect</td>
</tr>
<tr>
<td>Selenium</td>
<td>No benefit proven</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>No benefit proven</td>
</tr>
<tr>
<td>L-Carnitine</td>
<td>No benefit proven</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>No benefit proven in reducing the risk of CAD</td>
</tr>
<tr>
<td>L-arginine</td>
<td>No benefit proven</td>
</tr>
<tr>
<td>Taurine</td>
<td>No benefit proven</td>
</tr>
<tr>
<td>Amino acid mixtures</td>
<td>No benefit proven</td>
</tr>
</tbody>
</table>

* Supplementation is defined as prophylactic treatment beyond the normal daily requirements of substance.

anticoagulants by antagonizing vitamin K and prolonging prothrombin time.

**Megavitamins and Minerals**

**Vitamin E**

Vitamin E’s antioxidant and anticoagulant properties are thought to protect against myocardial infarction (MI) and thrombotic strokes. An extensive review article assessed the preventive effects of vitamin E on the development of atherosclerosis. α-Tocopherols are the key lipid-soluble, chain-breaking antioxidants found in the tissues and plasma. Oxidation of unsaturated fatty acids in LDL particles, as a pivotal factor in atherogenesis, is widely recognized. Vitamin E, a predominant antioxidant present in the LDL particle, blocks the chain reaction of lipid peroxidation by scavenging intermediate peroxyl radicals. Vitamin E supplementation can reduce lipid peroxidation by as much as 40%. Key cardioprotective effects of vitamin E are stabilizing plaque, decreasing inflammation, decreasing thrombolytic aggregation, reducing the expression of adhesion molecules on the arterial wall, and enhancing vasodilation. However, prospective controlled clinical trials have presented a confusing picture.

Past major human trials on vitamin E supplementation have included the Alpha Tocopherol Beta Carotene (ATBC), Cambridge Heart Antioxidant Study (CHAOS), Gruppo Italiano per lo Studio della Sopravvivenza nell-Infarto Miocardico (GISSI), Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease (SPACE), and Heart Outcomes Evaluation (HOPE) trials. A statistical reanalysis of the data, including the totality of the evidence, suggests that α-tocopherol supplementation does not have a place in treating patients with preexisting cardiovascular disease. In addition, the results of the MRC/BHF Heart Protection Study in 20,536 high-risk individuals showed no benefit from Vitamin E supplementation (600 mg daily) on morbidity and mortality. However, a recent study demonstrated that 100 and 200 mg of vitamin E caused a marked improvement in arterial compliance, and a recent report from the Women's Health Study demonstrated that women receiving vitamin E supplementation had a lower risk of venous thromboembolic disease. The Women's Antioxidant Cardiovascular Study (WACS) tested the effects of ascorbic acid (500 mg/d), vitamin E (600 IU every other day), and beta carotene (50 mg every other day) on the combined outcome of MI, stroke, coronary revascularization, or cardiovascular disease death among 8171 female health professionals and found no significant overall benefits. To prevent pregnancy-associated hypertension, 10,154 pregnant women were randomized to received 1000 mg of vitamin C and 400 IU of vitamin E or matching placebo. In the 9th to 16th week of gestation, vitamin therapy did not reduce the rate of adverse maternal or perinatal outcomes related to pregnancy-induced hypertension.

In addition, the Physician's Health Study II revealed no cardiovascular benefits from every other day supplements of 400 IU of vitamin E administered to 14,641 male physicians older than 50 years. NCCAM is studying the effect of α tocopherol supplementation (1200 IU/day) on the progression of carotid atherosclerosis in patients with CAD (stable angina pectoris or previous MI) in a placebo-controlled, randomized double-blind trial over 2 years. At this time, given the numerous studies and trials, the rationale for vitamin E use in healthy individuals and those with cardiovascular disease is still questionable.

There is also a suggestion that high doses of vitamin E may confer an increased risk for developing calcific atherosclerosis.

**Vitamin C**

Vitamin C is not only a scavenger antioxidant, but it also acts synergistically with vitamin E to reduce the peroxyl radical. In addition to blocking lipid peroxidation by trapping peroxyl radicals in the aqueous phase, vitamin C helps normalize endothelial vasodilative function in patients with heart failure by increasing the availability of nitric oxide. Although the evidence linking vitamin C to human cardiovascular disease is still being evaluated, one study did report that vitamin C slowed the progression of atherosclerosis in men and women older than 55 years.

It is also well known that many groups known to be at an increased risk for CAD have lower blood levels of vitamin C, including men, the elderly, smokers, patients with diabetes mellitus, patients with hypertension, and possibly women taking oral estrogen contraceptives. Female users of vitamin C supplement in the Nurse's Health Study were shown to be at lower risk for CAD.

British researchers found that higher blood levels of vitamin C were directly and inversely related to death from all causes and specifically death from ischemic heart disease in both men and women. The researchers strongly advocated modest consumption of fruits and vegetables, since their results suggested that the equivalent of 1 extra serving of vitamin C–rich food reduced the risk of death by 20%. However, the consumption of carotenoids, flavonoids, magnesium, and other health-promoting nutrients affected these data.

High doses of Vitamin C have also been associated with decreased levels of nitric oxide (NO) production by endothelial cells. Vitamin C at daily doses of 500 mg has been shown to increase red cell glutathione by 50%. Glutathione is not only the major antioxidant responsible for inhibiting lipid peroxidation but also a key contributing agent in stabilizing immune function.

However, the results of the MRC/BHF Heart Protection Study showed no benefit from vitamin C supplementation (250 mg daily) on morbidity and mortality in high-risk
patients with cardiovascular disease. The WACS also has recently showed that there were no overall effects of ascorbic acid on cardiovascular events among women at high risk for CVD. In addition, results from the Physician’s Health Study II did not show any benefit from 500 mg of vitamin C in prevention of cardiovascular disease.

Megadose vitamin C (> 500 mg a day) in patients who are vulnerable to iron overload states should also be avoided. Vitamin C supplements may exacerbate iron toxicity by mobilizing iron reserves. Such patients may accumulate harmful excessive iron with higher doses of vitamin C, so caution must be employed for those with genetic diseases such as hereditary hemochromatosis, thalassemia major, or other diseases that promote iron overload.

B Vitamins
Clinical cardiologists must be familiar with B vitamin support for their patients. B vitamin (thiamine) depletion commonly occurs as a result of high-dose diuretic therapy used in the treatment of congestive heart failure (CHF) and should be considered in any patient with refractory CHF that is unresponsive to high-dose diuretic therapy. The nocturnal leg cramps associated with diuretic therapy are a hallmark symptom of B vitamin depletion. The involuntary, painful contraction of the calf muscles and other areas of the leg can be alleviated with B vitamin support, resulting in an improved quality of life. A randomized placebo-controlled double-blind study validated the efficacy of B complex supplementation in the treatment of nocturnal cramps. Of 28 elderly patients, 86% taking vitamin B complex reported remission of prominent symptoms compared to the observation of no benefit in the placebo group.

Most cardiologists are now familiar with the idea of providing B vitamin supplementation to treat hyperhomocysteinemia. In 1969, McCully first proposed the homocysteine hypothesis, identifying accelerated vascular pathology as a sequel to homocystinurias, a rare autosomal recessive disease caused by a deficiency in cystathionine B-synthetase. Several investigations have confirmed his proposed connection between high plasma homocysteine levels and occlusive arterial disease, including peripheral vascular disease, CAD, and CHF.

Hyperhomocysteinemia may be even more detrimental in women than in men. One study reported that women with CAD had higher homocysteine levels than matched control subjects. In another study involving postmenopausal women, high homocysteine levels in combination with hypertension resulted in an alarming 25 times higher incidence of stroke.

It is well known that B vitamins reduce homocysteine levels significantly. Research shows a dose-dependent relationship between higher homocysteine levels and lower serum levels of B vitamins; therefore, much higher doses must be administered to those patients with severe hyperhomocysteinemia and documented CAD. Although this may have been shown previously, it is now more apparent that this may no longer be the case. The trials completed to date do not provide clear evidence of any beneficial effects of B vitamin supplementation in cardiovascular disease risk reduction. Several trials including the Vitamins Intervention for Stroke Prevention (VISP) trial, Heart Outcomes Prevention Evaluation (HOPE-2) trial, the Western Norway B-Vitamin Intervention Trial (WENBIT), and the Cambridge Heart Antioxidant Study (CHAOS-2) have failed to demonstrate benefits with vitamin B supplementation. Moreover, treatment with folic acid plus vitamin B12 was associated with an increased risk of cancer and all-cause mortality in patients with ischemic heart disease.

In a recent study, Albert et al showed that after 7.3 years of treatment and follow-up, a combination pill of folic acid, vitamin B6, and vitamin B12 did not reduce a combined endpoint of total cardiovascular events among high-risk women, despite significant homocysteine lowering. Some limitations of this study may be the introduction of mandatory folate-food–fortification policies in the United States and Canada resulting in lesser effects of B vitamin supplements on homocysteine levels; the vitamin doses used; and potential unexpected proatherosclerotic effects of folic acid supplementation, which may have counteracted benefits associated with homocysteine lowering. Recently it was shown that treatment with high doses of folic acid and B vitamins did not improve survival or reduce the incidence of vascular disease in patients with advanced chronic kidney disease and end-stage renal disease. A number of large trials are still in progress, including studies in populations with unfortified food supplies in Western Europe, Australia, and Asia. It is still necessary for ongoing clinical research to provide evidence on whether there may be any role for homocysteine-lowering B vitamin supplements in CVD prevention and for the overall importance of homocysteine as a cardiovascular disease risk factor before it can be recommended routinely.

Certainly, administration of B vitamins at the recommended daily allowance levels (folic acid = 400 µg; B6 = 2 mg; B12 = 6 µg) appears to be safe. A potential hazard of folic acid therapy is subacute degeneration of the spinal cord with a subclinical vitamin B12 deficiency; folic acid may mask the development of hematologic manifestations in these patients. This situation can be avoided by either ruling out B12 deficiency before initiating folic acid therapy or by supplementing folic acid with vitamin B12.

High-dose niacin (vitamin B3) is used in the treatment of hyperlipidemia and hypercholesterolemia and helps
curb the development of atherosclerosis and its complications (see Chapter 20, Lipid-Lowering Drugs). Recent studies indicate that niacin also increases the vascular endothelial cell redox state, resulting in the inhibition of oxidative stress and vascular inflammatory genes, key cytokines involved in atherosclerosis.43

Over-the-counter niacin preparations are marketed under different names; some have no free nicotinic acid, which is the cholesterol-lowering component of niacin.44 Adverse effects of niacin include cutaneous flushing, pruritus, gastrointestinal disturbances, exacerbation of asthma, and even acanthosis nigricans. Very high doses can cause liver toxicity. Vasodilation and flushing, the most common side effects of niacin, may help patients who suffer from Raynaud’s phenomenon.

In an attempt to find a safer form of niacin with fewer adverse effects, investigators have developed extended-release, once-daily formulations of niacin (Niaspan). This slowly metabolized form of niacin does not reach maximum serum levels for several hours after ingestion, resulting in fewer and less severe adverse effects.45,46 Randomized, double-blind, placebo-controlled investigations showed that sustained-released niacin had an impact in decreasing LDL-cholesterol, total cholesterol, and triglycerides while raising high-density lipoprotein (HDL)-cholesterol at the same time.45,46 A study by Ceali et al, which compared the incidence, intensity, and duration of flushing between the 1,000 mg reformulated niacin ER and the 1,000 mg commercially available formulation, when administered as a single 2,000 mg dose to healthy male volunteers, found it to be an improved therapeutic option.47

Studies have also resulted in a new combination drug (extended release niacin [ERN] and laropiprant). Niacin is not optimally used, mainly because of flushing, a process mediated primarily by prostaglandin D(2), which leads to poor patient adherence and suboptimal dosing. Laropiprant is a selective antagonist of the prostaglandin D(2) receptor subtype 1 (DP1), which may mediate niacin-induced vasodilation. A study by Paolini et al48 showed that laropiprant does not interfere with the beneficial lipid effects of niacin and can allow for the administration of a 2g dose of ERN in dyslipidemic patients. In another trial of 1,613 patients, 10.2% patients stopped taking the medication in the ERN and laropiprant group because of flushing versus 22.2% with niacin monotherapy.49 The FDA has not approved the niacin-laropiprant combination (Cordaptive) for clinical use, and the commercial sponsor has withdrawn the combination agent from further study.

Vitamin D
Vitamin D receptors have been found in the vascular smooth muscle,50 the endothelium,51 and in cardiomyocytes.52 There are data to suggest that low levels of 25-hydroxyvitamin-D may be associated with the development of cardiovascular disease (Figure 30-1).53-55 Studies have shown an inverse relationship between vitamin D levels and plasma renin activity,56 hypertension,56 and coronary artery calcification.57 Recently, results from the Framingham offspring study suggest a direct association of vitamin D deficiency and the incidence of cardiovascular disease.58 Low levels of vitamin D have also been associated with fatal strokes,59 HF,59 sudden cardiac death,60 and calcific aortic stenosis. It has also been observed that the prevalence of heart disease increases the further the distance from the equator, suggesting a deficiency of sunlight and vitamin D as the cause.61 Despite these findings, there is no suggested dose of vitamin D to prevent cardiovascular disease,62,62a and prospective studies need to be done to see if vitamin D supplementation can actually prevent cardiovascular disease.62b

Vitamin K
Insufficient vitamin K in the diet has been thought to increase the risk of soft tissue calcification and atherosclerosis.63 In various animal models, multiple forms of vitamin K have been shown to reverse the arterial calcification caused by vitamin K antagonists. In humans, these findings have not been confirmed, and vitamin K is not recommended as an antiatherosclerotic treatment.

Carotenoids
Serum carotenoids have been extensively studied in the prevention of CAD. There are approximately 600 carotenoids found in nature, predominantly in fresh fruits and
vegetables, with carrots being the primary source of β-carotene and tomatoes being the best source of lycopene. Although lycopene has twice the antioxidant activity of β-carotene, the latter has been the primary focus of study because of its activity as a precursor to vitamin A.

Elevated levels of serum β-carotene have been associated with a lower risk of cancer and overall mortality. Research studies have shown an association between a high dietary intake of β-carotene and a reduction in the incidence of cardiovascular disease, with 1 study reporting that increased β-carotene stores in subcutaneous fat were correlated with a decreased risk of MI. However, the results of the MRC/BHF Heart Protection Study showed no benefit from β-carotene 20 mg daily on morbidity and mortality in high-risk individuals. In addition, the WACS recently showed that β-carotene did not reduce cardiovascular risk in women with a high risk of cardiovascular disease, and results from the Physician's Health Study II did not reveal any benefit from β-carotene use in primary prevention of cardiovascular disease.

Lycopene, an oxygenated carotenoid with great antioxidant properties, has shown a reduction in cardiovascular risk both in epidemiological studies and supplementation human trials. A recent study in rats showed that tomatoes, containing or not containing lycopene, have a higher potential than lycopene to attenuate and/or to reverse oxidative stress-related parameters in a mild oxidative stress context. However, more recent controlled clinical trials and dietary intervention studies, using well-defined subject populations, have not provided any clear evidence for the use of lycopene in the prevention of cardiovascular diseases.

Flavonoids

Residents of France, whose diet is steeped in high-fat cheeses, rich sauces, gravies, pâtés, and other highly saturated fats, have a lower incidence of CAD than their American counterparts. The typical French diet is the routine consumption of fresh fruits and vegetables that contain vital phytonutrients that may effectively reduce peroxidative tendencies and retard the varied interactions involved in atherogenesis and thrombosis. Red wine consumption could be another factor. Recent research has shown that plant-derived polyphenolic compounds are promising nutraceuticals for control of various disorders such as cardiovascular, neurological, and neoplastic disease. The richness of the polyphenolic contents of green tea and red wine has made them popular choices for associated anticancer and cardiovascular health benefits.

The serum antioxidant activity of red wine was addressed in a small study of volunteers, the results indicating that 2 glasses of red wine consumed before a meal offered considerable antioxidant protection for at least 4 hours. Red wine increased antioxidant activity through a flavonoid-polyphenol effect. In another small investigation performed in the Netherlands, the use of dietary bioflavonoids, phenolic acids, and quercetin showed a reduction in the incidence of heart attack and sudden death. Quercetin-rich black tea, apples, and onions were the best foods evaluated, as they contain polyphenols in amounts similar to those found in the red grapes used in making wine and grape juice. Short- and long-term consumption of black tea was shown to reverse endothelial vasomotor dysfunction in patients with CAD.

Resveratrol, a component of wine, has been shown to activate platelet NO synthase and inhibit reactive oxygen species production and ultimately platelet function. This activity may contribute to the beneficial effects of moderate wine intake on ischemic cardiovascular disease. Resveratrol, as an isolated substance, is now being investigated as a potential drug for use in cardioprotection.

Oligomeric proanthocyanidins, like carotenoids, are found predominantly in brightly colored fruits and vegetables and represent a safe source of polyphenols and quercetin, which are believed to be the most active protective ingredients in preventing the oxidation of LDL. Oligomeric proanthocyanidins are significant free-radical scavengers that inhibit lipid peroxidation and contain anti-inflammatory and antiallergenic properties as well.

As this point, the optimal amount of flavonoids in the diet, the form or method of supplementation, and the dose are uncertain. A trial is being conducted to investigate the bioavailability of flavonoids and phenolic acids from cranberry juice cocktail and their breakdown products (in vivo metabolites) in healthy, older adults. Nonetheless, many flavonoids are available as food supplements in doses as high as 500 and 1000 mg, an amount that may be 10 to 20 times the daily intake in a typical vegetarian diet.

An epidemiologic report from the Physician's Health Study did not show a strong inverse association between intake of flavonoids and total CAD. A study at Boston University is currently recruiting subjects to compare the effect of drinking concord purple grape juice (7 ml/kg or about 16 oz/day for a 70 kg person) and the effect of a calorie-matched placebo on 24-hour ambulatory blood pressure, blood pressure reactivity, and vascular function in men and women in the category of prehypertension and Stage 1 hypertension.

Until the benefits of flavonoids are resolved in prospective controlled studies, patients may be encouraged to consume a diet that includes tea, apples, and onions in generous amounts. Current research does not support the benefits of supplemental flavonoid intake, but additional research in this area is needed and is ongoing. It does appear that ethyl alcohol in small amounts, without regard to beverage type, might provide protection against cardiovascular or cerebrovascular disease.
Table 30-3: Possible Benefits of Flavonol-Rich Cocoa and Chocolate

1. Antioxidant effect
2. Antiatherosclerotic effect (prevention of LDL oxidation)
3. Increase in HDL
4. Improved insulin sensitivity
5. Antiplatelet effect
6. Increases nitric oxide production and vascular relaxation
7. Anti-inflammatory effect
8. Blood pressure lowering action (interference with actions of angiotensin converting enzyme inhibition)

Can chocolate be considered a health food? There is a growing body of medical literature that describes the possible short-term in vitro and in vivo cardioprotective effects of cocoa and chocolate (Table 30-3). They may exert antioxidant, anti-inflammatory, antiplatelet, and antihypertensive effects and may improve vascular function. However, it should also be noted that the evidence for any cardiovascular benefits of cocoa flavonols (a type of flavonoid) has been gathered predominantly from short-term and uncontrolled studies. Therefore, additional research with well-designed, long-term clinical studies using cocoa would be most helpful in assessing whether flavonol-rich cocoa could be a potential candidate for the treatment and/or prevention of cardiovascular disease. The beneficial effects of chocolate also need to be balanced against its high caloric and high fat content. Ultimately, if flavonol-rich cocoa is shown to be of beneficial effects, calcium channel-blocking effects, improvement in NO release from coronary endothelium, and the ability to help prevent serum coagulation. Intravenous magnesium has been reported to be useful in preventing atrial fibrillation and ventricular arrhythmias after cardiac and thoracic surgery; in reducing the ventricular response in acute onset atrial fibrillation, including patients with Wolff-Parkinson-White syndrome; and in the treatment of digoxin-induced supraventricular and ventricular arrhythmias, multifocal atrial tachycardia, and polymorphic ventricular tachycardia or ventricular fibrillation from drug overdoses. Intravenous magnesium is, however, not useful in monomorphic ventricular tachycardia and electroshock-resistant ventricular fibrillation.

Magnesium has also shown considerable efficacy in relieving symptoms of mitral valve prolapse. In a double-blind study of 181 participants, subjective results in the magnesium group were dramatic, with significant reductions noted in weakness, chest pain, shortness of breath, palpitations, and even anxiety. Supplemental magnesium and potassium should be avoided in patients with renal insufficiency.

Ultimately, additional studies are needed to better understand the association between magnesium intake, indicators of magnesium status, and heart disease.

Trace Minerals
Cobaltous chloride is sometimes used in the treatment of iron deficiency and chronic renal failure. Excessive cobalt intake may cause cardiomyopathy and CHF, with pericardial effusions due to deposition of cobalt-lipoic acid complexes in the heart. High cobalt consumption has also been implicated in thyroid enlargement, polycythemia, neurologic abnormalities, and interference with pyruvate and fatty acid metabolism. Rarely, excessive iron ingestion may cause cardiomyopathy, CHF, and cardiac arrhythmias from hemochromatosis. Chromium assists in glucose and lipid metabolism. It may bring about regression of cholesterol-induced atherosclerosis. In a study of 40 hypercholesterolemic patients (total cholesterol 210 to 300 mg/dL), a combination of 200 μg of chromium polynicotinate and (proanthocyanidin-
massive ingestion of chromium has been associated with otinate have been observed at the dose of 400 no significant adverse reactions from chromium polynic-mium's favorable action on glucose/insulin metabolism may be the key factor in cholesterol lowering. Although no significant adverse reactions from chromium poly-otinate have been observed at the dose of 400. 400 mg per day, massive ingestion of chromium has been associated with renal failure.87

Selenium is an antioxidant and an essential mineral with immune-enhancing and cancer-fighting properties. Selenium is a cofactor of the enzyme glutathione peroxi-dase, which serves as an antioxidant and is found in the platelets and the arterial walls. In contrast to vitamin E, which prevents formation of lipid hydroperoxides in cell membranes and LDL by acting as a biological free-radical trap, selenium and glutathione peroxidase help destroy lipid hydroperoxides already formed by peroxidation of polyunsaturated fatty acids. Selenium thereby defends against the free-radical oxidative stress that escapes the protection of vitamin E.

In some areas of the world, soil deficiencies in sele-nium have produced Keshan disease, a disorder of cardiac muscle characterized by multifocal myocardial necrosis that causes cardiomyopathy, CHF, and cardiac arrhyth-mias. Men with low levels of serum selenium ( < 1.4 µmol/L) demonstrated increased thickness in the intima and media of the common carotid arteries.

A substudy report from the Physician’s Health Study showed no relationship between selenium blood levels and the risk of MI in well-nourished subjects.88 However, these findings do not rule out the possibility of an increased risk of MI in severe selenium deficiency. Also, questions have been raised about the reliability of plasma selenium levels; other methods to obtain accurate body measurements have been proposed.89

Several primary prevention trials and most of the sec-ondary prevention trials that have evaluated the effects of different antioxidant supplements on cardiovascular disease have had the same result as that of The Supple-mentation en Vitamines et Mineraux Antioxydants (SU. VI.MAX) study, a randomized, double-blind, placebo-controlled primary prevention trial that studied the ef-ficacy of several antioxidants including selenium.90 The results demonstrated that a 7.5-year low-dose antioxidant supplementation lowered total cancer incidence in men but not in women. A similar tendency was observed for all-cause mortality. Also the supplementation did not re-sult in any major effect on ischemic cardiovascular dis-ease incidence in men or women.

Although selenium is quite safe at levels below 200 µg, excessive selenium can result in alopecia, abnormal nails, emotional lability, lassitude, and a garlic odor to the breath. Skin lesions and polyneuritis have been reported in people taking selenium from health food stores.

Copper is a pro-oxidant that oxidizes LDL and may contribute to the development of atherosclerosis. Men with high serum copper (> 17.6 µmol/L) demonstrate increased thickening in the intima and media of the common carotid arteries.91 Excessive oral intake of copper may cause nausea, vomiting, diarrhea, and hemolytic anemia. Even higher doses can result in renal and hepatic toxicity as well as central nervous system disturbances similar to those of Wilson’s disease. Any multivitamin with a level of copper higher than the RDA level (2 mg) should be avoided. Excessive levels of copper in drinking water, especially noted in homes with copper pipes, can also contribute to elevated serum copper levels.

Other Nutraceuticals

Coenzyme Q10

Coenzyme Q10 present in most foods, especially organ meats and fish, facilitates electron transport in oxidative metabolism. Its reduced form, ubiquinol, protects mem-brane phospholipids and serum LDLs from lipid peroxi-dation as well as mitochondrial membrane proteins and DNA from free radical–induced oxidative damage. Ubiquino-ol’s antioxidant effects on membrane phospholipids and LDL directly antagonizes the atherogenesis process. Vitamin E regeneration is significantly improved by the addition of coenzyme Q10 because of the ability of the latter ‘ to recycle the oxidized form of vitamin E back to its reduced form. Coenzyme Q10 also prevents the pro-oxida nt effect of α-tocopherols. Supplemental coenzyme Q may also improve utilization of oxygen at the cellular lev-el, hence benefiting patients with coronary insufficiency.92

Coenzyme Q10 deficiency has been implicated in several clinical disorders, including but not confined to heart failure, hypertension, Parkinson’s disease, and ma lignancy. Although adverse effects of coenzyme Q10 (such as nausea and abdominal discomfort) are rare, it is not suggested for healthy pregnant or lactating women, as the unborn and the newborn both produce sufficient quanti-ties of the substance.

3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor therapy (statins) inhibits conversion of HMGCoA to mevalonate and lowers plasma Co Q levels. In a small number of individuals, coenzyme Q10 supplementation has been used successfully to counter-act the adverse effect of myalgia associated with statin therapy.93 Several trials are currently being conducted on a large scale to further study the effects of Co Q10 on my-algias due to statin therapy.

Additional work must be done in determining reliable Q10 levels for clinical purposes. In addition to cholesterol and triglycerides, several other factors (including gender,
alcohol consumption, age, and intensity of exercise) can affect coenzyme Q levels. Despite multiple claims of benefit, additional studies with coenzyme Q need to be done regarding dose (300 mg/d is the dose used in most studies) and clinical efficacy before a recommendation can be made regarding its use in treating various cardiovascular disorders as a primary or adjunctive treatment. A meta-analysis demonstrated a lack of mortality benefit in patients from the use of coenzyme Q supplementation. At this time, the value of coenzyme Q supplementation in patients with cardiovascular disease is still an open question, with neither convincing evidence supporting nor refuting evidence of benefit or harm.

L-Carnitine
Carnitine is a naturally occurring substance with several physiologic roles. It was approved by the FDA in 1986 in both its intravenous and oral forms as an orphan drug for the treatment of primary carnitine deficiency. It is also used for patients with conditions known to produce secondary carnitine deficiency, such as renal failure and various cardiovascular diseases. One to two g/day given orally in divided doses is adequate for most therapeutic purposes. Intravenous doses range from 40 to 100 mg/kg. For children, oral L-carnitine is given at 100 mg/kg/d.

L-carnitine has a synergistic relationship with coenzyme Q as it also penetrates the inner mitochondrial membrane. As a trimethylated amino acid, L-carnitine’s primary function is in the oxidation of long-chain fatty acids.

Animal studies and clinical trials indicate that carnitine may be effective in treating patients with various cardiovascular diseases, such as CAD, CHF, peripheral vascular disease, arrhythmia, and hyperlipidemia. Carnitine appears to boost fatty acid and carbohydrate oxidation in the cell, while helping to remove harmful substances, such as excessive acyl groups and free radicals, from the cells. The chronic administration of L-carnitine has been shown to reduce blood pressure and attenuate the inflammatory process associated with arterial hypertension. It might produce a partial inactivation of the renin-angiotensin system resulting in a reduction in the production and effects of angiotensin II. Additional clinical studies with this substance are warranted before a firm clinical recommendation for its use can be provided.

Omega-3 Fatty Acids
Omega-3 fatty acids—such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—are found in fish oils (See Chapter 20, Lipid-Lowering Drugs). Omega-3 fatty acids are supposed to exert their beneficial effects by reducing sympathetic overactivity, enhancing NO-mediated vasodilation, reducing monocyte adhesion, and reducing levels of arachidonic acid-derived mediators including thromboxane A2, thrombomodulin, and von Willebrand factor, and by also reducing insulin resistance probably through actions at the peroxisomal proliferator-activating receptor-gamma. In addition, consumption of EPA stimulates the production of prostaglandin I, an antithrombotic and antiplatelet-aggregating agent similar to prostacyclin. As an anticoagulant, omega-3 fatty acids can increase bleeding time, inhibit platelet adhesiveness, decrease platelet count, and reduce serum thromboxane levels. Omega-3 fatty acids can also blunt the vasopressor effects of angiotensin II and norepinephrine and may reduce blood pressure and the risk of arrhythmia. The recent Study on Omega 3 Fatty Acids and Ventricular Arrhythmia (SOFA) did not find any evidence of a strong protective effect of intake of omega-3 polyunsaturated fatty acids from fish oil against ventricular arrhythmia in patients with implantable cardioverter-defibrillators.

In a landmark decision in 2004, the FDA reported that it would allow products containing omega-3 fatty acids to claim that eating the product may reduce the risk of heart disease. The FDA based its decision on the wealth of scientific evidence that suggests a correlation between omega-3 fatty acids such as EPA and DHA and a reduced risk of CAD. The FDA subsequently approved omega-3 fatty acids as a treatment to reduce plasma triglycerides. The triglyceride-lowering effect of these fish oil components may be one of many factors that might inhibit the progression of atherosclerosis. In the GISSI-Prevenzione trial, Italian investigators reported overwhelming health benefits for participants who were placed on 1 g of omega-3 essential fatty acids a day. After the initial study had been re-evaluated, participants on the omega-3 program experienced a 20% reduction in all-cause mortality and a 35% decrease in sudden cardiac death. In another placebo-controlled trial in patients with CHF (GISSI-HF), the use of 1 g of omega-3 essential fatty acids was associated with a statistically significant 9% reduction in all-cause mortality. In an accompanying editorial, Fonarow recommended that omega-3 fatty acids be used as an adjunct to other standard therapies in the treatment of patients with HF. In addition, 1 case-controlled study showed that those participants eating the equivalent of 1 fish meal a week had a 50% less chance of sudden cardiac death compared to counterparts whose daily menus did not contain these vital fish oils.

Recently, it was shown that EPA, at a dose of 1800 mg per day, could be a very promising regimen for prevention of major coronary events, especially since EPA seems to act through several biological mechanisms. However, the results of this study were from a population that was exclusively Japanese and therefore cannot be generalized to other populations. It is therefore necessary to investigate whether EPA is effective for prevention of major coronary events in hypercholesterolemic patients with or
without CAD in other countries. A recent trial using fish oil supplementation in patients who had a myocardial infarction did not show benefit on subsequent cardiovascular events, and a recent meta-analysis suggested a possible pro-arrhythmic effect with fish oil in subsets of cardiac patients.

L-Arginine

L-arginine is an essential amino acid that serves as the substrate for the enzyme NO synthetase (eNOS), which converts L-arginine to l-citrulline and produces NO. L-arginine is also known to be the substrate for other processes, including arginine decarboxylase, which catalyzes the synthesis of agmatine. The latter is an endogenous noncatecholamine α agonist that decreases peripheral sympathetic outflow by an effect in the nucleus tractus solitarius and therefore might be involved in the antihypertensive effect of L-arginine.

Thirteen weeks of oral administration of L-arginine was shown to result in an increased generation of vascular NO, a reduced endothelial release of superoxide anions, and regression of intimal atherosclerotic lesions in rats on a high-cholesterol diet.

Previous studies have demonstrated that an intracoronary infusion of L-arginine normalizes the defective acetylcholine-induced vasodilation of coronary microvessels in patients with hypercholesterolemia and in patients with microvascular angina, as well as in those with atherosclerosis. A study by Lerman et al in 1997 examined the effects of 6 months of oral L-arginine supplementation (3 g three times a day). They demonstrated that the chronic oral L-arginine supplementation improved coronary small vessel endothelial function in association with a significant improvement in symptoms and a decrease in plasma endothelin concentrations. However, a study by Blum et al concluded that chronic oral L-arginine supplementation does not improve NO bioavailability in this population of patients. Possible explanations for the discrepant study results in the Blum study include the limited cellular uptake of arginine, a competitive inhibition of eNOS, or a limited cofactor availability for eNOS.

Quyyumi examined the topic of stereospecificity and concluded that parenteral arginine produces nonstereospecific peripheral vasodilation and improves endothelium-dependent vasodilation in patients with stable CAD.

The doses of L-arginine employed in clinical trials was 8-21 g/d. Adverse reactions associated with L-arginine include nausea, abdominal cramps, and diarrhea.

Taurine

Taurine is an essential sulfonic amino acid that is present in large quantities in the myocardium. A deficiency of taurine in the diet (animal food and seaweed) can cause cardiomyopathy, and replacement will lead to recovery of myocardial function. Taurine in supplementary doses of 500 mg to 3 g/d has been used in the treatment of CHF in pilot studies, with apparent hemodynamic benefit. Additional clinical study is needed. Taurine has also been shown to have possible antiatherosclerotic effects. No adverse reactions have been reported with supplemental taurine treatment.

Glutamic Acid

Glutamic acid is the predominant dietary amino acid, especially in vegetable protein. In a cross-sectional epimiologic study of 4680 participants, dietary glutamic acid may have independent blood pressure-lowering effects which may contribute to the inverse relationship of vegetable protein to blood pressure.

Amino Acid Mixtures

Rather than specific amino acids, the use of various amino acid mixtures has been proposed as a treatment for patients with chronic HF, cardiac cachexia, systolic dysfunction, and diabetes mellitus. The proponents of this nutritional supplement believe that essential amino acids would shift the energy preference away from fatty acids, which would enhance adenosine diphosphate production, with favorable effects on cellular metabolism. A study showed that oral amino acid supplementation, in conjunction with standard pharmacologic therapy, appears to increase exercise capacity by improving circulatory function, muscle oxygen consumption, and aerobic production of energy in elderly outpatients with chronic HF. Another study showed that long-term amino acid mixtures supplementation increased the number and volume of mitochondria and sarcomeres and decreased fibrosis in both skeletal and cardiac muscle in old rats. Therefore, amino acids might improve the mechanical function of organs. Amino acid supplementation may also have benefits in enhancing myocyte survival and preserving mitochondrial function during ischemia-perfusion injury.

Herbal Remedies (Botanicals)

Since the beginning of human civilization, herbs have been an integral part of society, valued for their culinary and medicinal properties. However, with the development of patent medicines in the early part of the twentieth century, herbal medicine lost ground to new synthetic medicines touted by scientists and physicians to be more effective and reliable. Nevertheless, about 3% of English-speaking adults in the United States still report having used herbal remedies in the preceding year. This figure is probably higher among non–English-speaking adults.
Cardiovascular Pharmacotherapeutics

Congestive Heart Failure

Cardiac Glycosides

A number of herbs contain potent cardioactive glycosides that have positive inotropic effects on the heart. The drugs digitoxin (derived from either Digitalis purpurea [foxglove] or Digitalis lanata) and digoxin (derived from "D. lanata alone) have been used in the treatment of CHF for many decades. Cardiac glycosides have a low therapeutic index, and the dose must be adjusted to the needs of each patient. The only way to control dosage is to use standardized powderized digitalis, digitoxin, or digoxin. Treating CHF with nonstandardized herbal agents would be dangerous and foolhardy. Accidental poisonings due to cardiac glycosides in herbal remedies are abundant in the medical literature.124

Some common plant sources of cardiac glycosides include: *D. purpurea* (foxglove, already mentioned); *Adonis microcarpa* and *Adonis vernalis* (Adonis); *Apocynum cannabinum* (black Indian hemp); *Asclepias curassavica* (redheaded cotton bush); *Asclepias fruticosa* (balloon cotton); *Calotropis precer* (king’s crown); *Carissa acokanthera* (bushman’s poison); *Carissa spectabilis* (wintersweet); *Cerbera manghas* (sea mango); *Cheiranthus cheiri* (wallflower); *Convallaria majalis* (lily of the valley, convallaria); *Cryptostegia grandiflora* (rubber vine); *Helleborus niger* (black hellebore); *Helleborus viridis*; *Nerium oleander* (oleander); *Plumeria rubra* (frangipani); *Selenicereus grandiflorus* (cactus grandiflorus); *Strophanthus hispidus* and *Strophanthus kombé* (strophanthus); *Thevetia peruviana* (yellow oleander); and *Urginea maritime* (squill). Even the venom glands of the *Bufo marinus* (cane toad) contain cardiac glycosides.125

Health providers should be aware of the cross-reactivity of cardiac glycosides from herbal sources with the digoxin radioimmunoassay. A recent study found that measuring free digoxin does not eliminate the modest interferences caused by these herbal supplements in serum digoxin measurement by the digoxin immunoassay.126 Treatment of intoxication with these herbal substances is directed at controlling arrhythmias and hyperkalemia, which are the usual causes of fatalities.

Berberine

Berberine is an example of an alkaloid that is distributed widely in nature and used in the Orient for the treatment of hypertension and congestive heart failure, without first consulting a physician.123,124

Table 30-4. Some Conditions in Which Herbal Medicines Are Used as Cardiovascular Treatments

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Examples of Herbs Used</th>
</tr>
</thead>
</table>
| Congestive heart failure       | *Digitalis purpurea*  
|                                | *Digitalis lanata*  
|                                | *Crataegus species*  
|                                | *Berberine*          |
| Systolic hypertension          | *Rauwolfia serpentine*  
|                                | *Stephania tetrandra*  
|                                | *Veratrum alkaloids*  |
| Angina pectoris                 | *Crataegus species*  
|                                | *Panax notoginseng*  
|                                | *Salvia miltiorrhiza*  |
| Atherosclerosis & Hyperlipidemia| *Garlic*  
|                                | *Commiphora mukul*  
|                                | *Monascus purpureus*  |
| Cerebral insufficiency          | *Ginkgo biloba*  
|                                | *Rosmarinus officinalis*  |
| Venous insufficiency            | *Aesculus hippocastanum*  
|                                | *Ruscus aculeatus*  |

of CHF. It is reported to also have antihypertensive and antiarrhythmic actions.

Hawthorn

Hawthorn (*Crataegus oxyacantha*) is a natural product that is popular in European and American herbal medicine practice. Some of its cardiac uses include the treatment of high and low blood pressure, rapid heartbeat, chest pain, and blocked arteries. Hawthorn has been used as an adjunct treatment with other cardiac drugs such as digoxin, warfarin, and amiodarone. A placebo-controlled study (Hawthorn Extract Randomized Blinded Chronic HF Study [HERB CHF]) funded by the NCCAM was carried out to determine the effect of hawthorn extract 450 mg twice a day versus the placebo in addition to standard medical therapy in ambulatory patients with NYHA class II to IV chronic HF on submaximal exercise as measured by the 6-minute walk test. The study reported no apparent benefit from hawthorn-extract in patients with class II-IV CHF who were followed for 6 months. Compared to the placebo, there was also no benefit of hawthorn on exercise tolerance or on quality of life. In addition, in a recent study, hawthorn was found to have no effects on HF progression in patients with known HF.

Hypertension

Rauwolfia Serpentina

The root of *Rauwolfia serpentina* (snakeroot), the natural source of the alkaloid reserpine, has been a Hindu Ayurvedic remedy since ancient times. Extracts of different parts and of plants resembling rauwolfia were used in Hindu medicine for snakebite, insomnia, insanity, and many other diseases and complaints. A 200 to 300 mg dose of powdered whole root taken orally is equivalent to 0.5 mg of reserpine.

Reserpine was the first potent drug widely used in the long-term treatment of hypertension. It acts by irreversibly blocking the uptake of biogenic amines (norepinephrine, dopamine, and serotonin) in the storage vesicles of central and peripheral adrenergic neurons, thus leaving the catecholamines to be destroyed by the intraneuronal monoamine oxidase in the cytoplasm. The depletion of catecholamines accounts for reserpine’s sympatholytic and antihypertensive actions.

Rauwolfia alkaloids are contraindicated for use in patients with a history of mental depression (especially with suicidal tendencies), or an active peptic ulcer or ulcerative colitis and in those receiving electroconvulsive therapy. The most common adverse effects are sedation and inability to concentrate and perform complex tasks. Reserpine may cause mental depression sometimes resulting in suicide and must be discontinued at the first sign of depression. Reserpine’s sympatholytic effect and its enhancement of parasympathetic actions account for its other well-described adverse effects: nasal congestion, increased secretion of gastric acid, and mild diarrhea.

Stephania Tetrandra

*Stephania tetrandra* is sometimes used in Traditional Chinese Medicine (TCM) to treat hypertension. Tetrandrine, an alkaloid extract of *S. tetrandra*, has been shown to be a calcium-channel antagonist, paralleling the effects of verapamil. Tetrandrine inhibits T and L calcium channels, interferes with the binding of diltiazem and methoxyverapamil at calcium-associated sites, and suppresses aldosterone production. A parenteral dose (15 mg/kg) of tetrandrine in conscious rats decreased mean, systolic, and diastolic blood pressures for greater than 30 minutes; however, an intravenous dose of 40 mg/kg killed the rats by myocardial depression. In stroke-prone hypertensive rats, an oral dose of 25 or 50 mg/kg produced a gradual and sustained hypotensive effect after 48 hours without affecting plasma renin activity.

Tetrandrine causes liver necrosis in dogs orally administered 40 mg/kg of tetrandrine thrice weekly for 2 months, reversible swelling of liver cells at a 20 mg/kg dose, and no observable changes at a 10 mg/kg dose. Given the evidence of hepatotoxicity, many more studies are necessary to establish a safe dosage of tetrandrine in humans.

Lingusticum Wallichii

The root of *Lingusticum wallichii* (chuan-xiong, chuan-hsiung) is used in TCM as a circulatory stimulant, hypotensive agent, and sedative. Tetramethylpyrazine, the active constituent extracted from *L. wallichii*, inhibits platelet aggregation in vitro and lowers blood pressure by vasodilation in dogs. With its actions independent of the endothelium, tetramethylpyrazine's vasodilatory effect is mediated by calcium antagonism and nonselective antagonism of alpha adrenoceptors. Some evidence suggests that tetramethylpyrazine can selectively act on the pulmonary vasculature. A recent study showed that a tetramethylpyrazine–eluting stent could inhibit the neointimal hyperplasia and did reduce in-stent restenosis in a porcine coronary artery restenosis model in comparison to bare metal stents. Currently, there is insufficient information to evaluate the safety and efficacy of this herbal medicinal for clinical use.

Uncaria Rhynchophylla

*Uncaria rhynchophylla* (gou-teng) is sometimes used in TCM to treat hypertension. Its indole alkaloids, rhynchophylline and hirsutine, are thought to be the active principles of *U. rhynchophylla*’s vasodilatory effect. The mechanism of *U. rhynchophylla*’s actions is unclear. Some studies point to an alteration in calcium flux in response to activation, whereas others point to hirsutine’s inhibition of nicotine-induced dopamine release. One in
vitro study has shown that U. rhynchophylla extract relaxes norepinephrine-precontracted rat aorta through endothelium-dependent and -independent mechanisms. For the endothelium-dependent component, U. rhynchophylla extract appears to stimulate endothelium-derived relaxing factor/NO release without involving muscarinic receptors. Also, in vitro and in vivo studies have shown that rhynchophylline can inhibit platelet aggregation and reduce platelet thromboses induced by collagen or adenosine diphosphate plus epinephrine. The safety and efficacy of this agent cannot be evaluated at present owing to a lack of clinical data.

Veratrum

Veratrum (hellebore) is a perennial herb growing in many parts of the world. All Veratrum plants contain poisonous Veratrum alkaloids, which are known to cause vomiting, bradycardia, and hypotension. Most cases of Veratrum poisonings are due to misidentification with other plants. A recent study showed that with Veratrum nigrum there was a dose-dependent reduction in blood pressure and heart rate after a single ingestion in rats. Once a treatment for hypertension, however, the use of Veratrum alkaloids has lost favor owing to a low therapeutic index and unacceptable toxicity, as well as the introduction of safer antihypertensive drug alternatives.

Angina Pectoris

Crataegus

Hawthorn, encompassing many Crataegus species such as C. oxyacantha and C. monogina in the West and C. pinnatifida in China, has also acquired a reputation in modern herbal literature as an important tonic for the treatment of angina. Crataegus leaves, flowers, and fruits contain a number of biologically active substances such as oligomeric procyanidins, flavonoids, and catechins. From current studies, Crataegus extract appears to have antioxidant properties and can inhibit the formation of thromboxane A_2. Also, Crataegus extract antagonizes the increases in cholesterol, triglycerides, and phospholipids in LDL and very low-density lipoprotein (VLDL) in rats fed a hyperlipidemic diet; thus, it may inhibit the progression of atherosclerosis.

According to one study, Crataegus extract in high concentrations has a cardioprotective effect on ischemic-reperfused heart without causing an increase in coronary blood flow. On the other hand, oral and parenteral administration of oligomeric procyanidins of Crataegus leads to an increase in coronary blood flow in cats and dogs. Double-blind clinical trials have demonstrated simultaneous cardiotropic and vasodilatory actions of Crataegus. Crataegus also lowers blood pressure due to its action in lowering peripheral vascular resistance. Animal studies have also indicated that peripheral and coronary blood flow increases while arterial blood pressure decreases. As mentioned previously, C. oxyacantha was shown to be of no clinical use in the treatment of HF.

Panax Notoginseng

Because of its resemblance to Panax ginseng (Asian ginseng), Panax notoginseng (san-qui) has acquired the common name of pseudoginseng, especially since it is often an adulterant of P. ginseng preparations. In TCM, the root of P. notoginseng is used for analgesia and hemostasis. It is also often used in the treatment of patients with angina and CAD.

Although clinical trials are lacking, in vitro studies using P. notoginseng do suggest possible cardiovascular effects. One study that used purified notoginsenoside R1 extracted from P. notoginseng on human umbilical vein endothelial cells showed a dose- and time-dependent synthesis of tissue-type plasminogen activator without affecting the synthesis of plasminogen activating inhibitor, thus enhancing fibrinolytic parameters.

Another study suggests that P. notoginseng saponins may inhibit atherogenesis by interfering with the proliferation of smooth muscle cells. According to a recent study, it appears that P. notoginseng exerts its therapeutic effects on atherosclerosis through an anti-inflammatory action and regulation of the blood lipid profile. In vitro and in vivo studies using rats and rabbits have demonstrated that P. notoginseng may be useful as an antianginal agent, since it dilates coronary arteries in all concentrations. The role of P. notoginseng in the treatment of hypertension is less certain, since it causes vasodilation or vasoconstriction depending on concentration and the target vessel. The results of these in vitro and in vivo studies are encouraging; however, clinical trials will be necessary to enable more informed decisions regarding the use of P. notoginseng. The most common adverse effects reported with ginseng were insomnia, diarrhea, and skin reactions.

Salvia Miltiorrhiza

Salvia miltiorrhiza (dan-shen), a relative of the Western sage S. officinalis, is native to China. In TCM, the root of S. miltiorrhiza is used as a circulatory stimulant, sedative, and cooling agent. One study showed that inhibition of calcium ion influx in the vascular smooth muscle cells is important for the vasorelaxant effect of dihydrotanshinone (an active component), and it is independent of pathways involving the endothelium, muscarinic receptors, beta-adrenoceptors, adenylyl cyclase, and guanylyl cyclase. In vitro, S. miltiorrhiza, in a dose-dependent fashion, inhibits platelet aggregation and serotonin release induced by either adenosine diphosphate (ADP) or epinephrine, which is thought to be mediated by an increase in platelet cyclic adenosine monophosphate.
heartburn, flatulence, and other gastrointestinal disturbances. Case reports have also described bleeding in patients ingesting large doses of garlic (average of 4 cloves per day). Because of its antithrombotic activity, garlic should also be used with caution in people taking oral anticoagulants. Some individuals have also reported allergic reactions to garlic.

**Berberine**

Similar efficacies were observed in the reduction of total cholesterol as well as triglyceride in patients using both simvastatin and berberine. The results showed the rationale, effectiveness, and safety of the combination therapy of both drugs for hyperlipidemia. The combination can be a possible new regimen for hypercholesterolemia.154

**Commiphora Mukul**

Commiphora mukul (guggul) has been a mainstay of Ayurveda medicine for thousands of years. It has definite hypolipidemic actions and appears to work by blocking an essential enzymatic step in cholesterol synthesis.155 The usual dose is 100 mg of guggulsterones daily. However, one must be especially careful with Ayurveda medicines sold via the internet since it has been observed that one-fifth of both US- and Indian-manufactured medicines contain detectable lead, mercury, and arsenic.156

**Monascus Purpureus**

Monascus purpureus (red yeast) has been a mainstay of TCM for thousands of years, and has been found to have hypolipidemic effects. A product of the yeast, monacolin K, is lovastatin, the first statin drug. The available red yeast formulations provide an equivalent lovastatin dose of 2.5 to 10 mg. Red yeast causes all the potential adverse effects seen with statin drugs, including rhabdomyolysis. It is also associated with drug–drug interactions similar to those of lovastatin. Some clinical trials are in progress to study the effect of red yeast on hypercholesterolemia in patients with statin intolerance157 and also as a therapeutic supplement in combination with lifestyle changes versus simvastatin.158 Results of a preliminary study159 demonstrated that red yeast and a therapeutic lifestyle decreased LDL cholesterol without increasing creatinine phosphokinase or pain levels, and suggested that red yeast may be a treatment option for dyslipidemic patients who cannot tolerate statin therapy.

**Ginkgo Biloba**

Dating back well over 200 million years, Ginkgo biloba (maidenhair tree) was apparently saved from extinction by human intervention, surviving in Far Eastern temple gardens while disappearing for centuries in the West.
Although the root and kernels of <i>G. biloba</i> have long been used in TCM, <i>Ginkgo</i> gained attention in the West during the twentieth century for its medicinal value after a concentrated extract of <i>G. biloba</i> leaves was developed in the 1960s. At least 2 groups of substances within <i>G. biloba</i> extract demonstrated beneficial pharmacologic actions. The flavonoids reduce capillary permeability and fragility and serve as free-radical scavengers. The terpenes (ie, ginkgolides) inhibit platelet-activating factor, decrease vascular resistance, and improve circulatory flow without appreciably affecting blood pressure. Recently a study that compared the effects of 300 mg/day of <i>G. biloba</i> versus the placebo in treadmill walking time and related cardiovascular measures among patients with peripheral artery disease showed no evidence for its therapeutic usage in patients.<ref>159</ref>

Continuing research appears to support the primary use of <i>G. biloba</i> extract for treating cerebral insufficiency and its secondary effects on vertigo, tinnitus, memory, and mood. In a study evaluating 327 demented patients<ref>160</ref> 120 mg of <i>G. biloba</i> extract produced improvements in dementia similar to other studies with donepezil and tacrine. However, a study by Solomon et al. showed no benefit of <i>G. biloba</i> on cognitive functioning.<ref>161</ref> Although approved as a drug in Europe, <i>Ginkgo</i> is not approved in the United States and is instead marketed as a food supplement, usually supplied as 40 mg tablets of extract. The recommended dose in Europe is one 40 mg tablet taken 3 times daily with meals (120 mg daily).<ref>161</ref>

Adverse effects of <i>G. biloba</i> extract are rare but can include gastrointestinal disturbances, headache, and skin rash. Several case reports of bleeding, including subarachnoid hemorrhage, intracranial hemorrhage, and subdural hematoma have been associated with <i>G. biloba</i>.<ref>162</ref> <i>G. biloba</i> should not be used in combination with analgesic agents such as aspirin, ticlopidine, and clopidogrel or anticoagulants such as warfarin and heparin, since it undermines the effect of the platelet inhibiting factor.<ref>163</ref>

**Rosmarinus Officinalis**

Known mostly as a culinary spice and flavoring agent, <i>Rosmarinus officinalis</i> (rosemary) is listed in many herbal sources as a tonic and all-around stimulant. Traditionally, rosemary leaves are said to enhance circulation, aid digestion, elevate mood, and boost energy. When applied externally, the volatile oils are supposedly useful for arthritic conditions and baldness.

Although research on rosemary is scanty, some studies have focused on antioxidant effects of diterpenoids, especially carnosic acid and carnosol, isolated from rosemary leaves. In addition to having antineoplastic effects (especially skin), the antioxidants in rosemary have been credited with stabilizing erythrocyte membranes and inhibiting superoxide generation and lipid peroxidation.<ref>164</ref>

Essential oils of rosemary have demonstrated antimicrobial, hyperglycemic, and insulin-inhibiting properties.<ref>165</ref> Rosemary leaves contain high amounts of salicylates, and its flavonoid pigment diosmin is reported to decrease capillary permeability and fragility.<ref>166</ref>

Due to a lack of studies, no conclusions can be reached regarding the use of the antioxidants of rosemary in inhibiting atherosclerosis. Although external application may cause cutaneous vasodilatation from the counterirritant properties of rosemary’s essential oils, there is no evidence to support any prolonged improvement in peripheral circulation.<ref>166</ref> While rosemary does have some carminative properties, it may also cause gastrointestinal and kidney disturbances in large doses.

**Venous Insufficiency**

**Aesculus Hippocastanum**

The seeds of <i>Aesculus hippocastanum</i> (horse chestnut) have long been used in Europe to treat venous disorders such as varicose veins. The medicinal qualities of horse chestnut reside mostly in its large seeds, which resemble edible chestnuts. The seeds contain a complex mixture of saponins, glycosides, and several other active ingredients. In addition to a high level of flavonoids, horse chestnuts contain several minerals including magnesium, manganese, cobalt, and iodine.

The saponin glycoside aescin from horse chestnut extract (HCE) inhibits the activity of lysosomal enzymes, which are thought to contribute to varicose veins by weakening vessel walls and increasing permeability, resulting in dilated veins and edema. In animal studies, HCE increases venous tone, venous flow, and lymphatic flow in a dose-dependent fashion. HCE also antagonizes capillary hyperpermeability induced by histamine, serotonin, or chloroform. HCE decreases edema formation of lymphatic and inflammatory origin. HCE’s dose-dependent antioxidant properties can inhibit in vitro lipid peroxidation. Randomized double-blind, placebo-controlled trials using HCE show a statistically significant reduction in edema, as measured by plethysmography.<ref>167</ref> Standardized HCE is prepared as an aqueous-alcohol extract of 16% to 21% of triterpene glycosides, calculated as aescin. The usual initial dose is 90 to 150 mg of aescin daily, which may be reduced to 35 to 70 mg daily after improvement.<ref>168</ref>

Standardized HCE preparations are not available in the United States, but nonstandardized products may be available. Some manufacturers promote the use of topical preparations of HCE for treatment of varicose veins as well as hemorrhoids; however, at least 1 study has demonstrated very poor aescin distribution at sites other than the skin and muscle tissues underlying the application site.<ref>168</ref> For now, research studies have yet to confirm any clinical effectiveness of topical HCE preparations.
Although adverse effects are uncommon, HCE may cause gastrointestinal irritation and facial rash. Parenteral aescin has produced isolated cases of anaphylactic reactions as well as hepatic and renal toxicity. In the event of toxicity, aescin is completely dialyzable, with elimination dependent on protein binding.

**Ruscus Aculeatus**

Like *A. hippocastanum*, *Ruscus aculeatus* (butcher's broom) is known for its use in treating venous insufficiency. *R. aculeatus* is a short evergreen shrub found commonly in the Mediterranean region. Two steroidal saponins extracted from the rhizomes of *R. aculeatus* (ruscogenin and neurogenin) are thought to be its active components. Topical *Ruscus* extract's vascular effects are also temperature-dependent and appear to counter the sympathetic nervous system's temperature-sensitive vascular regulation. Based on the influence of prazosin, diltiazem, and rauwolscine, the peripheral vascular effects of *Ruscus* extract appear to be selectively mediated by effects on calcium channels and alpha-adrenergic receptors.

Several small clinical trials using topical *Ruscus* extract support its role in treating venous insufficiency. One randomized double-blind, placebo-controlled trial involving 18 volunteers showed a statistically significant decrease in femoral vein diameter (median decrease of 1.25 mm) using duplex B-scan ultrasonography 2.5 hours after applying 4 to 6 g of a cream containing 64 to 96 mg of *Ruscus* extract. Another small trial (n = 18) showed that topical *Ruscus* extract may be helpful in reducing venous dilatation during pregnancy. Oral agents may be as useful as topical agents for venous insufficiency, although the evidence is less convincing.

Although capsule, tablet, ointment, and suppository (for hemorrhoids) preparations of *Ruscus* extract are available in Europe, only capsules are available in the United States. These capsules contain 75 mg of *Ruscus* extract and 2 mg of rosemary oil. Aside from occasional nausea and gastritis, adverse effects from using *R. aculeatus* have rarely been reported, even at high doses. Although there is ample evidence to support the pharmacologic activity of *R. aculeatus*, there is still a relative deficiency of clinical data to establish its actual safety and efficacy.

**Other Herbs with Adverse Cardiovascular Effects**

For the following noncardiovascular herbal remedies, only cardiovascular actions are emphasized (Table 30-5).

**Tussilago Farfara**

*Tussilago farfara* (coltsfoot, kuan dong-hua) is a perennial herb that is grown in many parts of northern China, Europe, Africa, Siberia, and North America. Over the years, its use has lost favor due to several studies that found senkirkine, a pyrrolizidine alkaloid known to cause hepatotoxicity, in all parts of the herb. In addition, rats fed a diet containing *T. farfara* had a high risk of developing hemangioendothelial sarcoma of the liver. A diterpene isolated from *T. farfara*, named tusilagone, is shown to be a potent respiratory and cardiovascular stimulant.

**Ephedra Sinica**

*Ephedra sinica* (joint fir, ma-huang), the natural source of the alkaloid ephedrine, has been used in TCM for over 5,000 years as an antiasthmatic and decongestant. Ephedra, also known as Ma Huang, was commonly used to enhance athletic performance, "fat burning," and weight loss before its removal from the United States in April 2004 due to acute adverse health reactions including lethal arrhythmias, stroke, vasoconstriction, and MI. A recent case report of MI in a 29-year-old patient exemplifies the long-term danger of ephedrine products and is the first report of coronary artery aneurysm associated with its use.

**Aconitum**

The roots of *Aconitum* species, such as *A. kusnezoffii* (cao-wu) and *A. carmichaeli* (chuan-wa), are sometimes used in TCM to treat rheumatism, arthritis, bruises, and fractures. Plant parts of *Aconitum* species contain diterpenoid ester alkaloids, including aconitine, which...
have been linked to several deaths in Hong Kong and Australia. Death usually results from cardiovascular collapse and ventricular tachyarrhythmias induced by aconite alkaloids. These alkaloids activate sodium channels and cause widespread membrane excitation in cardiac, neural, and muscular tissues. Characteristic manifestations of aconite intoxication include nausea, vomiting, diarrhea, hypersalivation, and generalized paresthesias (especially circumoral numbness). Muscarinic activation may cause hypotension and bradyarrhythmias. Aconite-induced cardiac arrhythmias can also lead to cardiac failure in as little as 5 minutes to as long as 4 days.

Management of aconite intoxication consists of symptomatic relief, since no specific antidote exists. Amiodarone and flecaïnide may be used as antiarrhythmic agents. Intragastric charcoal can decrease alkaloid absorption. A fatal dose can be as little as 5 mL of aconite tincture, 2 mg of pure aconite, or 1 g of plant. Considering their low therapeutic index and unacceptable toxicity, *Aconitum* and its products are not recommended even in therapeutic doses, since an erroneous dose can be fatal.

**Jin Bu Huan**

Often misidentified as a derivative of *Polygala chinensis*, jin bu huan is most likely derived from the *Stephania* genus. This herbal remedy contains an active alkaloid known as levotetrahydropalmatine, which is a potent neuroactive substance. Jin bu huan is used as an analgesic, sedative, hypnotic, and antispasmodic agent as well as a dietary supplement. It is associated with significant cardiorespiratory toxicity, including respiratory failure and bradycardia requiring endotracheal intubation. There is no specific antidote for the treatment of acute jin bu huan overdose. Several cases of hepatitis have also been associated with long-term ingestion of Jin bu huan. Although it is now banned in the United States, Jin bu huan is still being imported illegally as jin bu huan anodyne tablets.\(^{174}\)

**Drug–Herbal Interactions**

The increased use of alternative medicine in the United States has made information about potential drug–herb interactions very important, especially for medications with a narrow therapeutic index, such as warfarin and digoxin.\(^{175}\) Commonly used herbs that can interact with warfarin are listed in Table 30-6. There is also evidence to suggest that the herb *St. John’s Wort* (*Hypericum perforatum*) acts as an inducer of the cytochrome p450 3A4 enzyme.\(^{176}\) *St. John’s wort* can reduce digoxin blood levels.\(^{177}\) Cardiovascular drugs such as amiodarone, amlodipine, diltiazem, felodipine, lidocaine, losartan, lovastatin, nifedipine, propafenone, simvastatin, and verapamil are substrates of the enzyme. Patients receiving any of these medications along with *St. John’s wort* would be at risk for exacerbation of an arrhythmia, angina, or hypertension.\(^{178}\)

<table>
<thead>
<tr>
<th>Potential Increase in Risk of Bleeding</th>
<th>Documented Reports of Possible Decrease in Warfarin’s Effects</th>
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<tbody>
<tr>
<td>Chamomile</td>
<td>Ginseng</td>
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<tr>
<td>Feverfew</td>
<td>Horse chestnut</td>
</tr>
<tr>
<td>Garlic</td>
<td>Licorice root</td>
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<td>Ginger</td>
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There are herbal remedies (eg, cola, ginger, licorice) that have pharmacodynamic interactions with antihypertensive drugs that will counteract their hypotensive effects. Ginseng has been shown to increase digoxin levels and to reduce the effects of warfarin.\(^{179}\)

Suspected drug–herbal interactions should be reported by clinicians to the FDA’s Med Watch Program. The FDA has established the Special Nutritional Adverse Event Monitoring System, a computer database that includes information about suspected adverse effects related to dietary supplements as nutritional products. A recent study showed that the majority of *St. John’s Wort* products fail to adequately address clinically relevant safety issues on their labeling. Health care providers and consumers may benefit if the FDA re-examined labeling requirements for dietary supplements.\(^{180,180a}\)

**Homeopathic Remedies**

Homeopathy has been used widely to treat various cardiac disorders. It is a healing system dating back to the 18th century created by Samuel Christian Hahnemann, a German physician who lost faith in conventional allopathic medicine.\(^{181}\) Hahnemann based homeopathy on 3 laws: (1) the law of similars, (2) the law of infinitesimals, and (3) the law of chronic suppressions or law of chronic disease. The basic premise is that like is cured by like (*similia similibus curentur*)—diseases can be treated by substances that produce the same signs and symptoms in a healthy individual.\(^{184}\) The preparation of remedies involves serial dilution, commonly to the extent that no molecules of the original substance remain, and vigorous shaking between dilutions (potentisation). During this process, information is thought to be transferred from the diluted substance to the solvent, which in the light of current
knowledge seems implausible. Many people therefore assume that any effects of homeopathy must be from non-specific placebo effects.

Recently, homeopathy as a healing art has been under great scrutiny, especially in the United Kingdom, because of major meta-analyses showing no significant benefit with homeopathy that is greater than the placebo. There have been several reports of undertreatment for serious medical conditions by homeopathic physicians and advice given not to vaccinate for certain illnesses like mumps, measles, and rubella. However, homeopathy continues to show great popularity, especially in third-world communities that cannot afford more expensive, allopathic medicines.

Chelation

In general terms, chelation therapy is a process of using specific molecules (chelating agents) to form complexes that inactivate heavy metals (metal ions), which can then be excreted safely in the urine. The most popular application of this therapy has been in heavy metal toxicity (including hemachromatosis) when the binding of chelating agents to these metals forms soluble, inactive complexes that are eliminated in the urine. This aforementioned use of chelation therapy is well established and accepted.

However, a more intriguing and controversial aspect of chelation therapy is its use for treating atherosclerotic disease. Managing cardiovascular disease with this therapy involves the repeated administration of intravenous ethylenediaminetetraacetic acid (EDTA) supplemented with some “nutrients” (such as vitamins C, B complex and B6, heparin, and magnesium sulfate). This use of chelation began in the 1950s when a group from Michigan reported on its use in treating atherosclerotic cardiovascular disease. This led to great controversy about the benefits of chelation therapy that has continued to this day (Table 30-7). The focus of the arguments are related to efficacy, safety, and the possible mechanism of benefit. Despite the ongoing controversy, it is estimated that chelation therapy accounts for more than 800,000 patient visits in the United States each year.

The major questions surrounding EDTA chelation for clinical use have continued to revolve around its efficacy and safety. The perception is that there is no generally accepted scientific evidence from well-conducted studies to justify its use. One meta-analysis, however, did conclude that there was evidence to support the use of EDTA in treating cardiovascular disease. However, most of the studies included in the analysis were not controlled, and by 2001 not a single reputable cardiovascular society had endorsed chelation therapy for treating cardiovascular disease, including the American College of Cardiology/American Heart Association guidelines for managing patients with stable angina.

At the same time, how safe is chelation therapy? The concerns regarding the safety of EDTA treatment have been addressed by the proponents of this therapy, including the publication of guidelines for its safe use. However, it is well known that EDTA is not a benign drug when high doses are administered over a short time. Some of the adverse effects of high doses of EDTA include nephrotoxicity, bone marrow depression, hypocalcemic tetany, allergic reactions, insulin shock, hypotension, thrombocytopenia, electrocardiographic changes including cardiac arrhythmias, and prolongation of the prothrombin time.

The National Institutes of Health funded the Trial to Assess Chelation Therapy (TACT) at more than 100 centers in the United States and Canada. This randomized, controlled trial is designed to determine whether patients treated with EDTA chelation therapy in addition to standard medications and who have had a previous MI will have fewer cardiac events and deaths than others treated with standard medications alone. The trial began in 2003 and was terminated in 2008 for procedural reasons with no benefit from chelation demonstrated.

Conclusion

Alternative medicine represents those healing traditions that in the recent past were not part of standard allopathic medical training. However, more and more individuals are seeking CAM practitioners and remedies for part of their health care needs. Although most CAM therapies are relatively innocuous and often improve patient well-being most likely through a placebo effect, some involve the use of pharmacologically active substances (e.g., herbal medicine, megavitamin therapy, and some folk remedies) that could complicate existing medical therapy or even cause harm.

Physicians must be aware of CAM practices so that they can best counsel their patients in an atmosphere of
open communication. Rather than dismissing a patient’s highly motivated intentions towards health-conscious behaviors, it behooves the physician to understand the range of CAM treatments and when they might be safely integrated with conventional medicine.

Despite the lack of scientific rigor in previous studies of CAM therapies, the NCCAM, a part of the National Institute of Health is now actively coordinating clinical trials, advancing scientific research and training researchers to study CAM. Ultimately it will be the fusion of the best medical practices from those which are rigorously studied in clinical trials that will provide the most favorable clinical outcomes in medicine.

In addition, physicians must remember that many of our current drugs came out of herbal medicine practice (eg, digitalis, aspirin, lovastatin, reserpine), and homeopathy (nitroglycerin). Much of our bedside approach to sick patients was adopted and modified from ancient and deeply rooted cultures (eg, Ayurveda). We have the responsibility as medical professionals to preserve and protect the physical, psychological, and spiritual “heart” of our patients. Achieving a “placebo effect” while doing “no harm” is a benefit clinicians should not ignore.

Note: References for this chapter can be found here:
www.cvpct3.com
It has been estimated that 3.8 billion prescriptions were filled in 2007, representing a 72% increase from 1997 to 2007. It has also been estimated that the average number of prescriptions filled by each person in the United States increased from 8.9 a year in 1997 to 12.6 in 2007. In terms of prescription volume, cholesterol-lowering medications, angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers were among the top 5 therapeutic categories of drugs dispensed (antidepressants and codeine and combination pain medications were the other two). Given the increase in prescription drug utilization, especially among the elderly, drug–drug interactions are to be expected in many individuals. In addition, the volume of prescriptions written for cardiovascular medications increases the likelihood that a medication given for a cardiovascular indication will be involved in the interaction.

In the majority of instances, drug–drug interactions are deemed to be undesirable. Certainly, many untoward effects can be attributed to drug interactions, but the negative connotation associated with drug–drug interactions is sometimes unjustified. There are times when drug interactions are beneficial (for example, when a loop diuretic and a thiazide diuretic are given concomitantly to produce synergistic diuresis or when lisinopril and chlorthalidone are co-administered for synergistic antihypertensive effects). In addition, there are instances when 2 drugs are known to interact with each other, but the benefit is deemed to outweigh the risks; for example, giving amiodarone along with warfarin for a patient with chronic atrial fibrillation. In this case, the dosage of warfarin is reduced to compensate for the increased plasma concentrations induced by amiodarone and the patient is educated and monitored for signs and symptoms of digoxin toxicity.

Many reported drug–drug interactions are also of questionable clinical significance. For example, atorvastatin can increase the steady-state plasma concentrations of digoxin by 20%, but this interaction is unlikely to be of any clinical significance in the vast majority of patients. It is therefore important that patients are educated regarding any significant drug interactions with the medications they are taking. With the abundance of information available to the lay public on medications, resourceful but medically uneducated patients may rather easily find information on the medicines that they are taking and become falsely alarmed should they read about a drug interaction regarding some of their medicines that they were not made aware of, whether it be of clinical consequence or not.

Drug interactions of most concern are those with a low therapeutic index and serious adverse effects, such that even minor disruptions in plasma concentrations can result in toxicity (see Chapter 1, Basic Principles of Clinical Pharmacology Relevant to Cardiology). Also of concern are patients being treated for serious or potentially fatal diseases, in that maintenance of therapeutic drug concentrations is of critical importance for a favorable outcome. Drug–drug interactions can result as a consequence of pharmacokinetic (ie, alterations in drug absorption, distribution, metabolism, and/or excretion) and/or pharmacodynamic (ie, alterations in pharmacologic effect) interactions. It should be noted that drug–drug interactions will often involve multiple mechanisms, sometimes involving both pharmacokinetics and pharmacodynamics.

Pharmacokinetic Drug Interactions

Absorption

There are various ways that drug–drug interactions may occur as a consequence of altered drug absorption from
the gastrointestinal (GI) tract. These predominantly involve binding interactions, alterations in GI motility, alterations in gastric pH, and reductions in intestinal flora (Table 31-1). Binding interactions involve drug chelation or adsorption to form nonabsorbable drug complexes. This may be seen through cation binding (e.g., aluminum or magnesium-containing antacids; iron) to medicinal resins such as tetracycline, fluoroquinolones, digoxin, or quinapril, resulting in a nonabsorbable drug complex. Cholestyramine and colestipol may adsorb and thereby inhibit the absorption of several drugs such as hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, furosemide, digoxin, and warfarin.

Drugs that affect gastric transit time can also elicit drug–drug interactions. Metoclopramide and various laxatives can accelerate gastric motility, thereby reducing the bioavailability of medications in controlled-release formulations, and the reduction in gastric motility due to anticholinergic agents may result in delayed absorption of medications from the small intestine. Drugs with pH-dependent dissolution (e.g., rosuvastatin) may display reduced absorption when given with antacids or other drugs that increase stomach pH such as H2-receptor antagonists or proton-pump inhibitors. Aspirin is a weak acid that prefers an acidic environment for absorption, as seen when the drug exists in its lipid-soluble, nonionized form. In addition, many enteric-coated medications rely on the relatively alkaline environment of the small intestine for dissolution and as such may display altered absorption should the gastric pH increase. Antibiotics may enhance the efficacy of warfarin by altering intestinal flora and reducing the bacterial synthesis of vitamin K. The absorption of digoxin, which is partially metabolized by GI microorganisms, may be increased due to a reduction in bacterial metabolism caused by erythromycin therapy.

**Distribution**

Drug–drug interactions involving drug distribution center on alterations in plasma protein binding. Albumin binds acidic drugs, and α1-acid glycoprotein binds basic drugs. Displacement of a drug from its protein-binding site by another drug forms the basis for certain drug–drug interactions, as it is the free (unbound) drug that elicits pharmacologic actions. This is most commonly seen when 2 highly protein-bound (> 90%) drugs are co-administered. However, the clinical relevance of such interactions is frequently low since the newly displaced free drug is then susceptible to metabolism and elimination, which ultimately reduces the free drug concentration to that which was present before the interaction.

**Metabolism**

With regards to pharmacokinetic drug–drug interactions, alterations in drug metabolism may be most frequently cited as the cause of the interaction. Drug metabolism occurs at many different sites throughout the body, but the majority of drug metabolism involves enzymatic reactions in the liver and intestine, where drugs are metabolized to inactive or less active metabolites. These enzymes may be inhibited or induced, resulting in a variety of drug–drug interactions (Tables 31-1 and 31-2). Enzyme inhibition typically leads to an increase in drug plasma concentrations secondary to a reduction in drug metabolism. This is one of the most common mechanisms of drug–drug interactions.

Enzyme inhibition may also, however, lessen drug effect if the object drug is a prodrug to form the active moiety. In this instance, enzyme inhibition would lessen the therapeutic effect by reducing the formation of active drug. An example of this type of interaction involves the reduced conversion of clopidogrel to its active metabolite due to inhibition of the CYP2C19 isozyme by proton-pump inhibitors (PPIs). Enzyme induction typically leads to diminished drug effect secondary to accelerated metabolism. The CYP3A4 and 2C9 isozymes are especially susceptible to induction. However, if a drug has toxic metabolites, enzyme induction may actually increase drug toxicity, as may be seen with acetaminophen and its metabolism to hepatotoxic metabolites.

The enzymes of the cytochrome P450 (CYP450) system constitute the primary drug-metabolizing enzymes, and as such play a large role in drug–drug interactions (see Chapter 1, Basic Principles of Clinical Pharmacology Relevant to Cardiology). These enzymes facilitate drug elimination by converting them from a hydrophobic to a hydrophilic state. Drug–drug interactions are typically the result of a competitive binding interaction between a substrate drug and an inhibitor drug, in which both drugs compete for the enzyme’s binding site. The degree of inhibition is dependent on many factors, such as affinity of the substrate for the enzyme, the concentration of the substrate required for inhibition, and the half-life and time to steady-state concentrations of the inhibitor drug.

Of the more than 30 human CYP450 isoforms that have been identified, those most frequently involved with drug–drug interactions are CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, with the latter being responsible for the metabolism of about half of the drugs currently available on the market. Table 30-2 lists substrates, inhibitors, and inducers of each of these isoforms.
Table 31-1. Principles of Pharmacokinetic Drug–Drug Interactions

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Nature of interaction</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Chelation</td>
<td>Aluminum or magnesium-containing antacids or iron chelating to digoxin or quinapril</td>
</tr>
<tr>
<td></td>
<td>Adsorption</td>
<td>Cholestyramine adsorption to HMG-CoA reductase inhibitors, furosemide, digoxin, and warfarin</td>
</tr>
<tr>
<td></td>
<td>Altered gastrointestinal motility</td>
<td>Metoclopramide may increase gastric motility and thereby decrease digoxin absorption; the reduction in gastric motility due to anticholinergic agents may result in delayed absorption of many medications from the small intestine.</td>
</tr>
<tr>
<td></td>
<td>Altered gastrointestinal pH</td>
<td>Reduced rosuvastatin absorption (pH-dependent drug dissolution) with antacids or other drugs that increase stomach pH; aspirin absorption may also be decreased in a less acidic environment.</td>
</tr>
<tr>
<td></td>
<td>Reduction in intestinal flora</td>
<td>Increased efficacy of warfarin by antibiotics due to less bacterial synthesis of vitamin K; digoxin absorption may be increased by erythromycin due to a reduction in bacterial digoxin metabolism.</td>
</tr>
<tr>
<td>Distribution</td>
<td>Altered plasma protein binding</td>
<td>Valproic acid may displace warfarin from protein binding sites, resulting in a transient increase in warfarin effect.</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Enzyme inhibition increasing drug effect/toxicity</td>
<td>Amiodarone may interfere with the metabolism of warfarin through CYP2C9 inhibition, thereby potentiating the effects of warfarin.</td>
</tr>
<tr>
<td></td>
<td>Enzyme inhibition decreasing drug effect</td>
<td>Omeprazole may interfere with the conversion of clopidogrel to its active metabolite through CYP2C19 inhibition.</td>
</tr>
<tr>
<td></td>
<td>Enzyme induction increasing drug toxicity</td>
<td>Accelerated conversion of acetaminophen to hepatotoxic metabolites.</td>
</tr>
<tr>
<td></td>
<td>Enzyme induction reducing drug effect</td>
<td>Reduction in the hemodynamic effects of felodipine by carbamazepine induction of CYP 3A4.</td>
</tr>
<tr>
<td>Elimination</td>
<td>Decreased renal clearance</td>
<td>Reduction in digoxin clearance by amiodarone or quinidine, resulting in elevated serum digoxin concentrations. Antacids may decrease the urinary excretion of quinidine by alkalizing the urine.</td>
</tr>
<tr>
<td></td>
<td>Increased renal clearance</td>
<td>Antacids may reduce serum salicylate concentrations by alkalizing the urine and reducing renal tubular reabsorption of salicylate, thereby increasing renal clearance</td>
</tr>
<tr>
<td>Enzyme</td>
<td>Substrate</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td>CYP1A2</td>
<td>Aloeutron</td>
<td>Ramelteon</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>Rasagiline</td>
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<tr>
<td></td>
<td>Clozapine</td>
<td>Ropinirole</td>
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<td></td>
<td>Flutamide</td>
<td>Tarcine</td>
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<td></td>
<td>Frovatip坦</td>
<td>Theophylline</td>
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<td></td>
<td>Melatonin</td>
<td>Tizanide</td>
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<td></td>
<td>Mexiteline</td>
<td>Triamterene</td>
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<td></td>
<td>Mirtazapine</td>
<td>Zolmitriptan</td>
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<td>Olanzapine</td>
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<tr>
<td>CYP2C19</td>
<td>Aripiprazole</td>
<td>Methadone</td>
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<td></td>
<td>Carisoprodol</td>
<td>Moclobemide</td>
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<td></td>
<td>Citalopram</td>
<td>Nelfinavir</td>
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<td></td>
<td>Clomipramine</td>
<td>Olanzapine</td>
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<tr>
<td></td>
<td>Clopidogrel</td>
<td>Omeprazole</td>
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<td></td>
<td>Clozapine</td>
<td>Pantoprazole</td>
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<tr>
<td></td>
<td>Desipramine</td>
<td>Pentamidine</td>
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<td></td>
<td>Diazepam</td>
<td>Phenobarbital</td>
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<tr>
<td></td>
<td>Diphenhydramine</td>
<td>Phenytoin</td>
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<td></td>
<td>Doxepin</td>
<td>Proguanil</td>
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<td></td>
<td>Escitalopram</td>
<td>Propranolol</td>
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<td></td>
<td>Fluoxetine</td>
<td>Rabeprazole</td>
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<td>Imipramine</td>
<td>Sertraline</td>
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<td>Lansoprazole</td>
<td>Thalidomide</td>
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<td>Meprhenytoin</td>
<td>Voriconazole</td>
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<tr>
<td>CYP2C9</td>
<td>Aloeutron</td>
<td>Losartan</td>
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<td></td>
<td>Bosentan</td>
<td>Meloxicam</td>
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<td>Candesartan</td>
<td>Montelukast</td>
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<td>Celecoxib</td>
<td>Naproxen</td>
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<td>Chlorpropamide</td>
<td>Nateglinide</td>
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<td>Diclofenac</td>
<td>Phenobarbital</td>
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<td>Dronabinol</td>
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<td>Flurbiprofen</td>
<td>Piroxican</td>
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<td>Fluvastatin</td>
<td>Rosiglitazone</td>
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<td>Glimepiride</td>
<td>Rosuvasatin</td>
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<td>Glipizide</td>
<td>Sulfinpyr-azo</td>
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<td>Glyburide</td>
<td>Tolbutamide</td>
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<td>Ibufrofen</td>
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<td>Indomethacin</td>
<td>Valsartan</td>
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<td>Irbesartan</td>
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<tr>
<td>CYP2D6</td>
<td>Amitriptyline</td>
<td>Maprotiline</td>
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<td></td>
<td>Atomoxetine</td>
<td>Metoclopamide</td>
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<td></td>
<td>Carvedilol</td>
<td>Metoprolol</td>
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<td>Chlorpheniramine</td>
<td>Mexiletine</td>
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<td></td>
<td>Chlorpromazine</td>
<td>Nortriptyline</td>
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<td>Clomipramine</td>
<td>Palonosetron</td>
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<td></td>
<td>Codeine</td>
<td>Paroxetine</td>
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<td>Desipramine</td>
<td>Perhexiline</td>
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<td></td>
<td>Dextromethorphan</td>
<td>Promethazine</td>
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<td></td>
<td>Dihydrocodeine</td>
<td>Propafenone</td>
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<td>Diphenhydramine</td>
<td>Propranolol</td>
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<td>Dolasetron</td>
<td>Frotriptylne</td>
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<td>Doxepin</td>
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<td>Duloxetine</td>
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<td>Fluoxetine</td>
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<td>Fluvoxamine</td>
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<td>Haloperidol</td>
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<td>Hydrocodone</td>
<td>Venlafaxine</td>
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Elimination

The elimination of drugs from the body typically occurs through the kidney. This may take place through 1 of 3 mechanisms: (1) glomerular filtration, which depends on the protein binding of the drug as well as the glomerular filtration rate; (2) active tubular secretion, which occurs in the proximal renal tubule; and (3) passive tubular reabsorption of nonionized weak acids and bases in the proximal and distal renal tubules. Drug interactions involving glomerular filtration typically involve a nephrotoxic drug increasing the serum concentration of a drug dependent on glomerular filtration for elimination. This, however, is not considered a true drug–drug interaction as the interaction is due to a drug adverse effect as opposed to a pharmacokinetic or pharmacodynamic interaction. Alternatively, the methylxanthines (eg, caffeine) may increase renal blood flow and glomerular filtration, thereby accelerating drug clearance.

Interactions involving active tubular secretion are most commonly seen when 2 acidic or 2 basic drugs compete for the same transport system. For example, the basic drug quinidine may reduce the renal clearance of the basic drug digoxin by 30% to 50%. The reabsorption of drugs in the kidney is affected by pH, and drugs that either acidify or alkalinize the urine may elicit drug–drug interactions. For example, the urinary excretion of the basic drug quinidine may be decreased by antacids, which alkalinize the urine, resulting in increased quinidine tubular reabsorption due to reduced ionization in the alkaline urine. Alternatively, reabsorption of salicylates is reduced by antacids, resulting in increased renal salicylate clearance.
Drug Transporters

A relatively new development in our understanding of drug–drug interactions involves drug transporter proteins. Transporter proteins actively move drugs in (uptake) or out (efflux) of cells, and certain transporters may have their activity enhanced or reduced by various drugs. These proteins can affect various pharmacokinetic properties of medications. P-glycoprotein is an efflux transporter found on enterocytes that transports drugs from the cell cytoplasm back into the intestinal lumen, where they are then excreted. This ultimately results in a lower bioavailability for orally administered medications. The uptake transporters can transport either organic anions (organic anion transporters [OATs]) or organic cations (organic cation transporters [OCTs]) and are found on enterocytes, renal tubular cells, and bile canaliculi.

These transporters actively pump drugs into cells such as hepatocytes and renal tubular cells, where they may then be secreted into the bile, metabolized (liver), or secreted into the urine (kidney).

Digoxin is a P-glycoprotein substrate and is susceptible to interactions with P-glycoprotein inhibitors such as amiodarone, erythromycin, or clarithromycin. The elimination of several HMG-CoA reductase inhibitors is partially dependent on OATs. In fact, over 5-fold increases in plasma concentrations of pravastatin has been demonstrated when this drug was given concomitantly with the OAT inhibitor cyclosporine. Regarding cation transporters, procainamide is an OCT substrate and can compete with other OCT substrates for transport from the plasma into hepatocytes or renal tubular cells. Metformin, triamterene, and cimetidine are also OCT substrates, the latter of which has been shown to reduce the renal clearance of procainamide.

Pharmacodynamic Drug Interactions

Pharmacodynamic drug–drug interactions involve an alteration in pharmacologic drug response that may be either additive or antagonistic between the substrate drug and the interacting drug. Multiple examples of these types of interactions may be found involving cardiovascular medications. In terms of additive effects, some classic examples involve the use of thiazide diuretics to augment the antihypertensive efficacy of various medications such as ACE inhibitors or beta blockers. Thiazide diuretics are also routinely used to produce synergistic diuresis when added to a loop diuretic.

While these examples demonstrate therapeutic benefits, harm may also occur, for example, when administering spironolactone and potassium (producing hyperkalemia) or quinidine and erythromycin (additive QT prolongation). Antagonistic interactions may be seen when nonsteroidal anti-inflammatory medications (NSAIDs) are given with antihypertensives (reduced antihypertensive efficacy) or loop diuretics (reduced sodium and water excretion).

As mentioned above, for any given drug–drug interaction there may be multiple mechanisms contributing to the interaction. Also, not all drug interactions are of clinical relevance. It is the responsibility of the health care provider to recognize the significance of any given interaction and determine the applicability of this interaction to the patient.

This chapter will focus on cardiovascular drug–drug interactions, primarily those of clinical consequence. Drug interactions from major cardiovascular drug classes are described in terms of proposed mechanisms, clinical consequences, and suggested courses of action. Due to a high degree of interpatient variability in drug disposition and drug effects, significant interactions do not always occur in every patient given a drug interaction listed. Therefore, this chapter is intended to serve as a guide to important interactions that are likely to occur in clinical situations. Because information on drug interactions are constantly evolving due to new drugs that are released and new information being published in the literature, interested readers are encouraged to consult frequent-
ly updated references for a comprehensive list of drug interactions.13,23

Angiotensin Converting Enzyme Inhibitors

ACE inhibitors are used extensively for the management of hypertension and heart failure. A number of drug interactions have been cited with this class of agents, and a few clinically relevant ones are described here.24,25 Because ACE inhibitors lower blood pressure, they can work synergistically with other blood pressure lowering agents such as diuretics to further reduce blood pressure. In many cases, the combined use of ACE inhibitors and diuretics can provide better blood pressure control. However, the concurrent use of these 2 agents can also cause excessive hypotension. Thus, in patients who are already receiving diuretics, it may be preferable to initiate the ACE inhibitor at a lower dose or to temporarily discontinue the diuretic for 2 to 3 days before starting ACE inhibitor therapy.26 In addition, blood pressure and fluid status should be monitored in these patients.

Due to their ability to lower aldosterone levels and cause potassium retention, ACE inhibitors may cause an excessive rise in serum potassium levels when given concurrently with other agents that increase serum potassium, such as potassium-sparing diuretics, eplerenone, or potassium supplements. Thus, it is important to monitor serum potassium in patients using these combinations, especially in patients with renal impairment.27 Because ACE inhibitors and NSAIDs exert opposing effects on prostaglandin release, the concurrent use of both agents may theoretically lead to less vasodilation and diminished efficacy from ACE inhibitors.28 For example, indomethacin has been shown to diminish the antihypertensive effects of enalapril and perindopril in patients who were maintained on these ACE inhibitors for blood pressure control.26-27 Although uncommon, clinically significant nephrotoxicity has also occurred when ACE inhibitors were given concurrently with NSAIDs.25,28 Therefore, one must monitor renal function carefully, especially in patients with renal impairment, when ACE inhibitors and NSAIDs are given together.

Concerns have been raised regarding the counteracting effect of aspirin on the augmentation of prostacyclin synthesis by ACE inhibitors, thus diminishing the beneficial effects of ACE inhibitors in heart failure patients.29 Results from clinical trials investigating the interaction between ACE inhibitors and aspirin have been inconsistent.29-32 At this point, the evidence for benefit or harm from aspirin therapy in heart failure patients using ACE inhibitors remains inconclusive pending further study.29 Some evidence suggest that low doses of aspirin (40 to 80 mg) are sufficient to inhibit thromboxane synthesis, whereas higher doses of aspirin (> 325 mg) may be required to completely inhibit the synthesis of vasodilating prostaglandins.33 For this reason, it may be helpful to use a lower dose of aspirin (ie, 81 mg) in patients with heart failure who are treated with ACE inhibitors concurrently.29 Of note, ACE inhibitors increase insulin sensitivity and may therefore increase the hypoglycemic effect of antidiabetic agents.25,34-36 In patients using ACE inhibitors and antidiabetic therapy concurrently, blood glucose should be monitored regularly, and dosages of antihyperglycemic agents should be adjusted as needed.25,34 Other medications that interact with ACE inhibitors include allopurinol, azathioprine, cyclosporine, and lithium.36-45 These interactions are described in Table 31-4.25-45

Angiotensin Receptor Blockers (ARBs)

Compared to other classes of antihypertensive agents, ARBs are well tolerated and appear to have a low potential for drug interactions.46,47 Similar to ACE inhibitors, ARBs have a synergistic pharmacodynamic effect on blood pressure control by reacting with diuretics such as hydrochlorothiazide.48 Drugs that are likely to interact with all ARBs include lithium, NSAIDs, potassium-sparing diuretics, eplerenone, and potassium supplements. Other drug interactions involving ARBs are more specific to individual agents. Among the agents in this class, losartan and irbesartan have greater affinities for cytochrome P450 isoenzymes and thus are more likely to interact with other drugs.49

Losartan has affinity for CYP2C9, which facilitates the conversion of losartan to the carboxylic acid derivative E-3174 (a metabolite that has 10 to 14 times more antihypertensive activity than the parent compound, losartan). In addition, it has modest affinity for the CYP1A2 and CYP3A4 isoenzymes, both of which are also involved in the formation of E-3174.50 Fluconazole (an antifungal agent) is an effective CYP2C9 inhibitor that suppresses the conversion of losartan to E-3174. In healthy volunteers who received both losartan and fluconazole, an increase in the mean peak plasma concentration (Cmax) and area under the concentration-time curve (AUC) of losartan, as well as reductions in the plasma levels of E-3174, were observed.48 Alterations of these pharmacokinetic parameters could potentially lead to a decreased antihypertensive efficacy of losartan. However, the clinical significance of this interaction is unknown.49

Rifampin (an antibacterial agent frequently used for the treatment of tuberculosis and potent inducer of the CYP3A4 system) is another agent that has the potential to interact with losartan. The AUC of losartan was reduced by 35% and that of E-3174 by 40% when losartan and rifampin were concurrently administered to
Table 31-4. Selected Drug–Drug Interactions with ACE Inhibitors

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors (All)</td>
<td>Potassium-sparing diuretics, eplerenone, or potassium supplements</td>
<td>Increased potassium retention by all agents</td>
<td>Hyperkalemia</td>
<td>Monitor serum potassium levels (especially in patients with renal impairment) and renal function</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>NSAIDs interfere with the production of vasodilator and natriuretic prostaglandins</td>
<td>Diminished antihypertensive and natriuretic effects</td>
<td>Monitor blood pressure and adjust therapy as needed</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Reduced production of angiotensin II (which maintains GFR by efferent arteriolar constriction when kidneys are underperfused) by ACE inhibitors and reduced renal vasodilatory prostaglandins (which support adequate renal blood flow by afferent arteriolar vasodilation) by NSAIDs may cause a loss of synergistic action to sustain glomerular filtration.</td>
<td>Acute renal insufficiency</td>
<td>Monitor renal function, especially in patients with renal impairment</td>
<td></td>
</tr>
<tr>
<td>Antihyperglycemic Agents</td>
<td>ACE inhibitors increase insulin sensitivity and may increase the hypoglycemic effect of antidiabetic agents.</td>
<td>Hypoglycemia</td>
<td>Monitor blood glucose closely and adjust dosages of antihyperglycemic agents as needed. Patients should also be warned about the possibility of hypoglycemia when ACE inhibitors are given currently with antidiabetic agents.</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Unknown. Anemia may possibly be due to the erythropoietin-lowering effects of ACE inhibitors</td>
<td>Myelosuppression (anemia or leukopenia)</td>
<td>Avoid concurrent administration of azathioprine and ACE inhibitors. If these drugs must be given together, monitor hemoglobin, hematocrit, platelets, and white cell counts every 2 to 3 weeks.</td>
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</tr>
<tr>
<td>Cyclosporine</td>
<td>Long term cyclosporine therapy may cause renal hypoperfusion, which may activate the rennin-angiotensin system for maintenance of glomerular filtration. Under these circumstances, the co-administration of an ACE inhibitor (which decreases the production of angiotensin II) could trigger acute renal failure.</td>
<td>Acute renal failure</td>
<td>Monitor renal function closely</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>Because lithium is mostly excreted by the kidneys and is dependent on both glomerular filtration and sodium concentration in the proximal tubule, the possible reduction of glomerular filtration and sodium concentration by ACE inhibitors may lead to increased lithium retention.</td>
<td>Lithium toxicity (weakness, tremor, excessive thirst, confusion)</td>
<td>If lithium and ACE inhibitors are used concurrently, monitor serum lithium concentrations frequently, especially in patients with impaired renal function, congestive heart failure or volume depletion. Lower lithium doses may be required</td>
<td></td>
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</tbody>
</table>
In addition, the half-lives of losartan and E-3174 were reduced by 50%. Due to the extent of this pharmacokinetic effect, the interaction is likely to be clinically significant and may necessitate an increase in losartan dosage when it is given concurrently with rifampin.46,49

In common with losartan, irbesartan has a marked affinity for CYP2C9, CYP3A4, and CYP1A2.47 Drug interactions could occur with tolbutamide or warfarin since both of these agents competitively inhibit the oxidation of irbesartan. However, a pharmacokinetic interaction between irbesartan and tolbutamide or irbesartan and warfarin (along with other drugs such as nifedipine, magnesium and aluminium hydroxides, simvastatin, or digoxin) was not observed.50 Furthermore, a study in healthy volunteers showed that irbesartan did not affect the steady-state pharmacodynamics and pharmacokinetics of warfarin.51 Therefore, dosage adjustment of irbesartan or warfarin, or additional anticoagulation monitoring, is probably not necessary when irbesartan and warfarin are used concurrently.51

Telmisartan has no CYP-dependent metabolites and is mainly excreted via the bile.46 Thus, there is a low potential for interaction with this agent. Although the Cmax of digoxin was increased by 50% when telmisartan was given concurrently with digoxin, it was suggested that this elevation is transient and is unlikely to be of clinical significance.46-47 Clinically relevant drug interactions with ARBs are summarized in Table 31-5.23,46-51

### Antiarrhythmic Agents

Due to their narrow therapeutic index, small alterations in the serum concentrations of antiarrhythmics can lead to decreased therapeutic effectiveness or increased adverse effects. As most antiarrhythmics are metabolized via the CYP450 enzymes, pharmacokinetic interactions comprise the majority of clinically significant interactions seen with this class of agents.52 Using the Vaughn-Williams classification, more frequently used class I agents include quinidine, procainamide, disopyramide, lidocaine, mexiletine, flecainide, and propafenone. All of these agents except procainamide are metabolized via the CYP450 enzymes and are implicated in numerous drug–drug interactions.52

For example, quinidine alone has been involved in more than 30 different drug interactions, many of which can lead to major clinical consequences. Notable interactions include that of quinidine and digoxin, where quinidine was shown to decrease the clearance of digoxin and caused an increase in digoxin concentrations and possible digoxin toxicity.14 Another interaction is between quinidine and erythromycin, where erythromycin increased quinidine concentrations through inhibition of quinidine metabolism via CYP3A4 and induced possible quinidine toxicity.53

Class II and IV antiarrhythmics consist of beta-blockers and calcium antagonists; interactions involving these agents are discussed under their respective classifications in this section. Class III antiarrhythmic agents include amiodarone, dofetilide, dronedarone, ibutilide, and sotalol. Of these agents, amiodarone is commonly used and is involved in large numbers of drug interactions since it is metabolized by CYP3A4 and it is a potent inhibitor of several CYP450 enzymes (CYP1A2, 2C9, 2D6, and 3A4). A well-known interaction involving the enzyme-inhibitory effect of amiodarone is its reaction with warfarin, where amiodarone decreases warfarin metabolism via inhibition of CYP3A4 and causes an elevation in plasma
Another well-known interaction with amiodarone that involves a different mechanism is the interaction with digoxin, where the oral bioavailability of digoxin is increased due to the inhibition of P-glycoprotein by amiodarone. Thus, dosages of warfarin and digoxin should empirically be reduced by one-half when amiodarone is added.52

Grapefruit juice has been reported to interact with many drugs by inhibiting CYP3A4 and the P-glycoprotein transport system.54 Because a number of antiarrhythmic agents are metabolized through CYP3A4, grapefruit juice should be avoided in patients taking antiarrhythmic drugs such as amiodarone and dronedarone that undergo extensive hepatic metabolism with this enzyme.23,55 Besides pharmacokinetic interactions, antiarrhythmic agents are involved in many pharmacodynamic interactions. For example, additive negative inotropic effects may be observed when beta-blockers are added to fle-

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs (All)</td>
<td>Potassium-sparing diuretics, eplerenone, or potassium supplements</td>
<td>Increased potassium re-</td>
<td>Hyperkalemia</td>
<td>Monitor serum potassium levels (especially in patients with renal impairment) and renal function</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>NSAIDs interfere with the production of vasodilator and natriuretic prostaglandins</td>
<td>Diminished antihypertensive and natriuretic effects. Increased risk of renal impairment, especially in volume-depleted patients.</td>
<td>Monitor blood pressure, fluid status, and renal function. Therapy should be adjusted as needed.</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>Increased renal lithium reabsorption at the proximal tubular site</td>
<td>Lithium toxicity (weakness, tremor, excessive thirst, confusion)</td>
<td>If lithium and ARBs are used concurrently, monitor serum lithium concentrations frequently, especially in patients with impaired renal function, congestive heart failure, or volume depletion. Lower lithium doses may be required.</td>
<td></td>
</tr>
<tr>
<td>ARBs (losartan)</td>
<td>Fluconazole</td>
<td>Fluconazole decreases the conversion of losartan to its active metabolite, E-3174</td>
<td>Diminished antihypertensive effects from losartan</td>
<td>Monitor blood pressure and adjust dosage of losartan as needed.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifampin significantly induces the metabolism of losartan and E-3174, resulting in a decrease in the AUC and half-life of both compounds.</td>
<td>Diminished antihypertensive effects from losartan</td>
<td>Monitor blood pressure and adjust dosage of losartan as needed.</td>
<td></td>
</tr>
</tbody>
</table>

**Table 31-5. Selected Drug–Drug Interactions with Angiotensin Receptor Blockers**

ARBs = Angiotensin receptor blockers; NSAIDs = nonsteroidal anti-inflammatory drugs; AUC = area under the concentration-time curve
cainide or intravenous disopyramide. Additive effects on the reduction of atrioventricular nodal conduction and myocardial contractility may also be observed when amiodarone is added to other agents such as diltiazem, verapamil, digoxin, and beta-blockers.

A number of drugs such as erythromycin, cotrimoxazole, clarithromycin, azithromycin, gatifloxacin, ketoconazole, moxifloxacin, pentamide, chloroquine, quinine, cisapride, tricyclic antidepressants, haloperidol, phenothiazines, and risperidone have been implicated in the prolongation of QT interval, resulting in an increased risk of proarrhythmia. Concurrent use of drugs that prolong QT interval with Class Ia or Class III antiarrhythmics (which may also prolong QT interval) could increase the risk of drug-induced arrhythmia due to the combined pharmacodynamic effects. Therefore, clinicians should be aware of this possible interaction and monitor patients accordingly when concurrent use of more than one QT prolongation drug is necessary. Overall, antiarrhythmic agents have been implicated to interact with a number of drugs that include other antiarrhythmic agents, antibiotics, antidepressants, antifungals, antiretrovirals, beta blockers, calcium antagonists, digoxin, enzyme inducers, H₂ blockers, neuromuscular blockers, theophylline, and warfarin. Selected interactions involving antiarrhythmic agents are listed on Tables 31-6 and 31-7.

Anticoagulant Agents

Anticoagulants play an important role in various therapies including the prophylaxis and/or treatment of venous thrombosis, pulmonary embolism and atrial fibrillation with thromboembolism. Because these agents inhibit or diminish the synthesis of clotting factors, bleeding is a worrisome adverse effect. Concomitant use of an anticoagulant with other antiarrhythmic agents, antiplatelet drugs, fibrinolytics, and/or NSAIDs may cause pharmacodynamic interactions that further increase the risk of bleeding. Therefore, patients who are required to use more than one of these drugs must be monitored closely for signs and symptoms of bleeding; laboratory tests such as international normalized ration (INR) and activated partial thromboplastin time (aPTT) should be performed when appropriate.

In the United States, warfarin is used almost exclusively when oral anticoagulation is needed. Warfarin has a relatively narrow therapeutic index, requiring regular monitoring for safety and efficacy. Because warfarin is almost entirely metabolized in the liver, impaired hepatic function may increase sensitivity to this drug. Drug interactions with warfarin are plentiful and may be attributed to several mechanisms, such as a reduction in warfarin metabolism or clearance (increases warfarin effect); displacement of warfarin from plasma protein binding sites (increases warfarin effect); or an increase in warfarin metabolism (decreases warfarin effect). Due to the complex response of warfarin to concurrent drug therapy, it is difficult to predict the occurrence and degree of influence from other drugs on anticoagulation in individual patients. For clinical practice, one should monitor for changes in INR when adding or discontinuing any drugs suspected to cause an interaction in patients receiving warfarin. In many cases, the onset of the adverse prothrombin time response from warfarin might begin between 1 to 2 days after starting the concurrent drug regimen. However, the potentiation of warfarin effects may occur within 2 weeks and even up to 2 months in some cases after initiating amiodarone. Selected drug interactions with warfarin are listed on Table 31-8.

Antiplatelet Agents

Antiplatelet agents are frequently used drugs; they are employed in various therapies including the reduction of cardiac events in patients with acute coronary syndrome. Similar to anticoagulants, bleeding is a concerning adverse effect. Concurrent use of an antiplatelet agent with other antiplatelet drugs, anticoagulants, fibrinolytics, and/or NSAIDs may further increase the risk of bleeding.

In addition to pharmacodynamic interactions with other drugs that could potentiate the risk of bleeding, pharmacokinetic interactions involving antiplatelet agents have been reported. For example, ticlopidine has shown to decrease the metabolism of phenytoin and theophylline. Thus, ticlopidine may increase the plasma concentrations of phenytoin and theophylline and cause an increased risk of toxicity of the latter agents. It is important to monitor patients closely for signs and symptoms of phenytoin or theophylline toxicity and adjust dosages accordingly when either of these agents is used concomitantly with ticlopidine.

The pharmacokinetic interaction between clopidogrel and PPIs has caused much research and debate. Clopidogrel, a thienopyridine, is a prodrug that is transformed in vivo to an active metabolite, which irreversibly binds to the platelet P2Y₁₂ receptor and subsequently blocks platelet activation and aggregation. The active metabolite of clopidogrel is formed through the CYP450 enzyme system after 2 sequential reactions involving CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4, with CYP2C19 playing a major role. PPIs inhibit the CYP2C19 pathway and may interfere with the conversion of clopidogrel to its active form, which may subsequently lead to a diminished clinical efficacy from clopidogrel. A number of studies have examined the effects of PPIs on clopidogrel's clinical efficacy. However, results of these
studies have been conflicting and inconsistent. While some large observational studies found an increase in cardiovascular events in participants prescribed clopidogrel who also took PPIs, others did not find a significant difference in clinical outcomes based on PPI exposure.108-112

It is interesting that more reports finding a drug interaction between clopidogrel and PPIs were associated and clopidogrel should be avoided.113 Because esomeprazole is a component of omeprazole, this PPI should also be avoided in combination with clopidogrel.113 Further, other drugs that are potent inhibitors of the CYP2C19 enzyme, such as cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine, should be avoided in patients taking clopidogrel.113

In addition to the FDA recommendations, several suggestions have been made to address the uncertainties of the clopidogrel-PPI interaction. One suggestion is for clinicians to consider using pantoprazole when a PPI is indicated.107,114 Because pantoprazole is a weak inhibitor of CYP2C19, a significant interaction with clopidogrel will probably occur. Another suggestion is to stagger the dosing of clopidogrel and PPIs.114 Because most PPIs are eliminated within 10 hours, inhibition of CYP2C19 is likely to be short lived, and separation of clopidogrel and PPI by 12 to 20 hours should in theory prevent an interaction.115

In contrast to the above recommendation by some authors, the FDA stated that separating the dose of clopidogrel and omeprazole in time would not reduce the possibility of a drug interaction.113 Perhaps the most important suggestion of all is that clinicians must evaluate the necessity of PPI therapy.107,114 In patients whom PPIs are not absolutely indicated, switching PPI therapy to H2 antagonists (ie, ranitidine, famotidine, nizatidine) or antacids would help to avoid a clopidogrel-PPI interaction.113

### Beta-Adrenergic Blockers

Beta blockers are generally well tolerated and are widely used for various cardiovascular and other clinical conditions (see Chapter 5, Alpha- and Beta-Adrenergic Blocking Drugs). Heart rate, myocardial contractility, and blood pressure are all reduced with beta-blockade; some of these effects may be additive with those of digoxin or nondihydropyridine calcium channel blockers. Specifically, digoxin and beta-blockers can have additive inhibiting effects on AV nodal activity.116 The concurrent use of verapamil and beta-blockers can lead to hypotension, hemodynamically significant bradycardia, and heart failure, as well as hemodynamic collapse.116-119

Rebound hypertension may occur following the abrupt withdrawal of clonidine in patients who received concurrent treatment with clonidine and beta-blocker.23 This phenomenon may be due to an unopposed alpha effect following clonidine withdrawal.23 This exaggerated clonidine withdrawal response may be minimized with the use of cardioselective beta-blockers (eg, atenolol, metoprolol) or by the use of a combined alpha- and beta-adrenergic blocker such as labetalol.12,118 Alternatively, the beta-blocker may be discontinued first before clonidine is to be withdrawn from concomitant therapy with a beta-blocker.23 Use of alpha blockers (eg, prazosin and doxazosin) may also help to prevent rebound hypertension associated with clonidine withdrawal.23

Several beta-blockers (bisoprolol, carvedilol, metoprolol, propranolol, and timolol) are substrates of CYP2D6; carvedilol is also a substrate of CYP2C9 and propranolol a substrate of CYP2C19.12,128 Some beta blockers may also inhibit the metabolism of other drugs.12 Therefore, many beta blockers are susceptible to pharmacokinetic interactions that would affect either the metabolism of the beta-blocker itself or the metabolism of other drugs. The concurrent use of amiodarone and metoprolol or propranolol has been associated with bradycardia, cardiac arrest, and ventricular arrhythmias.12 This adverse effect may be attributed to the additive cardiac effects from both amiodarone and beta blockers. In addition, amiodarone may inhibit beta-blocker metabolism leading to increased beta-blocker effects and possibly beta-blocker toxicity.23

Another important interaction is that between propranolol and thioridazine. Propranolol may inhibit the metabolism of thioridazine, thus increasing thioridazine plasma levels and increasing the risk of cardiac arrhythmias and tardive dyskinesia.122 For this reason, the concurrent administration of thioridazine and propranolol is contraindicated. Other interactions involving beta blockers are described in Table 31-9.12,23,24,116-127 Note that propranolol is involved in more drug interactions compared to other beta-blockers. This may be due to the propensity of propranolol’s metabolism to be affected by other drugs or its ability to inhibit the metabolism of some drugs. Furthermore, propranolol is the oldest beta-blocker, thus it is the most comprehensively studied.

### Calcium Antagonists

Calcium antagonists are a diverse class of drugs commonly used in the management of cardiac conditions such as hypertension, supraventricular arrhythmias and angina pectoris (see Chapter 8, Calcium Channel Blockers). Due
to their high frequency in usage, there is an increased potential for calcium antagonists to be administered concurrently with other agents and cause drug interactions.  

Diltiazem and verapamil may produce additive depression on AV nodal conduction and myocardial contractility when they are used concurrently with amiodarone, beta-blockers, or digoxin.  

Because calcium antagonists are metabolized by CYP3A4, they are also susceptible to pharmacokinetic interactions with drugs that either inhibit or induce CYP3A4.  

Carbamazepine, phenytoin and phenobarbital are inducers of CYP3A4 and have led to decreases in the hemodynamic effects of calcium channel blockers, particularly felodipine.  

Inhibitors of the CYP3A4, such as itraconazole and grapefruit juice, have been demonstrated or would be expected to cause increased serum concentrations of calcium antagonists, particularly the dihydropyridines.  

In addition to being a substrate of CYP3A4, verapamil and diltiazem are inhibitors of CYP3A4 and can interact with drugs that are metabolized by this isoenzyme.  

For example, verapamil and diltiazem may inhibit the CYP3A4-mediated metabolism of certain HMG-CoA reductase inhibitors (atorvastatin, lovastatin, and simvastatin) and increase the risk of myopathy and rhabdomyolysis.  

Because pravastatin is not extensively hepatically metabolized and both fluvastatin and rosuvastatin are metabolized via CYP2C9, these statins may serve as safer alternatives in patients who are on concurrent diltiazem or verapamil therapy.  

Another noteworthy interaction is between that of calcium antagonists and cyclosporine. Diltiazem, verapamil, amiodipine, felodipine, and nifedipine all have shown to increase cyclosporine serum concentrations to various degrees.  

Therefore, one must monitor cyclosporine levels closely and reduce the dose of cyclosporine accordingly when this agent is given concomitantly with interacting calcium antagonists.  

This interaction may be a desirable one since it could result in decreased cost as a result of lower cyclosporine dosage requirements.  

A particularly important interaction is that of calcium antagonists and digoxin. Diltiazem and verapamil reduce the clearance of digoxin and may increase serum digoxin concentrations by as much as 50% and 70%, respectively.  

Therefore, one must monitor digoxin levels carefully and adjust the dosage of this drug accordingly when it is given concurrently with interacting calcium antagonists. Selected interactions involving calcium antagonists are summarized on Table 31-10.  

Digoxin is the most commonly used digitalis glycoside (see Chapter 13, Inotropic Agents). This drug has been used frequently for the management of atrial fibrillation and heart failure. Because digoxin has a narrow therapeutic index, a change in drug concentration due to drug interactions may lead to clinical adverse effects. Interactions with digoxin have been discussed under other therapeutic classes in this section; a few important ones are highlighted here.  

Due to its negative chronotropic effect, the concurrent use of digoxin with diltiazem, verapamil, amiodarone, or beta-blockers may cause additive effects on AV nodal conduction and lead to bradycardia or heart block.  

Serum electrolyte disturbances, such as hypokalemia and hypomagnesemia may predispose patients to digoxin toxicity. Thus, serum electrolytes should be monitored routinely in patients on chronic digoxin therapy, especially in those who are also on diuretic therapy, which can cause a decrease in serum electrolytes.  

Antibiotic therapy with erythromycin or tetracycline can reduce digoxin bioinactivation by destroying specific bacteria flora in the colon, thus increasing its availability for absorption and can lead to increased digoxin concentration and possible digoxin toxicity.  

Amiodarone, propafenone and quinidine have all shown to decrease digoxin clearance and increase digoxin serum concentrations.  

Therefore, one must monitor digoxin concentrations carefully and adjust the dosage of digoxin accordingly when it is given concurrently with interacting agents. Selected interactions involving digoxin are listed on Table 31-11.  

Diuretics and Nitrates  

Diuretics, especially thiazide diuretics, are commonly used in combination with ACE inhibitors, ARBs, and beta-blockers for additive antihypertensive effects. However, combinations of diuretics and ACE inhibitors may also cause postural hypotension in some patients due to vasodilation and relative intravascular volume depletion. A good way to prevent first-dose hypotension is to start an ACE inhibitor on a lower dose for patients who are using diuretics concurrently.  

Blood pressure, fluid status, and body weight should be monitored regularly upon initiation of both diuretic and ACE inhibitor therapy. Thiazide and loop diuretics may cause potassium loss and should be used carefully with other drugs that can decrease potassium levels, such as corticosteroids, amphotericin, and itraconazole.  

The hypokalemic effect of diuretics can usually be overcome by concurrent use of drugs that increase serum potassium. Concomitant use of agents such as ACE inhibitors, ARBs, and potassium-sparing diuretics not only prevent potassium loss from thiazide diuretics; they also provide enhanced effects on blood pressure control. On the contrary, use of agents that increases serum potassium such as ACE inhibitors
and potassium supplements, along with potassium-sparing diuretics (ie, triamterene, spironolactone, amiloride), may cause hyperkalemia. Therefore, it is important to perform periodic determination of serum electrolytes in all patients receiving diuretic therapy.

NSAIDs can reduce the diuretic and antihypertensive efficacy of diuretics by inhibiting renal sodium excretion and decreasing renal prostaglandin production. Anotable interaction is between thiazide diuretics and lithium. Hydrochlorothiazide may decrease lithium clearance and increase serum lithium concentration and cause lithium toxicity. Therefore, it is important to monitor serum lithium concentrations and adjust lithium doses accordingly during concomitant therapy with thiazide diuretics.

Nitrate administration is considered. A suitable time interval following vardenafil dosing for the safe administration of nitrates has not been determined.164 A suitable time interval following vardenafil dosing for the safe administration of nitrates has not been determined.165

**Lipid-Lowering Drugs**

The bile acid sequestrants (cholestyramine, colestipol, and colesevelam) are safe and effective agents for the treatment of hyperlipidemia. Because they are not absorbed into the circulation, they may be used with other agents that lower blood pressure. The interaction between nitrates and sildenafil has caught much media attention due to a number of deaths associated with this interaction. Co-administration of nitrates and sildenafil significantly increases the risk of potentially life-threatening hypotension. Thus, the administration of nitrates should be avoided in patients who have taken sildenafil within the past 24 hours. Similarly, the concurrent use of nitrates with other phosphodiesterase 5 inhibitors such as tadalafil and vardenafil is contraindicated. In patients who are using tadalafil for erectile dysfunction, at least 48 hours should elapse after the last dose of this agent before nitrate administration is considered. A suitable time interval following vardenafil dosing for the safe administration of nitrates has not been determined.

Further, fenofibrate may be the preferred fibric acid derivative for combination therapy since it does not undergo extensive hepatic metabolism. Many drug–drug interactions, however, may be detected and resolved through knowledge and sound clinical judgments based on pharmacokinetic and pharmacodynamic data. Major drug–drug interactions that lead to significant clinical consequences should be committed to memory, especially if the drugs involved are used frequently in one’s area of practice. Furthermore, prevention of polypharmacy through periodic medication regimen review is a good way to avoid unfavorable drug–drug interactions.

**Conclusion**

With the vast and growing number of cardiovascular drugs in our armamentarium, the task of tracking every drug interaction can be overwhelming if not impossible. Many drug–drug interactions, however, may be detected and resolved through knowledge and sound clinical judgments based on pharmacokinetic and pharmacodynamic data. Major drug–drug interactions that lead to significant clinical consequences should be committed to memory, especially if the drugs involved are used frequently in one’s area of practice. Furthermore, prevention of polypharmacy through periodic medication regimen review is a good way to avoid unfavorable drug–drug interactions.

**Note:** References for this chapter can be found here: www.cvptct3.com
### Table 31-6. Selected Drug-Drug Interactions with Class I Antiarrhythmic Agents

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Antiarrhythmics</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Monitor blood pressure and ECG; concurrent use of two or more Class IA antiarrhythmic agents is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>(procaainamide,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>disopyramide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiarrhythmics</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>If concurrent use of quinidine and a class III antiarrhythmic is absolutely necessary, monitor ECG carefully.</td>
</tr>
<tr>
<td></td>
<td>(Amiodarone, dofetilide, dronedarone, ibutilide, sotalol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Additive cardiac toxicity; additive effects on QT prolongation</td>
<td>May increase serum quinidine concentration; increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>The concurrent use of a Class Ia and a Class III antiarrhythmic agent is generally not recommended. If concurrent use is deemed necessary, quinidine dose should be reduced by one-third, and the patient should be monitored for signs of arrhythmias.</td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td>Additive cardiac effects</td>
<td>Slight increase in disopyramide concentrations</td>
<td>Monitor for disopyramide toxicity (dosage adjustment for both drugs may be needed).</td>
</tr>
<tr>
<td></td>
<td>Flecaïnine</td>
<td>Inhibition of CYP2D6 hepatic enzymes by quinidine results in decreased metabolism of flecaïnine</td>
<td>Increased serum flecaïnine concentration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propafenone Methadone</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td>Hepatic metabolism of propafenone may decrease</td>
<td>Increased plasma propafenone concentrations</td>
<td>Monitor for propafenone toxicity and adjust dosage of propafenone as needed.</td>
</tr>
<tr>
<td></td>
<td>Antibacterials</td>
<td>Additive effects on QT prolongation; clarithromycin and erythromycin may decrease metabolism of quinidine</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest); increased quinidine plasma concentration by clarithromycin and erythromycin</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended; monitor for quinidine toxicity</td>
</tr>
<tr>
<td></td>
<td>(ciprofloxacine, clarithromycin, cotrimoxazole, erythromycin, gatifloxacine, levofloxacine, moxifloxacine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antifungals</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>(Itraconazole,</td>
<td>Decreased quinidine metabolism</td>
<td>Increased plasma quinidine concentration</td>
<td>Monitor for quinidine toxicity; concurrent use of itraconazole and quinidine is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>fluconazole,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketoconazole)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antifungals</td>
<td>Inhibition of quinidine metabolism</td>
<td>Increase of QT prolongation and torsades de pointes; increased quinidine plasma concentration</td>
<td>Concurrent use of posaconazole or voriconazole and quinidine is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>(Posaconazole,</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Voriconazole)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of quinidine and thioridazine or ziprasidone is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>(Thioridazine,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ziprasidone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiretrovirals</td>
<td>Inhibition of quinidine metabolism</td>
<td>Increased quinidine plasma concentration; increased risk of quinidine toxicity</td>
<td>Monitor for quinidine toxicity and adjust dosage of quinidine as needed.</td>
</tr>
<tr>
<td></td>
<td>(Amprenavir, atazanavir, darunavir, fosamprenavir, lopinavir)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beta blockers</td>
<td>Inhibition of quinidine metabolism</td>
<td>Increased quinidine plasma concentration; increased risk of quinidine toxicity</td>
<td>Concurrent use of these antiretroviral agents and quinidine is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>(Atenolol, metoprolol, propranolol, timolol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium antagonists</td>
<td>Inhibition of quinidine metabolism</td>
<td>Increased plasma quinidine concentrations</td>
<td>Monitor for quinidine toxicity.</td>
</tr>
<tr>
<td></td>
<td>(verapamil, diltiazem)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Reduced renal and nonrenal clearance of digoxin</td>
<td>Increased plasma digoxin concentration and increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin level, and decrease dose of digoxin as needed.</td>
</tr>
<tr>
<td></td>
<td>Enzyme Inducers</td>
<td>Increase quinidine metabolism and elimination</td>
<td>Decreased plasma quinidine concentration; decreased quinidine effectiveness</td>
<td>Assess the therapeutic efficacy of quinidine and adjust dosage as needed.</td>
</tr>
<tr>
<td></td>
<td>(Carbamazepine, Phenytin, Phenobarbital, rifampin)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 31-6. Selected Drug-Drug Interactions with Class I Antiarrhythmic Agents

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Neuromuscular Blockers (Succinylcholine, atracurium, pancuronium, Vecuronium)</td>
<td>Altered metabolism of succinylcholine by quinidine; additive effects of pancuronium or vecuronium with quinidine</td>
<td>Increased toxicity of interacting drugs (respiratory depression, apnea, prolonged neuromuscular blockade)</td>
<td>Monitor for respiratory depression and prolonged neuromuscular blockade; respiratory support should be provided as needed.</td>
</tr>
<tr>
<td></td>
<td>Tricyclic Antidepressants (amitriptyline, desipramine, imipramine, nortriptyline)</td>
<td>Decreased antidepressant metabolism; additive cardiac effects</td>
<td>Increased adverse effects from antidepressants (dry mouth, urinary retention, sedation) and increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Monitor for increased antidepressant adverse effects and signs and symptoms of additive cardiac effects (changes in ECG). Concurrent use of a Class Ia antiarrhythmic and a tricyclic antidepressant is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Urinary alkalinizers (acetaminophen, acetazolamide, antacids)</td>
<td>Increase in urinary pH may result in a significant decrease in quinidine renal elimination</td>
<td>Possible increased serum quinidine concentrations and quinidine toxicity</td>
<td>Monitor for quinidine toxicity and adjust dosage of quinidine as needed.</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Decreased clotting factor synthesis</td>
<td>Increased bleeding risk from warfarin</td>
<td>Monitor INR, adjust warfarin dose as needed.</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Antiarrhythmics (disopyramide, quinidine)</td>
<td>Additive cardiac effects; quinidine also decreases procainamide clearance via competition for renal tubular secretion.</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Monitor blood pressure and ECG; concurrent use of two or more class IA antiarrhythmic agents is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Antiarrhythmics (Amiodarone, dofetilide, dronedarone, ibutilide, sotalol)</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>If concurrent use of propranolol and a class III antiarrhythmic is absolutely necessary, monitor ECG carefully.</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Decreased procainamide clearance</td>
<td>May increase serum procainamide concentration and lead to procainamide toxicity.</td>
<td>Monitor for signs of procainamide toxicity (QT prolongation, torsades de points), assess propranolol levels, and reduce procainamide dose accordingly.</td>
</tr>
<tr>
<td></td>
<td>Flecainide</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended; monitor ECG and procainamide serum concentration and adjust procainamide dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Antibacterials (Ciprofloxacin, clarithromycin, cotrimoxazole, erythromycin, gatifloxacin, levofloxacin, moxifloxacin, oloxacin)</td>
<td>Additive effects on QT prolongation. Oloxacin inhibits the active renal tubular secretion of procainamide.</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended; monitor ECG and procainamide serum concentration and adjust procainamide dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Antifungals (fluconazole)</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics (Haloperidol, quetiapine, risperidone, thioridazine, ziprasidone)</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of a Class IA antiarrhythmic and an antipsychotic is generally not recommended. Concurrent use of propranolol and thioridazine or ziprasidone is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>β1 Antagonists (Cimetidine, ranitidine)</td>
<td>Decreased procainamide renal clearance due to competition for active tubular secretion</td>
<td>Increased risk of procainamide toxicity (cardiac arrhythmias, hypotension, CNS depression)</td>
<td>Monitor for signs and symptoms of procainamide toxicity. Monitor procainamide plasma concentration. Decrease dose of procainamide as needed.</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular Blockers (Succinylcholine, atracurium, pancuronium, vecuronium)</td>
<td>Reduction of acetylcholine release by procainamide</td>
<td>Excessive neuromuscular blockade</td>
<td>Monitor for prolonged neuromuscular blockade; adjust doses of neuromuscular blocker as needed.</td>
</tr>
<tr>
<td></td>
<td>Tricyclic Antidepressants (Amitriptyline, desipramine, imipramine, nortriptyline)</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Monitor for signs and symptoms of additive cardiac effects (changes in ECG). Concurrent use of a Class IA antiarrhythmic and a tricyclic antidepressant is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td>Antiarrhythmics (Propranolol, quinidine)</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
</tr>
<tr>
<td></td>
<td>Antiarrhythmics (Amiodarone, dofetilide, dronedarone, ibutilide, sotalol)</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>If concurrent use of disopyramide and a class III antiarrhythmic is absolutely necessary, monitor ECG carefully.</td>
</tr>
<tr>
<td>Primary Drugs</td>
<td>Interacting Drugs</td>
<td>Proposed Mechanism of Interaction</td>
<td>Possible Effects</td>
<td>Clinical Management</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------</td>
<td>----------------------------------</td>
<td>-----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Flecainide &amp; Propafenone</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de points, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Antibacterials (Azithromycin, ciprofloxacin, clarithromycin, crotimosoxol, erythromycin, gatifloxacin, levofloxacin, moxifloxacin)</td>
<td>Additive effects on QT prolongation; azithromycin, clarithromycin, and erythromycin may decrease metabolism of disopyramide</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de points, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended; monitor for signs and symptoms of disopyramide toxicity (antiadrenergic effects, hypotension, heart failure, cardiac arrhythmias).</td>
</tr>
<tr>
<td></td>
<td>Antifungals (fluconazole)</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de points, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Antifungals (itraconazole)</td>
<td>Decreased disopyramide concentration and risk of disopyramide toxicity.</td>
<td>Monitor for signs and symptoms of disopyramide toxicity.</td>
<td>Monitor for signs and symptoms of disopyramide toxicity. Adjust dose of disopyramide as needed.</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics (haloperidol, quetiapine, risperidone, thioridazine, ziprasidone)</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de points, cardiac arrest)</td>
<td>Concurrent use of a Class IA antiarrhythmic and an antipsychotic is generally not recommended. Concurrent use of disopyramide and thioridazine is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Antiretrovirals (atazanavir, ritonavir, saquinavir)</td>
<td>Inhibition of disopyramide metabolism</td>
<td>Increased disopyramide plasma concentration and increased risk of disopyramide toxicity</td>
<td>Monitor for signs and symptoms of disopyramide toxicity and adjust dose of disopyramide as needed.</td>
</tr>
<tr>
<td></td>
<td>Beta blockers (atenolol, betaxolol, propranolol)</td>
<td>Additive cardiovascular effects</td>
<td>Bradycardia, hypotension, decreased cardiac output</td>
<td>Monitor blood pressure, heart rate, and cardiac function and adjust dosages as needed.</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Unknown</td>
<td>Increased plasma digoxin concentrations and increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin level, and decrease dose of digoxin as needed.</td>
</tr>
<tr>
<td></td>
<td>Enzyme Inducers (Phenobarbital, rifampin)</td>
<td>Increase disopyramide metabolism and elimination</td>
<td>Decreased plasma disopyramide concentration; decreased disopyramide effectiveness</td>
<td>Assess the therapeutic efficacy of disopyramide and adjust dosage as needed.</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants (amitriptyline, desipramine, imipramine, norclopyrine)</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de points, cardiac arrest)</td>
<td>Monitor for signs and symptoms of additive cardiac effects (changes in ECG). Concurrent use of a Class IA antiarrhythmic and a tricyclic antidepressant is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
<td>Amiodarone</td>
<td>Decreased lidocaine metabolism</td>
<td>Increased serum lidocaine concentration; increased lidocaine toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antiretrovirals (amprenavir, atazanavir, darunavir, fosamprenavir, lopinavir, ritonavir)</td>
<td>Inhibition of lidocaine metabolism</td>
<td>Increased lidocaine plasma concentration; increased risk of lidocaine toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beta blockers (Metoprolol, nadolol, propranolol)</td>
<td>Decreased lidocaine metabolism</td>
<td>Increased lidocaine plasma concentration; increased risk of lidocaine toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cimetidine</td>
<td>Decreased lidocaine metabolism possibly due to decreased hepatic blood flow</td>
<td>Increased lidocaine plasma concentration; increased risk of lidocaine toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenytoin</td>
<td>Increased lidocaine metabolism and elimination</td>
<td>Decreased plasma lidocaine concentration and decreased lidocaine effectiveness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Succinylcholine</td>
<td>Unknown</td>
<td>Increased toxicity of neuromuscular blockers (respiratory depression, apnea, prolonged neuromuscular blockade)</td>
</tr>
<tr>
<td></td>
<td>Mexiletine</td>
<td>Antiarrhythmics (amiodarone, quinidine)</td>
<td>Decreased metabolism of mexiletine</td>
<td>Increased mexiletine plasma concentration; increased risk of mexiletine toxicity (nausea, dizziness, cardiac arrhythmias)</td>
</tr>
</tbody>
</table>

*Table 31-6 continued on p. 509*
Table 31-6. Selected Drug-Drug Interactions with Class I Antiarrhythmic Agents (continued)

<table>
<thead>
<tr>
<th>Primary Drug</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexiletine (continued)</td>
<td>Enzyme inducers (phenytoin, rifampin)</td>
<td>Increased mexiletine metabolism and elimination</td>
<td>Decreased plasma mexiletine concentration and decreased mexiletine effectiveness</td>
<td>Assess the therapeutic efficacy of mexiletine and adjust dosage as needed.</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Inhibition of mexiletine metabolism</td>
<td>Increased mexiletine plasma concentration; increased risk of mexiletine toxicity</td>
<td>Monitor for signs and symptoms of mexiletine toxicity and adjust dosage of mexiletine accordingly.</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Mexiletine inhibits the CYP1A2 metabolism of theophylline</td>
<td>Increased theophylline plasma concentration; increased risk of theophylline toxicity (nausea, vomiting, palpitation, seizures)</td>
<td>Monitor for signs and symptoms of theophylline toxicity, check theophylline serum concentration, and adjust dose of theophylline as needed.</td>
<td></td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>Amiodarone</td>
<td>Amiodarone inhibits CYP2D6 and decreases metabolism of flecaïnide; additive effects on QT prolongation</td>
<td>Increased flecaïnide plasma concentration; increased risk of flecaïnide toxicity (cardiac arrhythmias, neurologic effects, exacerbation of heart failure).</td>
<td>Monitor ECG and monitor for signs and symptoms of flecaïnide toxicity and reduce dosage of flecaïnide accordingly.</td>
</tr>
<tr>
<td></td>
<td>Antibacterials (ciprofloxacin, clarithromycin, cotrimoxazole, erythromycin, gatifloxacin, levofloxacin, moxifloxacin)</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Antifungals (fluconazole)</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics (Thioridazine, ziprasidone)</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of flecaïnide and thioridazine or ziprasidone is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Antiretrovirals (darunavir, delavirdine ritonavir, saquinavir, tipranavir)</td>
<td>Inhibition of flecaïnide metabolism</td>
<td>Increased flecaïnide plasma concentration; increased risk of flecaïnide toxicity.</td>
<td>Monitor for signs and symptoms of flecaïnide toxicity and reduce dosage of flecaïnide accordingly. Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>Decreased flecaïnide renal clearance</td>
<td>Increased flecaïnide plasma concentration; increased risk of flecaïnide toxicity</td>
<td>Monitor for signs and symptoms of flecaïnide toxicity and reduce dosage of flecaïnide accordingly.</td>
</tr>
<tr>
<td></td>
<td>Selective serotonin inhibitors (fluoxetine, sertraline)</td>
<td>Decreased metabolism of flecaïnide</td>
<td>Increased flecaïnide plasma concentration; increased risk of flecaïnide toxicity</td>
<td>Monitor for signs and symptoms of flecaïnide toxicity and reduce dosage of flecaïnide accordingly.</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Amiodarone</td>
<td>Decreased metabolism of propafenone; additive effects on QT prolongation</td>
<td>Increased propafenone plasma concentration; increased risk of propafenone toxicity (blurred vision, CNS depression, tachycardia)</td>
<td>Monitor ECGs and monitor for signs and symptoms of propafenone toxicity and reduce dosage of propafenone accordingly.</td>
</tr>
<tr>
<td></td>
<td>Antibacterials (ciprofloxacin, clarithromycin, cotrimoxazole, erythromycin, gatifloxacin, levofloxacin, moxifloxacin)</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Antifungals (fluconazole)</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics (risperidone, thioridazine, ziprasidone)</td>
<td>Additive cardiac effects</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of propafenone and thioridazine or ziprasidone is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Antiretrovirals (darunavir, delavirdine ritonavir, saquinavir, tipranavir)</td>
<td>Inhibition of propafenone metabolism</td>
<td>Increased propafenone plasma concentration; increased risk of propafenone toxicity</td>
<td>Monitor for signs and symptoms of propafenone toxicity and reduce dosage of propafenone accordingly. Concurrent use of propafenone and ritonavir or saquinavir or tipranavir is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers (metoprolol, propranolol)</td>
<td>Decreased beta-blocker metabolism</td>
<td>Increased beta-blocker adverse effects (fatigue, bradycardia, hypotension)</td>
<td>Monitor heart rate and blood pressure; decrease dose of beta-blocker as needed.</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>Decreased metabolism or increased gastrointestinal absorption of cyclosporine</td>
<td>Increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias)</td>
<td>Monitor cyclosporine concentration and adjust dosage of cyclosporine as needed.</td>
</tr>
</tbody>
</table>
### Table 31-6. Selected Drug-Drug Interactions with Class I Antiarrhythmic Agents (continued)

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propafenone (continued)</td>
<td>Cimetidine</td>
<td>Decreased propafenone metabolism</td>
<td>Increased propafenone plasma concentration; increased risk of propafenone toxicity</td>
<td>Monitor for signs and symptoms of propafenone toxicity and reduce dosage of propafenone accordingly.</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Decreased digoxin volume of distribution and decreased nonrenal clearance of digoxin</td>
<td>Increased digoxin plasma concentration; increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin concentration, and reduce dosage of digoxin accordingly.</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Decreased propafenone metabolism</td>
<td>Increased propafenone plasma concentration; increased risk of propafenone toxicity</td>
<td>Monitor for signs and symptoms of propafenone toxicity and reduce dosage of propafenone accordingly.</td>
</tr>
<tr>
<td></td>
<td>Selective serotonin inhibitors (fluoxetine, sertraline)</td>
<td>Decreased metabolism of propafenone</td>
<td>Increased propafenone plasma concentration; increased risk of propafenone toxicity</td>
<td>Monitor for signs and symptoms of propafenone toxicity and reduce dosage of propafenone accordingly.</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>Decreased theophylline metabolism</td>
<td>Increased theophylline plasma concentration; increased risk of theophylline toxicity (nausea, vomiting, palpitation, seizures)</td>
<td>Monitor for signs and symptoms of theophylline toxicity and adjust dose of theophylline as needed.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Decreased warfarin clearance</td>
<td>Increased bleeding risk from warfarin</td>
<td></td>
<td>Monitor INR; adjust warfarin dose as needed.</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram; INR = international normalized ratio (for anticoagulant monitoring); CNS = central nervous system

### Table 31-7. Selected Drug-Drug Interactions with Class III Antiarrhythmic Agents*

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone Antiretrovirals</td>
<td>Inhibition of CYP3A4-mediated amiodarone metabolism by antiretrovirals</td>
<td>Increased amiodarone plasma concentration; increased risk of amiodarone toxicity (hypotension, bradycardia, sinus arrest)</td>
<td></td>
<td>Monitor for signs and symptoms of amiodarone toxicity, check amiodarone concentration, and reduce dosage of amiodarone accordingly. Concurrent use of amiodarone and ritonavir or nelfinavir or tipranavir is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers (metoprolol, propranolol)</td>
<td>Additive cardiac effects; possible inhibition of beta-blocker metabolism by amiodarone</td>
<td>Hypotension, bradycardia, cardiac arrest</td>
<td>Monitor cardiac function (especially heart rate); adjust dosages of beta blockers accordingly.</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>Decreased bioavailability of amiodarone</td>
<td>Decreased plasma amiodarone concentration and decreased amiodarone effectiveness</td>
<td>Administer amiodarone 2 hours before or 4 hours after cholestyramine.</td>
</tr>
<tr>
<td></td>
<td>Calcium antagonists (diltiazem, verapamil)</td>
<td>Additive calcium channel blocker activity due to inhibition of metabolism of either agent through CYP3A4</td>
<td>Additive reductions in heart rate and myocardial contractility</td>
<td>Monitor for bradycardia and signs and symptoms of reduced cardiac output</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>Inhibition of CYP3A4-mediated cyclosporine metabolism</td>
<td>Increased cyclosporine plasma concentration; increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias)</td>
<td>Monitor for signs or symptoms of cyclosporine toxicity, check serum cyclosporine concentrations, and adjust cyclosporine dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Inhibition of p-glycoprotein by amiodarone; reduced digoxin clearance</td>
<td>Increased digoxin plasma concentration; increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin concentration, and reduce dosage of digoxin accordingly.</td>
</tr>
<tr>
<td></td>
<td>Dofetilide</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Concurrent use of 2 Class III antiarrhythmics is not recommended.</td>
</tr>
<tr>
<td></td>
<td>Dolasetron</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Cardiac function should be closely monitored.</td>
</tr>
</tbody>
</table>

*Table 31-7 continued on p. 512*
Table 31-7. Selected Drug-Drug Interactions with Class III Antiarrhythmic Agents*

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone (continued)</td>
<td>Flecainide</td>
<td>Decreased flecainide metabolism; additive effects on QT prolongation</td>
<td>Increased flecainide plasma concentration; increased risk of flecainide toxicity (cardiac arrhythmias, neurologic effects, exacerbation of heart failure)</td>
<td>Monitor ECG and monitor for signs and symptoms of flecainide toxicity. Check serum flecainide concentration and reduce dosage of flecainide accordingly.</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td></td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td></td>
<td>Increased oral absorption of dofetilide by verapamil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
<td>Monitor cardiac function closely. Concurrent use of two or more drugs that prolong QT interval is generally not recommended.</td>
</tr>
<tr>
<td></td>
<td>Grapefruit Juice</td>
<td>Inhibition of CYP3A-mediated metabolism of amiodarone to N-DEA by grapefruit juice</td>
<td>Increased amiodarone plasma concentration and decreased metabolite (N-DEA) activity, which may lead to inconsistent clinical effects from amiodarone</td>
<td>Co-administration of amiodarone and grapefruit juice should be avoided.</td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine</td>
<td>Inhibition of renal cation transport system; reduced elimination of dofetilide</td>
<td>Increased dofetilide plasma concentration; increased risk of cardiac arrhythmia</td>
<td>Monitor for signs and symptoms of lidocaine toxicity (neuropathy, cardiac arrhythmias, hypotension, seizures) and reduce lidocaine dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Megestrol</td>
<td>Inhibition of renal cation transport system; reduced elimination of doxetilide</td>
<td>Increased dofetilide plasma concentration; increased risk of cardiac arrhythmia</td>
<td>Monitor serum prochlorperazine concentrations and adjust dosage accordingly. Assess amiodarone clinical responses.</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>Decreased theophylline metabolism</td>
<td>Increased theophylline plasma concentration; increased risk of theophylline toxicity (nausea, vomiting, palpitation, seizures)</td>
<td>Monitor for signs and symptoms of theophylline toxicity (neuropathy, cardiac arrhythmias). Check theophylline serum concentration, and adjust dose of theophylline as needed.</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Decreased warfarin metabolism</td>
<td>Increased bleeding risk from warfarin</td>
<td>Monitor INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Dofetilide</td>
<td>Cimetidine inhibits dofetilide renal tubular secretion and metabolism through CYP3A4</td>
<td>Increased dofetilide plasma concentration; increased risk of cardiac arrhythmia</td>
<td>Concurrent use of dofetilide and cimetidine is contraindicated. If antacid therapy is required, use omeprazole, ranitidine, or antacids containing aluminum and magnesium hydroxides.</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>Inhibition of CYP3A4-mediated dofetilide metabolism; inhibition of renal cation transport system; additive effects on QT prolongation</td>
<td>Increased dofetilide plasma concentration; increased risk of cardiac arrhythmia</td>
<td>Concurrent use of dofetilide and ketoconazole is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Megestrol</td>
<td>Inhibition of renal cation transport system; reduced elimination of dofetilide</td>
<td>Increased dofetilide plasma concentration; increased risk of cardiac arrhythmia</td>
<td>Concurrent use of dofetilide and megestrol is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine</td>
<td>Inhibition of renal cation transport system; reduced elimination of dofetilide</td>
<td>Increased dofetilide plasma concentration; increased risk of cardiac arrhythmia</td>
<td>Concurrent use of dofetilide and prochlorperazine is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim (including cotrimoxazole)</td>
<td>Inhibition of renal cation transport system; reduced elimination of dofetilide</td>
<td>Increased dofetilide plasma concentration; increased risk of cardiac arrhythmia</td>
<td>Concurrent use of dofetilide and trimethoprim is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td></td>
<td>Increased oral absorption of dofetilide by verapamil</td>
<td>Concurrent use of dofetilide and verapamil is contraindicated.</td>
</tr>
</tbody>
</table>
### Table 31-7. Selected Drug-Drug Interactions with Class III Antiarrhythmic Agents* (continued)

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronedarone</td>
<td>Potent CYP3A inhibitors (clarithromycin, itraconazole, nefazodone ritonavir, telithromycin voriconazole)</td>
<td>Inhibition of CYP3A4-mediated dronedarone metabolism</td>
<td>Increased dronedarone plasma concentration; increased risk of cardiac arrhythmia</td>
<td>Concurrent use of dofetilide and potent CYP3A inhibitors is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>CYP3A inducers (carbamazepine, phenobarbital, phenytoin, rifampin)</td>
<td>Increased dronedarone metabolism</td>
<td>Decreased plasma dronedarone concentration and decreased dronedarone effectiveness</td>
<td>Concurrent use of dronedarone and enzyme inducers may result in decreased dronedarone exposure and should be avoided.</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Inhibition of p-glycoprotein transporter of digoxin by dronedarone; reduced digoxin clearance</td>
<td>Increased digoxin plasma concentration; increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin concentration, and reduce dosage of digoxin accordingly.</td>
</tr>
<tr>
<td></td>
<td>Grapefruit juice</td>
<td>Inhibition of CYP3A-mediated dronedarone metabolism</td>
<td>Increased dronedarone plasma concentration; increased risk of dronedarone toxicity</td>
<td>Co-administration of dronedarone and grapefruit juice should be avoided.</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>Possible CYP2D6 inhibition of beta-blocker metabolism by dronedarone</td>
<td>Increased bioavailability of metoprolol; increased risk of bradycardia</td>
<td>Monitor cardiac function (especially heart rate); adjust metoprolol dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Ibutilide</td>
<td>Dolasetron</td>
<td>Additive effects on QT prolongation</td>
<td>Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td>Alpha-adrenergic blockers (doxazosin, prazosin, terazosin)</td>
<td>Suppression of beta-mediated compensatory increases in heart rate</td>
<td>Increased hypotensive effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dihydropyridine calcium blockers</td>
<td>Additive cardiovascular effects</td>
<td>Increased hypotensive effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digoxin</td>
<td>Additive cardiac effects, possibly increased digoxin bioavailability</td>
<td>Increased bradycardic effects</td>
</tr>
</tbody>
</table>

*All class III antiarrhythmic agents may interact with other drugs that prolongs QT intervals (ie, class I or class III antiarrhythmics, antibacterials, antidepressants, antifungals, antipsychotics) to cause additive effects on QT prolongation. Some of these interactions are not listed in this table.

N-DEA = N-desethylamiodarone

### Table 31-8. Selected Drug–Drug Interactions with Warfarin

<table>
<thead>
<tr>
<th>Primary Drug</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Allopurinol</td>
<td>Decreased warfarin metabolism and clearance</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Decreased warfarin metabolism and clearance; protein binding displacement (increased free fraction of warfarin)</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; reduce warfarin dose by one-third to one-half as appropriate.</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>Decreased warfarin metabolism and clearance; protein binding displacement (increased free fraction of warfarin); direct hypoprothrombinemic effect of aspirin</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td>Impaired warfarin absorption; increased warfarin metabolism</td>
<td>Decreased anticoagulant effectiveness</td>
<td>Monitor INR and adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Azole antifungals (flucytosine, itraconazole, ketoconazole)</td>
<td>Decreased warfarin metabolism</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Barbiturates (butalbital, phenobarbital, secobarbital, and others)</td>
<td>Increased metabolism and clearance of warfarin</td>
<td>Decreased anticoagulant effectiveness</td>
<td>Monitor INR and adjust warfarin dose as needed.</td>
</tr>
</tbody>
</table>

(Table 31-8 continued on p. 514)
Table 31-8. Selected Drug–Drug Interactions with Warfarin (continued)

<table>
<thead>
<tr>
<th>Primary Drug</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (continued)</td>
<td>Carbamazepine</td>
<td>Increased metabolism and clearance of warfarin</td>
<td>Decreased anticoagulant effectiveness</td>
<td>Monitor INR and adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>Decreased absorption of warfarin; interference with enterohepatic recirculation</td>
<td>Decreased anticoagulant effectiveness</td>
<td>Monitor INR and adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>Decreased warfarin metabolism and clearance</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed. Alternative H₂ antagonists such as famotidine and nizatidine are preferable.</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Decreased warfarin metabolism and clearance</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Fibrates (fenofibrate, gemfibrozil)</td>
<td>Reduction of plasma fibrinogen and platelet aggregation. Gemfibrozil may decrease warfarin metabolism and displace warfarin from protein binding sites.</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>Decreased warfarin metabolism and clearance</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased warfarin metabolism and clearance; protein binding displacement (increased free fraction of warfarin)</td>
<td>Increased risk of bleeding</td>
<td>Avoid concurrent use. Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td>Decreased warfarin clearance</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>Increased metabolism and clearance of warfarin</td>
<td>Decreased anticoagulant effectiveness</td>
<td>Monitor INR and adjust warfarin dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Sulfamethoxazole</td>
<td>Decreased warfarin clearance</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and INR; adjust warfarin dose as needed.</td>
</tr>
</tbody>
</table>

INR = International normalized ratio

Table 31-9. Selected Drug–Drug Interactions with Beta-Blockers

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers (all)</td>
<td>Alpha-blockers (Doxazosin, prazosin, terazosin)</td>
<td>Suppression of beta-mediated compensatory increases in heart rate</td>
<td>Increased risk for first-dose hypotension</td>
<td>Initiate the alpha blocker with a lower dose, preferably at bedtime. Monitor patient for hypotension.</td>
</tr>
<tr>
<td></td>
<td>Antidiabetics</td>
<td>Altered glucose metabolism and beta blockade</td>
<td>Prolonged hypoglycemia; masking of hypoglycemic effects</td>
<td>Monitor patient's blood glucose closely; educate patients on the recognition of signs of hypoglycemia and action to take when hypoglycemic.</td>
</tr>
<tr>
<td></td>
<td>Beta-2 adrenergic agonists (Albuterol, levalbuterol, terbutaline)</td>
<td>Pharmacological antagonism</td>
<td>Decreased effectiveness of either beta-blocker and/or the beta-2 agonist</td>
<td>Consider use of a cardioselective beta-blocker with caution.</td>
</tr>
<tr>
<td></td>
<td>Calcium antagonists (diltiazem, verapamil)</td>
<td>Additive cardiovascular effects Diltiazem and verapamil may decrease the metabolism of propranolol</td>
<td>Increased risk of hypotension, bradycardia, AV conduction disturbances</td>
<td>Monitor cardiac function and blood pressure closely; adjust dosages as needed.</td>
</tr>
<tr>
<td></td>
<td>Clonidine</td>
<td>Unopposed alpha effect following withdrawal of clonidine in patients who received a beta blocker and clonidine concurrently</td>
<td>Rebound hypertension following withdrawal of clonidine in patients who received a beta blocker and clonidine concurrently</td>
<td>Consider use of cardioselective beta-blockers (eg, atenolol, metoprolol) or an alpha-beta-blocker (eg, labetalol); consider withdrawal of beta-blocker before clonidine withdrawal; monitor blood pressure closely.</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Additive cardiac effects</td>
<td>Potentiation of bradycardia and AV block</td>
<td>Monitor patient for bradycardia and AV conduction delay on ECG and adjust dosages as needed.</td>
</tr>
</tbody>
</table>
Disopyramide Additive negative inotropic effects Bradycardia, decreased cardiac output Monitor heart rate, signs and symptoms of reduced cardiac output.

Epinephrine Enhanced pressor response to adrenaline due to unopposed peripheral alpha-receptor effects Blocked beta effects of epinephrine Hypertension, bradycardia, resistance to epinephrine in anaphylaxis Avoid this combination or use adrenaline cautiously in patients on beta-blockers; monitor blood pressure carefully.

NSAIDs (Indomethacin, phenylbutazone) Decreased production of vasodilating and renal prostanoids Attenuation of the antihypertensive effect of beta-blockers with possible loss of blood pressure control Monitor blood pressure regularly and adjust dose of beta-blocker as needed. Use NSAIDs for short durations to minimize risk of interaction.

Betablockers (Metoprolol, propranolol) Amiodarone, dronedarone Additive cardiac effects; possible inhibition of beta-blocker metabolism by amiodarone Potential for bradycardia or arrhythmias on initiation of combination therapy Initiate combination therapy in a controlled clinical environment; monitor heart rate and ECG.

Fluoxetine Decreased metabolism of beta-blockers Potentiation of beta-blocker effects Monitor for signs and symptoms of beta-blocker toxicity; consider switching to a renally eliminated beta-blocker (eg, atenolol) or an SSRI that does not inhibit CYP2D6 (eg, citalopram, nefazodone)

Lidocaine Decreased hepatic clearance of lidocaine by lipid-soluble beta-blockers Enhanced lidocaine toxicity (anxiety, myocardial depression, cardiac arrest) Use combination with caution; use lower doses of lidocaine.

Propafenone Decreased metabolism of beta-blockers Potentiation of beta-blocker effects Monitor blood pressure and cardiac function; adjust dosage of beta-blocker as needed.

Rifampin Increased metabolism of beta-blockers Decreased beta-blocker effectiveness Monitor blood pressure and adjust dosages of beta-blockers accordingly. Consider use of atenolol or nadolol which are not likely to be affected.

Beta-blocker (Propranolol) Chlorthalidone Decreased chlorothalidone metabolism; decreased propranolol clearance Chlorthalidone toxicity (sedation, extrapyramidal effects, delirium); increased propranolol effect Monitor for an enhanced effect of either drug and reduce the dosage of one or both drugs if needed.

Haloperidol Unknown Increased risk of hypotension and cardiac arrest Use concomitant therapy with caution. Monitor for signs of hypotension.

Thioridazine Inhibition of thioridazine metabolism Increased risk of thioridazine toxicity and cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) Concurrent use of propranolol and thioridazine is contraindicated.

Flecainide Additive cardiovascular effects, decreased flecainide metabolism, decreased propranolol metabolism Additive negative inotropic effects Monitor for signs and symptoms of reduced cardiac output. Adjust dosages as needed.

Theophylline Pharmacological antagonism Theophylline clearance may also be decreased by propranolol. Attenuation of bronchodilatory effects of theophylline; more pronounced with noncardioselective beta-blockers Monitor theophylline serum concentration. Use of cardioselective beta-blockers is preferable.

ECG = electrocardiogram; AV = atrioventricular; NSAIDs = nonsteroidal anti-inflammatory drugs; SSRI = selective serotonin reuptake inhibitor

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium antagonists (all)</td>
<td>Cimetidine</td>
<td>Decreased hepatic metabolism of calcium antagonists</td>
<td>Increased effects/toxicity of calcium antagonists</td>
<td>Monitor heart rate and blood pressure and adjust dosages as needed. Consider using another H₂ antagonist such as ranitidine.</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>Decreased cyclosporine metabolism (interaction is more prominent with diltiazem and verapamil)</td>
<td>Increased risk of cyclosporine toxicity (renal dysfunction, neurotoxicity)</td>
<td>Monitor for signs and symptoms of cyclosporine toxicity. Monitor circulating cyclosporine levels and adjust cyclosporine dosage as needed. Alternative calcium antagonist with minimal impact on cyclosporine levels such as isradipine may be used.</td>
</tr>
</tbody>
</table>

(Table 31-10 continued on p. 516)
Table 31-10. Selected Drug–Drug Interactions with Calcium Antagonists (continued)

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium antagonists (all) (continued)</td>
<td>Enzyme inducers (Carbamazepine, phenytoin, Phenobarbital)</td>
<td>Increased metabolism of calcium antagonists</td>
<td>Decreased effectiveness of calcium antagonists</td>
<td>Monitor patients for loss of calcium antagonist effects, including clinical signs or symptoms of hypertension or angina. Adjust dose of calcium antagonist accordingly.</td>
</tr>
<tr>
<td></td>
<td>Enzyme inhibitors (fluconazole, itraconazole, ketoconazole)</td>
<td>Decreased hepatic metabolism of calcium antagonists</td>
<td>Increased effects/toxicity of calcium antagonists</td>
<td>Monitor heart rate and blood pressure and adjust dosages as needed.</td>
</tr>
<tr>
<td></td>
<td>Grapefruit juice</td>
<td>Decreased hepatic metabolism of calcium antagonists (Interaction is more prominent with certain dihydropyridines: felodipine, nicardipine, nimodipine, nisoldipine and nitrendipine)</td>
<td>Increased effects/toxicity of calcium antagonists</td>
<td>Tell patients to avoid grapefruit juice if possible (drink orange juice instead). Otherwise, monitor blood pressure and adjust dosages as needed to avoid hypotension.</td>
</tr>
<tr>
<td>Calcium antagonists (diltiazem, verapamil)</td>
<td>Amiodarone</td>
<td>Additive cardiac effects; inhibitor of metabolism of either agent via CYP3A4</td>
<td>Bradycardia, AV block and/or sinus arrest</td>
<td>Monitor for bradycardia and signs and symptoms of reduced cardiac output; avoid concurrent use in patients with sick sinus syndrome or partial AV block.</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
<td>Digoxin</td>
<td>Potential for bradycardia and/or heart block</td>
<td>Monitor heart and PR interval; adjust dosages as needed.</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Decreased carbamazepine metabolism</td>
<td>Carbamazepine toxicity (ataxia, nystagmus, headache, vomiting, seizures)</td>
<td>Avoid concurrent use; use dihydropyridine calcium antagonists such as nifedipine instead.</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Decreased renal and/or extra-renal clearance of digoxin</td>
<td>Increased serum digoxin concentration and toxicity (nausea, vomiting, arrhythmias)</td>
<td>Monitor patients for signs and symptoms of digoxin toxicity, check digoxin levels, and adjust dosage as needed.</td>
</tr>
<tr>
<td></td>
<td>HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)</td>
<td>Reduce metabolism of HMG-CoA reductase inhibitors</td>
<td>Increased risk of myopathy and rhabdomyolysis</td>
<td>Consider using alternative HMG-CoA reductase inhibitors such as pravastatin, fluvastatin, or rosuvastatin.</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Additive cardiac effects; inhibition of quinidine metabolism</td>
<td>Increased quinidine concentration and toxicity (ventricular arrhythmias, hypotension, exacerbation of heart failure)</td>
<td>Monitor for signs and symptoms of quinidine toxicity, check quinidine concentrations, and adjust dosage of quinidine as needed. Consider alternative calcium antagonists.</td>
</tr>
<tr>
<td>Calcium antagonist (nifedipine)</td>
<td>Quinidine</td>
<td>Altered metabolism</td>
<td>Decreased quinidine effectiveness and/or increased risk of nifedipine adverse effects (headache, peripheral edema, hypotension, tachycardia)</td>
<td>Monitor quinidine concentrations before and following implementation of combination therapy. Adjust dose of either agent as needed.</td>
</tr>
</tbody>
</table>

AV = atrioventricular; HMG-CoA = hydroxymethylglutaryl coenzyme A

Table 31-11. Selected Drug–Drug Interactions with Digoxin

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Alprazolam</td>
<td>Decreased renal clearance of digoxin</td>
<td>Increased digoxin plasma concentration; increased risk of digoxin toxicity (nausea, vomiting, arrhythmias)</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin concentration, and reduce dosage of digoxin accordingly.</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Dronedarone</td>
<td>Inhibition of p-glycoprotein; reduced digoxin clearance</td>
<td>Increased digoxin plasma concentration; increased risk of digoxin toxicity</td>
</tr>
<tr>
<td></td>
<td>Antibiotics (erythromycin, tetracycline)</td>
<td>Decreased digoxin bioavailability by bacteria flora</td>
<td>Increased digoxin plasma concentration; increased risk of digoxin toxicity</td>
<td>Monitor digoxin serum concentrations when antibiotic is added to or withdrawn from therapy.</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
<td></td>
<td>Additive cardiac effects</td>
<td>Potentiation of bradycardia and atrioventricular block</td>
</tr>
<tr>
<td></td>
<td>Calcium, intravenous</td>
<td></td>
<td>Additive or synergistic cardiac effects</td>
<td>Arrhythmias and cardiovascular collapse</td>
</tr>
</tbody>
</table>
Table 31-11. Selected Drug-Drug Interactions with Digoxin (continued)

<table>
<thead>
<tr>
<th>Primary Drugs (continued)</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Calcium antagonists (diltiazem, verapamil)</td>
<td>Decreased renal and/or extra-renal clearance of digoxin</td>
<td>Increased serum digoxin concentration and toxicity</td>
<td>Monitor patients for signs and symptoms of digoxin toxicity, check digoxin levels and adjust dosage as needed.</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine-Colestipol</td>
<td>Cholestyramine and colestipol bind to digoxin, reducing its absorption.</td>
<td>Decreased digoxin concentration and possible effectiveness</td>
<td>Administer digoxin 2 hours before or four to six hours after cholestyramine or colestipol. Monitor digoxin serum concentration and observe patient for changes in response to digoxin.</td>
</tr>
<tr>
<td></td>
<td>Disopyramide-Piccinide</td>
<td>Unknown</td>
<td>Increased plasma digoxin concentrations and increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin level and decrease dose of digoxin as needed.</td>
</tr>
<tr>
<td></td>
<td>Diuretics (loop diuretics, thiazide diuretics and other potassium or magnesium wasting drugs)</td>
<td>Potassium and magnesium loss</td>
<td>Increased risk of digoxin toxicity</td>
<td>Monitor electrolytes and provide replacements as needed. Educate patient regarding the importance of maintaining adequate dietary potassium intake. Alternatively, use potassium sparing diuretics.</td>
</tr>
<tr>
<td></td>
<td>Itraconazole</td>
<td>Decreased digoxin metabolism and clearance</td>
<td>Increased plasma digoxin concentrations and increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin level and decrease dose of digoxin as needed.</td>
</tr>
<tr>
<td></td>
<td>Neomycin</td>
<td>Decreased digoxin absorption</td>
<td>Decreased digoxin serum concentration</td>
<td>Monitor digoxin serum concentrations.</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td>Decreased digoxin volume of distribution and decreased nonrenal clearance of digoxin</td>
<td>Increased digoxin plasma concentration; increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin concentration, and reduce dosage of digoxin accordingly.</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Decreased renal and non-renal clearance of digoxin</td>
<td>Increased plasma digoxin concentrations and increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity, check digoxin level and decrease dose of digoxin as needed.</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>Increased digoxin hepatic metabolism</td>
<td>Decrease plasma digoxin concentration and possibly effectiveness</td>
<td>Monitor digoxin concentration and adjust dose accordingly.</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td>Additive cardiac effects, possibly increased digoxin bioavailability</td>
<td>Increased bradycardic effects</td>
<td>Monitor electrocardiogram and serum digoxin concentrations; adjust dose accordingly.</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>Inhibition of active tubular secretion of digoxin</td>
<td>Increased plasma digoxin concentrations and increased risk of digoxin toxicity</td>
<td>Monitor for signs and symptoms of digoxin toxicity. False elevation of digoxin concentrations may occur with some testing methods.</td>
</tr>
</tbody>
</table>

Table 31-12. Selected Drug-Drug Interactions with Lipid-Lowering Agents

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile-acid sequestrants (Cholestyramine, Colesevelam, Colestipol)</td>
<td>Most drugs</td>
<td>Decreased absorption (bioavailability) of other drugs</td>
<td>Decreased plasma concentration and effectiveness of other drugs</td>
<td>Administer other drugs either 2 hours before or 4-6 hours after bile-acid sequestrants.</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor (Ezetimibe)</td>
<td>Fenofibrate-Gemfibrozil</td>
<td>Additive increase of cholesterol excretion into the bile</td>
<td>Increased ezetimibe plasma concentrations and increased risk of cholelithiasis</td>
<td>Concurrent use of ezetimibe and gemfibrozil is not recommended. If ezetimibe is used concurrently with fenofibrate, monitor patients for signs and symptoms of cholelithiasis. If cholelithiasis is suspected, initiate gall bladder studies and consider alternative lipid-lowering therapy.</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor (Ezetimibe)</td>
<td>Niacin</td>
<td>Unknown</td>
<td>Increased risk of myopathy and rhabdomyolysis</td>
<td>Monitor patients closely for symptoms of myopathy or rhabdomyolysis. Check CPK levels periodically and discontinue therapy if CPK levels show a marked increase.</td>
</tr>
<tr>
<td>Fibrin acid derivatives (Fenofibrate, Gemfibrozil)</td>
<td>Warfarin</td>
<td>Reduction of plasma fibrinogen and platelet aggregation</td>
<td>Increased risk of bleeding</td>
<td>Monitor for signs of bleeding and check INR; adjust warfarin dose as needed.</td>
</tr>
</tbody>
</table>

(Table 31-12 continued on p. 518)
### Table 31-12. Selected Drug-Drug Interactions with Lipid-Lowering Agents (continued)

<table>
<thead>
<tr>
<th>Primary Drugs</th>
<th>Interacting Drugs</th>
<th>Proposed Mechanism of Interaction</th>
<th>Possible Effects</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibric acid derivatives (Gemfibrozil)</td>
<td>Glyburide</td>
<td>Displacement of glyburide from protein binding sites; competition for renal tubular secretion</td>
<td>Hypoglycemia</td>
<td>Monitor patient’s blood glucose carefully; reduce glyburide dose as needed.</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (All)</td>
<td>Fenofibrate</td>
<td>Unknown</td>
<td>Increased risk of myopathy and rhabdomyolysis</td>
<td>Monitor patients closely for symptoms of myopathy or rhabdomyolysis (myalgias, muscle stiffness and weakness, darkened urine), check CPK levels periodically, and limit the dose of statins. The use of fenofibrate is generally recommended over gemfibrozil in this setting.</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
<td>Unknown</td>
<td>Increased risk of myopathy and rhabdomyolysis</td>
<td>Monitor patients closely for symptoms of myopathy or rhabdomyolysis, check CPK levels periodically and discontinue therapy if CPK levels show a marked increase. Reduction of statin dosages may also be needed.</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (Atorvastatin Lovastatin Simvastatin)</td>
<td>CYP3A4 inhibitors (Amiodarone, Azole antifungals, Clarithromycin, Cyclosporine, Diltiazem, Erythromycin, Grapefruit juice, Nefazodone, Protease inhibitors, Verapamil)</td>
<td>Inhibition of cytochrome P450 3A4-mediated statin metabolism</td>
<td>Increased statin exposure and an increased risk of myopathy or rhabdomyolysis</td>
<td>Avoid concurrent use of atorvastatin, lovastatin, or simvastatin with CYP3A4 inhibitors (including grapefruit juice; orange juice may be taken instead). Alternative statins such as pravastatin or fluvastatin may be considered. If concurrent use of interacting agents is necessary, monitor patients closely for symptoms of myopathy or rhabdomyolysis, check CPK levels, and adjust dosage of statin as needed.</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (Fluvastatin Rosuvastatin)</td>
<td>Warfarin</td>
<td>Fluvastatin inhibits CYP2C9-mediated S-warfarin metabolism thus increasing serum concentrations of warfarin</td>
<td>Increased INR and increased risk of bleeding</td>
<td>Monitor INR periodically following institution of concomitant therapy and adjust dose of warfarin as needed.</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (Pravastatin)</td>
<td>Cyclosporine</td>
<td>Decreased elimination of pravastatin</td>
<td>Increased plasma pravastatin concentrations and increased risk of myopathy</td>
<td>Initiate pravastatin with 10 mg daily and titrate dose up cautiously. Monitor patients closely for symptoms of myopathy or rhabdomyolysis, check CPK levels and discontinue statin therapy if necessary.</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (Rosuvastatin)</td>
<td>Cyclosporine</td>
<td>Cyclosporine inhibition of organic anion transport protein-mediated hepatic rosuvastatin metabolism</td>
<td>Increased plasma rosuvastatin concentrations and increased risk of myopathy</td>
<td>When rosuvastatin is used concomitantly with cyclosporine, limit rosuvastatin dose to 5 mg once daily.</td>
</tr>
</tbody>
</table>

CPK = creatine phosphokinase; HMG-CoA = hydroxymethylglutaryl coenzyme A; INR = international normalized ratio
Infants and children with cardiovascular disorders, even those with complex problems, are living through childhood into their adult years. The quality of life, with growth, development, and successful psychologic maturation as markers, continues to steadily improve as well for these patients. Much of this success is related to better refinement of pharmacologic supports, which has developed through increased understanding of the interplay of developing biologic systems and pharmacotherapeutics.

This chapter reviews several important issues relating to the treatment of cardiovascular problems in infants and children with the broadening spectrum of agents available to the clinician. In many instances, pharmacologic treatments reflect modification of approaches learned from practice in the adult population. In others, novel approaches have been developed specifically for the unique problems encountered in children, either as a result of their primary disorder or as a result of its palliation. In all circumstances, however, documented differences in gastrointestinal physiology, in volumes of distribution, in receptor physiology, and in other key elements of metabolic and circulatory dynamics exist that impact on cardiovascular pharmacotherapeutics. Many of these important differences are reviewed in this chapter as well.

Recognition of the fact that important differences exist between infants and children as compared to adults with regard to pharmacotherapeutics has led to continuing actions on the part of the US Food and Drug Administration (FDA) and the pharmaceutical industry to understand how these differences impact on the use of specific pharmaceuticals. However, given the large amount of information still to be developed, the overall view should be one of a work in progress, as each day more and more agents become officially approved for use in children with attendant modification and alteration.

Finally, this chapter builds upon the information developed in the pediatric chapter in previous editions of this text, reiterating important points made in those efforts, amplifying them where appropriate, and updating them as new information has developed.

There are important conditions that do have overlap between the adult and pediatric populations, and we will start with a review of the pharmacotherapeutics of these problems.

**Congestive Heart Failure**

Table 32-1 reviews the causes of congestive heart failure (CHF) in childhood. Most of these problems are amenable to surgical correction or to substantial palliation of the underlying anatomic disorder. An important proportion, however, are related to either inherited or acquired problems of cardiac muscle mechanics. Survival in this population is generally increasing, although recovery can require an extended period, even as long as several years. Thus, medical therapy has become increasingly important in the childhood management of CHF for a variety of reasons: (1) to allow underlying reparative mechanisms to develop after acquired or iatrogenic acute insults to cardiac muscle; (2) to enable chronic survival while awaiting extreme interventions, such as orthotopic transplantation or longer-term mechanical supports; (3) to improve lifestyle quality after surgical intervention for complete repair or for palliation.

**Inotropes and Vasopressors**

*Digoxin*

In the pediatric population, digoxin remains the most extensively used digitalis glycoside and, essentially, the
only inotropic agent available for oral administration. The desired effects of digoxin are mechanical and electrical; that is, to improve contractility of the failing heart and prolong the refractory period of the atrioventricular (AV) node, respectively (see Chapter 13, Inotropic Agents). Inhibition of the sarcolemmal Na+/K+ -ATPase pump with an associated increase in available intracellular calcium results in digoxin's positive inotropic effect. It slows conduction velocity and increases refractoriness at the AV node, mediated mostly through its vagal effect. In canine studies, the electrophysiologic effects of digoxin are less pronounced in neonatal Purkinje fibers than they are in human adult myocardium.6 This difference may be related, in part, to the increased concentrations of Na+/K+ -ATPase (the enzyme inhibited by digoxin) in the neonatal myocardium.

Digoxin is used in a variety of circumstances causing CHF. In infants with large left-to-right shunts or with severe valvular regurgitation, surgical correction is preferred, but when not feasible, digoxin may help with the accommodation to large-volume loads. This has been a controversial indication because in many of these situations, normal or even increased myocardial contractility is present. In this circumstance, if useful at all, the effect of digoxin on sympathetic tone is probably key as it helps to counter the catabolic effects of increased catecholamine output in these infants. The classic indication for digoxin involves diminished myocardial performance, when it is used in conjunction with diuretics and afterload reduction agents.

Digoxin toxicity is relatively common because of the drug's narrow therapeutic window. As in adults, digoxin toxicity in children includes sinus bradycardia, sinus arrest, complete AV block, and ventricular arrhythmias.7 Other effects include anorexia in older children and vomiting in infants, as well as central nervous system (CNS)
lo

The dose of digoxin. However, although quinidine has no effects of quinidine on digoxin in childhood may differ from those seen in adults. It is well established that quinidine increases serum digoxin levels in adult patients on a stable regimen. In fact, infants younger than 2 months did not show an increase in digoxin levels at all. In adult patients taking maintenance digoxin, amiodarone is also reported to cause significant elevation of serum digoxin levels. After the initiation of amiodarone therapy, increases of digoxin levels associated with prolongation of the digoxin half-life have been observed in children as well. Verapamil, like quinidine, inhibits the renal elimination of digoxin without changing the glomerular filtration rate (GFR) and thereby increases plasma digoxin concentrations. Hence, in settings where it is accepted practice to use verapamil and digoxin simultaneously, such as therapy for certain arrhythmias in children, frequent measurements of serum digoxin levels should be performed. It is common practice that when starting either quinidine or amiodarone in children on maintenance digoxin, the serum digoxin level should be measured and the digoxin dose reduced by 40% to 50%. Serial digoxin levels should then be measured and the digoxin dose titrated upward.

Because digoxin is primarily eliminated by the kidneys, any drug given simultaneously that could cause renal impairment may change the pharmacokinetics of digoxin. This is particularly true when digoxin is used in combination with vasodilators (see below), such as enalapril and with diuretics. Potassium loss can also potentiate toxicity; therefore, potassium monitoring is required whenever these drugs are used together. There is no specific correlation of higher serum levels and enhanced digoxin effect. Therefore, current recommendations suggest a serum level of 0.8 to 2 ng/mL as an appropriate target for maintenance therapy. In neonates, endogenous “digoxin-like” substances can interfere with digoxin level interpretation.

Newborns, particularly those born prematurely, present a problem with regard to loading dosages (the commonly prescribed method of initiating treatment with digoxin because of the large volume of distribution). Thus, reductions in loading dose regimens have been devised, taking into account gestational age and weight, in order to decrease the risk for toxicity, as noted in Table 32-2.

Dopamine
Dopamine is an endogenous catecholamine and the precursor of norepinephrine. In adults, it is particularly useful for the treatment of heart failure associated with hypotension and poor renal perfusion because of the unusual, dose-dependent combination of actions that it exerts (see also Chapter 26, Selective and Nonselective Dopamine Receptor Agonists). At low doses (0.5 to 2 µg/kg/minute), it interacts primarily with D1 dopaminergic receptors, which are distributed in the renal and mesenteric vascular beds. Their stimulation causes local vasodilation and augments renal blood and GFR, facilitating diuresis. Moderate doses of dopamine (2 to 5 µg/kg/minute) directly increase contractility by stimulation of cardiac β1 receptors and indirectly by causing the release of norepinephrine from sympathetic nerve terminals. At high doses (5 to 10 µg/kg/minute), dopamine stimulates

### Table 32-2. Use of Digoxin in Children

<table>
<thead>
<tr>
<th>Weight (g)</th>
<th>Usual Dose (IM or oral) (TDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature infants</td>
<td></td>
</tr>
<tr>
<td>500–1000</td>
<td>20 µg/kg or 0.02 mg/kg</td>
</tr>
<tr>
<td>1000–1500</td>
<td>20–30 µg/kg or 0.02–0.03 mg/kg</td>
</tr>
<tr>
<td>1500–2000</td>
<td>30 µg/kg or 0.03 mg/kg</td>
</tr>
<tr>
<td>2000–2500</td>
<td>30–40 µg/kg or 0.03–0.04 mg/kg</td>
</tr>
<tr>
<td>Term to 6 yr</td>
<td>40–60 µg/kg or 0.04–0.06 mg/kg</td>
</tr>
<tr>
<td>(no dose &gt; 1.5 mg TDD)</td>
<td></td>
</tr>
</tbody>
</table>

TDD = total digitalizing doses; Digitalizing regimen usually given as initial dose = one-half of TDD; second dose = one-fourth of TDD at 8 to 12 h; third dose = final one-fourth TDD at 8 to 12 h after second dose. Maintenance is then started as one-eighth TDD every 12 h. (Note: Parenteral preparation contains 100 µg/mL, and oral preparation contains 50 µg/mL).


Disturbances. A variety of drugs may predispose to digoxin toxicity, especially antiarrhythmic medications such as quinidine, verapamil, and amiodarone, although the effects of quinidine on digoxin in childhood may differ from those seen in adults. It is well established that quinidine increases serum digoxin levels in adult patients on a stable dose of digoxin. However, although quinidine has no effect on the serum digoxin level of neonatal dogs, quinidine does result in higher levels of digoxin in the brain.

In one pediatric study, no relationship was observed between quinidine and digoxin levels. In fact, infants younger than 2 months did not show an increase in digoxin levels at all. In adult patients taking maintenance digoxin, amiodarone is also reported to cause significant elevation of serum digoxin levels. After the initiation of
the systemic α-adrenergic receptors, thereby causing potent vasoconstriction and an elevation in systemic vascular resistance (SVR).

It is often stated that infants display reduced sensitivity to dopamine; however, the evidence is far from conclusive. In support of reduced sensitivity, it has been found that in critically ill neonates, infusion rates of 50 μg/kg/minute did not cause evidence of impairment of cutaneous or renal perfusion. There is also some experimental evidence for diminished sensitivity to dopamine in infants; however, this is limited to studies in immature animals.

A contrary observation was made by Padbury and co-workers who measured cardiac output in a group of infants and found that mean blood pressure (BP) increased at doses of 0.5 to 1 μg/kg/minute, whereas heart rate increased with doses beyond 2 to 3 μg/kg/minute. Cardiac output (and stroke volume) increased before heart rate, and SVR did not change within the range of dopamine infusion rates (0.5 to 8 μg/kg/minute).

The dose-response relationship is best described by a threshold model; that is, below a threshold level of drug concentration, no clinical response is seen, and beyond that level, a log-linear dose-response relationship is seen. The threshold values obtained were 14 ± 3.5 ng/mL for increase in mean BP; 18 ± 4.5 ng/mL for increase in systolic BP; and 35 ± 5 ng/mL for increase in heart rate. Steady-state concentration reached at infusion rates between 1 and 2 μg/kg/minute was 16.5 ± 3.4 ng/mL. Thus, newborns may exhibit clinical response using doses as low as 0.5 to 1 μg/kg/minute. This is good evidence against the concept that newborns are relatively insensitive to dopamine.

Low infusion rates of dopamine are frequently employed to augment renal function during critical illness. Although there is evidence that this may promote salt excretion and urine flow rate, there are no adequate data to conclude that the chances of renal failure are thereby made lower.

Plasma dopamine clearance ranges from 60 to 80 mL/kg/minute in normal adults. The half-life has not been reliably determined but probably is in the range of 2 to 4 minutes. Clearance is lower in patients with renal or hepatic disease. Age has a striking effect upon clearance of dopamine, and clearance in children younger than 2 years is approximately twice as rapid as it is in older children (82 versus 46 mL/kg/minute). This observation has been confirmed in a study by Allen demonstrating that during the first 20 months, the clearance of infused dopamine decreases by almost 50% with an additional 50% decrease from ages 1 to 12 years. This pharmacokinetic difference, rather than a difference in receptors or myocardial sensitivity, may account for the observation that infants require tolerate higher infusion rates.

In clinical practice, dopamine is an effective inotropic and vasopressor agent in neonates and infants with a variety of conditions associated with circulatory failure, including hyaline membrane disease, asphyxia, sepsis syndrome, and cyanotic congenital heart disease. Although there is surprisingly little formal data concerning use of dopamine in critically ill children, clinicians employ dopamine in order to enhance renal function and to exploit its inotropic and vasopressor properties. Dopamine is less likely to produce severe tachycardia or dysrhythmias than either epinephrine or isoproterenol.

Dopamine is indicated in the context of moderately severe degrees of distributive shock (sepsis, hypoxia-ischemia) and cardiogenic shock. It is also indicated in the absence of hypotension, when clinical signs or hemodynamic measurements suggest a state of compensated shock or inadequate peripheral perfusion. However, dopamine is not the agent of choice when hemodynamic measurements reveal an elevated cardiac output in the context of a markedly reduced SVR and profound hypotension. This pattern is often observed in septic shock, and suggests judicious use of a vasopressor such as norepinephrine (see below).

Dopamine is also not the first drug of choice to treat severe hypotension associated with the most severe reductions in cardiac index (eg, < 2 to 2.5 L/minute/M²). Epinephrine is probably more appropriate. Additionally, children with primary myocardial disease not complicated by substantial hypotension may benefit from a more selective inotropic agent such as dobutamine. Infusion rates of dopamine needed to improve signs of severe myocardial dysfunction may be associated with troublesome tachycardia or dysrhythmia, and may increase myocardial oxygen consumption disproportionately to myocardial perfusion.

Although dopamine is extensively employed following cardiac surgery, there have been reports that dopamine may be less effective following cardiac surgery in young infants than it is in older children or adults. Lang et al treated a small series of children with dopamine following cardiac surgery. For the group as a whole, hemodynamic improvement did not occur at infusion rates < 15 μg/kg/minute. When cardiac output did increase, it was attributed to an increase in heart rate, rather than to improved stroke volume. More recently, another study indicated that following cardiac surgery, dopamine and dobutamine have similar inotropic efficacy, but that dopamine was associated with pulmonary vasoconstriction at doses > 7 μg/kg/minute.

To treat shock associated with hypotension, therapy is initiated with an infusion rate of 5 to 10 μg/kg/minute. The rate of infusion is increased in steps of 2 to 6 μg/kg/minute, guided by evidence of improved blood flow (skin temperature, capillary refill, sensorium, urine output) and by restoration of a BP appropriate for age. Infusion rates > 25 to 30 μg/kg/minute of dopamine are not customary, even if they maintain a “normal” BP. At
infusion rates at this dose, the effect upon BP is likely to represent an increase in SVR (α-adrenergic activation) rather than cardiac output. Although infusion rates of this magnitude or higher have been proposed, a requirement for a dopamine infusion at this high dose suggests that the physician reassees the physiologic diagnosis or select a different agent, such as epinephrine or norepinephrine.

Dopamine can produce cardiovascular toxicity, including tachycardia, hypertension, and dysrythmia. With the possible exception of the bipyridines, all inotropes increase myocardial oxygen consumption because they increase myocardial work. If the resulting increase in oxygen consumption is balanced by improved coronary blood flow, the net effect upon oxygen balance is beneficial. When shock is caused by or complicated by myocardial disease, then improved myocardial contractility may reduce preload and afterload (decrease oxygen consumption); improve coronary perfusion pressure (increase oxygen supply); and prolong diastolic coronary perfusion by reducing heart rate. If the same drug is administered to a patient with normal myocardial contractility, then the result may be an increase in cardiac oxygen consumption without an increase in oxygen delivery to the myocardium. Tachycardia is a particular burden because it both increases oxygen consumption and shortens diastole. Thus, the net effect of dopamine upon myocardial oxygen balance may be better than it is for isoproterenol, but not as good as for dobutamine, inamrinone, and milrinone (see below).32–34

Dopamine depresses the ventilatory response to both hypoxemia and hypercarbia by as much as 60%.35 Dopamine (and other β-agonists) can decrease P O 2 by interfering with hypoxic vasoconstriction. In one study, dopamine increased intrapulmonary shunting in patients with adult respiratory distress syndrome from 27% to 40%.36 Dopamine can cause or worsen limb ischemia and gangrene of distal parts and of entire extremities, and result in extensive loss of skin.37 Infusion rates as low as 1.5 μg/kg/minute have been associated with limb loss.39–40 The presence of an arterial catheter also increases the possibility of limb ischemia.

Because dopamine promotes release of norepinephrine from synaptic terminals (and is also converted to norepinephrine in vivo), it is more often associated with limb ischemia than other adrenergic compounds. Extravasation of dopamine should be treated immediately by local infiltration with a solution of phenolamine (5 to 10 mg in 15 mL normal saline) administered with a fine hypodermic needle. Dopamine should not be administered by mixing with sodium bicarbonate because alkaline solutions inactivate this agent.

Dobutamine

Dobutamine is a synthetic analogue of dopamine that stimulates β1-, β2-, and α-adrenergic receptors (see Chapter 13, Inotropic Agents). It increases cardiac contractility via its β1 effect, and may not significantly alter SVR because of the balance between α1-mediated vasoconstriction and β1-mediated vasodilation. Unlike dopamine, dobutamine does not stimulate dopaminergic receptors (it is not a primary renal vasodilator), nor does it facilitate the release of norepinephrine from peripheral nerve endings.41

In adults with CHF, dobutamine can produce a 50% to 80% increase in cardiac output, which is almost entirely due to improvement in stroke volume. Left atrial pressure falls, and SVR either decreases or remains the same. Heart rate increases little, if at all. Although renal function is not directly affected by dobutamine, renal function and urine output may improve as the increase in cardiac output fosters relaxation of sympathetic tone and improved perfusion. Dobutamine is a dilator of the pulmonary vasculature.42

A threshold model with a log-linear dose–response relationship above the threshold has been demonstrated in critically ill term and preterm neonates43 and in children between ages 2 months and 14 years.44 In one small study, dobutamine infusion (10 μg/kg/minute) was associated with increase in cardiac output (30%), BP (17%), and heart rate (7%). The thresholds for these increases were 13, 23, and 65 ng/mL, respectively, demonstrating that dobutamine is a relatively selective inotrope with little effect on heart rate at customary infusion rates.45 Somewhat greater thresholds for improved cardiac output were observed in a second group of children46 and in infants,47 but in all studies, dobutamine improved cardiac contractility without substantially altering heart rate unless high infusion rates were employed.

The half-life is about 2 minutes in adults and the volume of distribution is 0.2 L/kg. CHF increases the volume of distribution. In adults, clearance is about 2 L/M2/minute. Typical clearance values in children are 70 to 100 mL/kg/minute. Infusions in the range used clinically yield plasma dobutamine concentrations from approximately 50 ng/mL to 160 to 190 ng/mL in both children48 and in adults.49 The principal route of elimination is methylation by catechol methyltransferase (COMT), followed by hepatic glucuronidation and excretion into urine and bile. Dobutamine is also cleared from the plasma by non-neuronal uptake. Some investigators report nonlinear elimination kinetics, but other data suggest that dobutamine's kinetics can be adequately described by a simple first-order (linear) model.50

Several studies in infants and children43–45,48,49 demonstrate that dobutamine improves myocardial function in a variety of settings. Stroke volume and cardiac index improve without a substantial increase in cardiac rate. SVR and pulmonary vascular resistance (PVR) may decrease toward normal.

Dobutamine has been evaluated in children following cardiac surgery with cardiopulmonary bypass. In a study
by Bohn et al., dobutamine enhanced cardiac output by increasing heart rate. Indeed, tachycardia prompted discontinuation of the infusion in several patients. The expected fall in SVR was not observed in children receiving the drug after cardiopulmonary bypass. The authors found no benefit over isoproterenol or dopamine. These differences between adults and children may be due to the fact that myocardial dysfunction and CHF are not necessarily characteristic of the circulatory status of many children undergoing repair of congenital heart disease. Unlike adults, in these patients indication for operation involves abnormalities in ventricular architecture or abnormal circulatory anatomy. Berner and associates found that children undergoing operations for mitral valve disease responded to dobutamine with an increase in stroke volume; children having repair of tetralogy of Fallot did not, and their cardiac output increased only through higher heart rate and volume manipulation. A more recent report by the same group indicated that following repair of tetralogy of Fallot, dobutamine did enhance cardiac output when it was combined with atrial pacing to increase heart rate. Isoproterenol without pacing provided a higher cardiac output than either dobutamine alone or dobutamine in combination with pacing.

Specific indications for prescribing dobutamine in the pediatric age group include those conditions associated with a low cardiac output and normal to moderately decreased BP. Typical examples include viral myocarditis, cardiomyopathy associated with use of anthracyclines, cyclophosphamide or hemochromatosis (related to hypertransfusion therapy), or myocardial ischemia (Kawasaki disease). Patients with CHF who have a normal or slightly low BP may benefit by combining dobutamine with a left ventricular afterload-reducing agent. For rapid titration in the unstable patient, nitroprusside is available (see below). When rapid adjustment is not necessary, angiotensin-converting enzyme (ACE) inhibitors such as captopril or enalapril (see below) can be employed for this purpose. A decrease in afterload improves stroke volume and may enhance cardiac output at a lower cost of oxygen consumption than use of an inotropic agent alone.

Dobutamine is not a first-line agent to treat low output states caused by intracardiac shunt. Dobutamine is employed following corrective or palliative cardiovascular surgery in the child; however, in this context, its use should also be limited to occasions in which demonstrated or suspected myocardial dysfunction exists.

Dobutamine may be of adjunctive value in treating myocardial dysfunction that complicates a primary condition such as adult respiratory distress syndrome (ARDS) or septic shock. It is unusual, however, to employ dobutamine as the sole agent to treat hemodynamic compromise associated with sepsis, ARDS, or shock following an episode of severe hypoxia-ischemia.

Dobutamine can be useful when combined with other adrenergic agonists such as norepinephrine to treat myocardial dysfunction associated with so-called “hyperdynamic” shock. For example, the child with anthracycline cardiotoxicity who develops septic shock may be candidate for this type of combined therapy.

Dobutamine usually increases myocardial oxygen demand. In subjects with myocardial dysfunction, coronary blood flow and oxygen supply improve with the increase in demand. However, if dobutamine is employed when myocardial contractility is normal, oxygen balance will be adversely affected. Tachycardia greatly increases oxygen use by the heart, and should prompt a reduction in the dose of dobutamine (or an alternate agent).

Although less likely than other catecholamines to induce serious atrial and ventricular dysrhythmias, these do occur in patients receiving dobutamine, particularly in the context of myocarditis, electrolyte imbalance, or high infusion rates. Dobutamine and other inotropes should be administered cautiously, if at all, to patients with dynamic left ventricular outflow obstruction (hypertrophic subaortic stenosis).

Isoproterenol

Isoproterenol is an intravenously administered, synthetic catecholamine. As a nonselective β-agonist, it augments myocardial contractility, increases heart rate, reduces afterload, and dilates the bronchial tree. It is useful for the treatment of bradycardia in all age groups and for life-threatening reactive airway disease in young children. The dosage varies with clinical indication. Lower dosages are required for the treatment of bradyarrhythmias than those needed for brachial hyper-reactivity. In the neonate, isoproterenol produces a greater increase in heart rate than either dopamine or dobutamine.

In the past, isoproterenol was used for a variety of indications, including septic shock and cardiogenic shock associated with myocardial infarction. Newer agents, such as dopamine and dobutamine, together with a more subtle understanding of the pathophysiology of shock, have limited the use of isoproterenol to very few specific indications. Isoproterenol may be employed to treat hemodynamically significant bradycardia. However, epinephrine infusion may be preferable. When important bradycardia results from heart block, then atropine is the initial urgent form of drug therapy, and placement of a pacemaker is definitive treatment. Bradycardia due to anoxia is treated by administering oxygen and improving gas exchange, but isoproterenol may be a useful adjunct in this setting.

Some clinicians still prefer isoproterenol as a first-time agent for infants following cardiac surgery with cardiopulmonary bypass. Although this indication is not well explored in the literature, the agent may be effective in
improving cardiac output by combining inotropic and chronotropic activity with a capacity for both pulmonary and systemic vasodilation. Isoproterenol may provide greater improvement in cardiac output than either atrial pacing or atrial pacing combined with dobutamine.

The main concerns regarding the use of isoproterenol include sinus tachycardia, which can be counterproductive to ventricular filling and to myocardial oxygen debt burden, and induction of arrhythmias, especially ventricular extrasystoles. Patients must be monitored closely for this latter complication when receiving isoproterenol.

Epinephrine
Epinephrine is an endogenous catecholamine that acts on both $\alpha$- and $\beta$-adrenergic receptors resulting in increased heart rate, contractility, and SVR. These actions make it especially useful under circumstances of severe myocardial dysfunction associated with hypotension.60

A wide interindividual variation in epinephrine clearance is observed in healthy adults. In critically ill children receiving epinephrine at doses from 0.03 to 0.2 $\mu$g/kg/minute, plasma concentrations at steady state ranged from 0.67 to 8.5 ng/mL and were linearly related to dose.59

Epinephrine is employed to treat shock associated with substantial myocardial dysfunction. Thus, it is an appropriate drug for treatment of cardiogenic shock unresponsive to dopamine or following open cardiac surgery.61 Additionally, the septic patient who does not improve adequately after intravascular volume repletion and treatment with dopamine or dobutamine may benefit from infusion of epinephrine. Epinephrine is most likely to be useful when hypotension exists in the context of a low cardiac index and stroke index. At modest infusion rates (0.05 to 0.1 $\mu$g/kg/minute), SVR decreases slightly; heart rate, cardiac output, and systolic BP increase somewhat. At intermediate infusion rates, $\alpha_1$-adrenergic activation becomes important but is balanced by the improved cardiac output and activation of vascular $\beta_1$ receptors. Although epinephrine constricts renal and cutaneous arterioles, renal function and skin perfusion may improve. Very high infusion rates (>1 to 2 $\mu$g/kg/minute) are associated with significant $\alpha_1$-adrenergic-mediated vasoconstriction; blood flow to individual organs will be compromised and the associated increase in afterload may further impair myocardial function. Epinephrine by infusion is also the agent of choice for hypotension or shock following successful treatment of cardiac arrest. Shock following an episode of hypoxemia or ischemia is usually cardiogenic52 and may respond to epinephrine infusion.

Bolus injections of epinephrine are used to treat asystole and other nonperfusing rhythms. The recommended initial dose during cardiopulmonary resuscitation (American Heart Association [AHA]) is 0.01 mg/kg (10 $\mu$g/kg or 0.1 mL/kg of the 1:10,000 solution). Subsequent doses are tenfold greater (“high-dose epinephrine”): 0.1 mg/kg (100 $\mu$g/kg or 0.1 mL/kg of a 1:1000 solution). Although initial studies using high-dose epinephrine were encouraging, published reports indicate no improvement in return of spontaneous circulation or survival after high-dose epinephrine following out-of-hospital cardiac arrest in children.63 Epinephrine may also be given by endotracheal tube (dose is 100 $\mu$g/kg). Intravenous administration is appropriate for both bolus and continuous administration of epinephrine. The dose is the same as for intravenous injection. The intravenous route is effective in briskly achieving high plasma levels of epinephrine and other catecholamines when direct vascular access is difficult.64

Epinephrine has the potential to cause multiple adverse reactions. The drug produces CNS excitation manifested as anxiety, dread, nausea, and dyspnea. Enhanced automaticity and increased oxygen consumption are the main serious toxicities of epinephrine. Extreme tachycardia carries a substantial oxygen penalty, as does hypertension. A severe imbalance of myocardial oxygen delivery and oxygen consumption produces characteristic ECG changes of ischemia. A subischemic, but persistently unfavorable, ratio of oxygen delivery to consumption may also be harmful to the myocardium.

Epinephrine-produced tachycardia at high infusion rates can lead to successively more serious events, including atrial and ventricular extrasystoles, atrial and ventricular tachycardia, and ultimately, ventricular fibrillation. Ventricular dysrhythmias in children are not frequent but may occur in the presence of myocarditis, hypokalemia, or hypoxemia.

Epinephrine overdose is serious. Several neonates have died when inadvertently subjected to oral administration of huge amounts of epinephrine. The syndrome mimicked an epidemic of neonatal sepsis with shock and metabolic acidosis.65 Intra-aortic injection in infants (per umbilical artery) produces tachycardia, hypertension, and renal failure.66 Intravenous overdosage of epinephrine is immediately life-threatening. Manifestations include myocardial infarction, ventricular tachycardia, extreme hypertension, cerebral hemorrhage, seizures, renal failure, and pulmonary edema. Paradoxically, bradycardia has also been observed.67

Manifestations of acute overdosage are treated symptomatically, but $\beta$-Receptor antagonists, such as propranolol, are contraindicated. Hypertension is treated with short-acting antihypertensives (ie, nitroprusside). Hypokalemia can be produced during epinephrine infusion due to stimulation of $\beta_2$-adrenergic receptors, which are linked to sodium-potassium-ATPase located in skeletal muscle. Hyperglycemia results from $\alpha$-adrenergic-mediated suppression of insulin release. Other
metabolic abnormalities include hyperlactemia and hypophosphatemia.

Epinephrine is an $\alpha_1$-adrenergic agonist, and infiltration into local tissues or intra-arterial injection can produce severe vasospasm and tissue injury. Interestingly, the concurrent activation of $\beta_2$ receptors by epinephrine limits vasospasm; local injury to tissue is less frequent than with either norepinephrine or dopamine.

Norepinephrine

Norepinephrine is an endogenous catecholamine that stimulates $\beta_1$ and $\alpha$-adrenergic receptors, thereby increasing contractility and SVR. Its effect on heart rate is variable and is the net result of opposing forces. Some of its inotropic activity may result from $\alpha_1$-receptor stimulation as well as $\beta$-receptor agonism. Whereas its direct cardiac $\beta_1$ effect favors an increase in heart rate, its peripheral $\alpha$-adrenergic effect, which leads to activation of the baroreceptor reflex, favors a decrease in heart rate.

Published pediatric data in infants and children are quite limited, but the observed hemodynamic response to norepinephrine seems to resemble that seen in adults. Its use, for the most part, is reserved for the persistently hypotensive patient, such as the child in whom hypotension persists in spite of being given doses as high as 20 $\mu$g/kg per minute of dopamine. It should not be used as a positive inotrope in the context of depressed myocardial contractile function unaccompanied by hypotension, because its marked vasoconstrictive effects may result in an extremely high SVR with reduced renal blood flow. Its adverse effects profile is similar to epinephrine.

Norepinephrine improves perfusion in children with low BP and a normal or elevated cardiac index, as occurs in septic shock. Norepinephrine is administered only after intravascular volume repletion and is best guided by knowledge of cardiac output and SVR. There is very little published experience on the use of norepinephrine to treat distributive shock in children; however, a randomized study (in adults) suggested that norepinephrine may be superior to dopamine for treating hypotension and other hemodynamic abnormalities associated with hyperdynamic septic shock. In this study, the average infusion rate for norepinephrine was 1.5 $\mu$g/kg/minute, although others have reported that somewhat lower average doses (0.4 $\mu$g/kg/minute) were effective in adults with sepsis. Thus, titration is important and may entail fairly rapid escalation of dosage.

Norepinephrine produces increases in SVR, arterial BP, and urine flow. It is most valuable in the context of tachycardia because infusion of the drug does not produce significant elevation of heart rate and may even lower heart rate through reflex mechanisms.

The usual starting dose is an infusion of 0.1 $\mu$g/kg/minute. The goal is to elevate perfusion pressure so that the flow to vital organs is above the threshold needed to meet metabolic requirements. The lowest infusion rate should be employed that improves perfusion as judged by skin color and temperature, mental status, urine flow, and reduction in plasma lactate level. Other causes of distributive shock (eg, vasodilator ingestion, intoxication with CNS depressants) should also respond to norepinephrine infusion when the predominant hemodynamic problem is low SVR and BP.

The net effect of norepinephrine infusion upon oxygen balance varies. The increase in afterload that it produces should increase myocardial oxygen consumption, but norepinephrine also decreases myocardial oxygen consumption, which tends to reduce oxygen consumption and improve diastolic coronary perfusion. Injudicious use of norepinephrine can lead to compromised organ blood flow. Norepinephrine infusion may elevate BP yet not improve clinical indices of perfusion.

Phosphodiesterase Inhibitors

Inamrinone and milrinone are intravenously administered nondigitalis, noncatecholamine, and bipyridine derivatives that exert their positive inotropic effects by inhibiting cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE) in cardiac myocytes (see Chapter 13, Inotropic Agents). Increased levels of cAMP, by inhibition of its breakdown, promote Ca$^{2+}$ entry into the cell, thereby increasing contractility. There is also a "lusitropic" effect with diastolic relaxation increased. These drugs may cause adverse effects, including ventricular arrhythmias.

Inamrinone is a typical PDE inhibitor. It is used as an adjunct to dopamine or dobutamine in the intensive care unit and as a vasodilator with some inotropic effect. The cardiovascular effects of both inamrinone and milrinone appear to be markedly age dependent. Studies have shown a lack of responsiveness to either inamrinone or milrinone in the newborn dog and rabbit. Yet, by 2 weeks, the response of rabbit myocardium to milrinone exceeds that of an adult. In the treatment of children with cor pulmonale using inamrinone, additional beneficial effects on the pulmonary vasculature have been reported.

Compared to dobutamine, milrinone produces a greater reduction in SVR for a given degree of improvement in inotropic status. Blood pressure is well maintained, even in the face of reduced SVR, because of the associated improvement in contractility and stroke volume. However, when given to patients who are intravascularly volume-depleted or in whom the expected improvement in cardiac output does not occur, hypotension may result. In patients with CHF, amelioration in global hemodynamic function is associated with an improvement in the ratio of myocardial oxygen delivery to consumption. Inamrinone may improve contractility in patients who have failed
to respond to catecholamines, and may further increase cardiac index even in patients who have responded to dobutamine.\textsuperscript{79}

Inamrinone reduces pulmonary artery pressure and resistance in children with intracardiac left-to-right shunts. In one study, children with elevated PVR enjoyed a 47\% reduction in PVR upon infusion of inamrinone.\textsuperscript{80} The PVR/SVR ratio decreased by 45\%. In these children, both pulmonary blood flow and left-to-right shunt increased. In children with normal pulmonary pressure, inamrinone infusion was associated with a decrease in SVR but not PVR. Inamrinone may be undesirable in children with an elevated pulmonary artery pressure associated with a high-flow left-to-right shunt but normal PVR. Conversely, inamrinone (and probably also milrinone) may be effective adjunctive therapy in the child with elevated pulmonary vascular resistance and reduced pulmonary blood flow.\textsuperscript{80}

Milrinone was approved for use in the United States in 1992. A derivative of inamrinone, it shares the same mechanism of action and pharmacodynamic profile. The major advantage of milrinone is that, unlike inamrinone, it does not appear to evoke thrombocytopenia.\textsuperscript{81} It is eliminated through the kidneys. In adults, milrinone acts both as an inotrope and vasodilator. In adults with CHF, milrinone causes a much greater change in left and right filling pressures and SVR than does dobutamine, even at equivalent increases in contractility.\textsuperscript{82} It has been extensively employed following cardiac surgery, where it increases cardiac index and reduces SVR, filling pressure, and, often, systemic BP.\textsuperscript{83,84} One study evaluated treatment of neonates following congenital heart disease repair.\textsuperscript{85} In this study, a loading dose of 50 µg/kg followed by a continuous infusion of 0.5 µg/kg/minute was associated with mild tachycardia and a slight decrease in systemic BP. Cardiac index increased from 2.1 to approximately 3.1 L/minute/M\textsuperscript{2}, while SVR index decreased from approximately 2100 to 1300 dyne·sec/cm\textsuperscript{5}m\textsuperscript{2}. PVR index also decreased from approximately 488 to 360 dyne·sec/cm\textsuperscript{5}, as did right and left atrial mean pressures. Thus, in children, the pharmacodynamic properties of milrinone are similar to those observed in the case of inamrinone, at least in this limited group of patients. Unfortunately, this study did not examine the pharmacokinetic properties of milrinone.

Inamrinone is metabolized by N-acetyl transferase. In addition, up to 40\% is eliminated unchanged in the urine.\textsuperscript{86} In healthy adults, the half-life of inamrinone in slow acetylators is 4.4 hours and in fast acetylators, it is 2 hours.\textsuperscript{87} It is not known whether this difference is clinically important. Protein binding is not extensive. The rate of elimination of inamrinone appears to be reduced in CHF.\textsuperscript{88} There is little pharmacokinetic information available regarding the use of inamrinone in children and virtually no information derived from children with organ system failure. One study of children younger than 1 year following cardiopulmonary bypass found that the half-life was prolonged in those younger than 4 weeks and that volume of distribution (1.7 to 1.8 L/kg) was threefold greater than others have reported in adults.\textsuperscript{89,90}

A second study found wide interpatient variability in pharmacokinetic measurements. Beyond 1 month, there was no relation between age and any measured pharmacokinetic parameter. The average clearance was approximately 2 mL/kg/minute, which is similar to that recorded in adults and was associated with a mean half-life of about 5.5 hours.\textsuperscript{80} There are no published pharmacokinetic data for milrinone in infants or children. In adults, the volume of distribution of milrinone is 0.5 L/kg and the clearance is 0.11 to 0.1 L/kg/hour. The half-life is approximately 2 hours in adults with CHF.\textsuperscript{91,92} Typically, the plasma level during therapy is in the range of 80 to 120 ng/mL. It appears that neonates and young infants require greater loading doses (up to 4.5µg/kg/minute) compared to adults in order to achieve therapeutic serum levels. Subsequent 5 to 15 µg/kg/minute infusion rates are then optimum.

In patients with CHF, inamrinone and milrinone are safe and effective, and their clinical place in short-term management of patients with refractory heart failure is clearly established.\textsuperscript{78} The bipyridines are most useful in management of children and adolescents with isolated cardiac dysfunction, particularly when it is due to myocardial dysfunction. They provide both inotropic support and afterload reduction and may be an alternative to co-administration of dobutamine and an afterload-reducing agent.

These drugs should not have a major role in management of critically ill children in whom the primary disturbance is other than myocardial dysfunction. The relatively long half-life and the observation that clearance is depressed in patients with cardiac or hepatic dysfunction\textsuperscript{83} are important limitations in the patient with multiple organ system failure. In patients with septic shock or ARDS, for example, inamrinone or milrinone should be reserved for the individual with impaired myocardial performance who has not responded adequately to aggressive support with other agents, such as dobutamine, dopamine, or epinephrine.

Inamrinone produces reversible dose-dependent thrombocytopenia (incidence 2.4\%),\textsuperscript{93} which is more common during prolonged therapy. This was not seen in the largest published pediatric study,\textsuperscript{76} but anecdotal reports suggest that it occurs in children as well. Supraventricular and ventricular dysrhythmias have occurred during infusion of inamrinone but may have been related to the underlying condition of the patient. Overdosage has been fatal in a child\textsuperscript{94} when progressive hypotension developed and peritoneal dialysis was not effective. This
case involved excessive administration due to a computing error. A rapid infusion of inamrinone or milrinone during the loading dose can produce hypotension. This problem is exacerbated in volume-depleted patients who may require volume expansion as a countermeasure, despite the heart failure state. In the past few years, inamrinone has been advocated to be used early in the post cardiac surgery course of pediatric patients as a means to "prevent" or to minimize the impact of low cardiac output. While this appears to be an appropriate rationale in selected patients, conclusive data have yet to be published confirming initial favorable results of this approach.

**Diuretics**

These drugs, which reduce central congestion and pulmonary edema directly, remain key to anticongestive therapy (see Chapter 11, Diuretic Therapy in Cardiovascular Disease). Traditionally, these agents are classified by principal site of action in the kidney.

**Loop Diuretics**

Loop diuretics, which act by inhibiting the Na-K-2Cl transporter in the thick ascending limb of the nephron’s loop of Henle, are widely used in pediatric patients.

Furosemide is the most commonly used agent of this type. This drug also has effects mediated through renal prostaglandin agonism. It increases renal blood flow, reduces renal vascular resistance, and stimulates renin release. There may also be beneficial pulmonary, nondonitory effects from furosemide, making it a useful agent in children with combined cardiopulmonary disorders, such as bronchopulmonary dysplasia. In general, it is used for both acute and chronic management of congestive circulatory states and for causing diuresis after cardiac surgery. In the treatment of infants with CHF, the existing hyperaldosteronism may decrease the patient’s response to furosemide. The addition of an aldosterone antagonist such as spironolactone is then indicated as a means to "prevent" or to minimize the impact of low cardiac output. While this appears to be an appropriate rationale in selected patients, conclusive data have yet to be published confirming initial favorable results of this approach.

Adverse effects at all ages include hypovolemia and electrolyte disturbances. Hypokalemia is a relatively common adverse effect that is usually not of clinical significance in children during chronic therapy unless they also are taking digoxin. However, at high doses of furosemide, potassium supplementation may be necessary. Hypochloremic metabolic alkalosis is also a well-documented adverse effect with chronic therapy and, if severe, may necessitate chloride supplementation. In infants with bronchopulmonary dysplasia, chloride depletion has been implicated as a cause of increased mortality. Hyponatremia may occur and, in the setting of CHF, furosemide may worsen existing hyponatremia.

Ototoxicity may also occur. There is an increased prevalence of ototoxicity in premature infants that may be due to an immature barrier to the inner ear. Whereas in patients with normal renal function the risk of ototoxicity is minimal with standard dosages, in patients with renal dysfunction, the risk of ototoxicity is higher. Additionally, the risk increases in those patients receiving other ototoxic drugs.

Ethacrynic acid is now rarely used in pediatric patients and reserved only for those refractory to furosemide therapy. The drug is sometimes used in the acute management of volume overload. While the pharmacokinetics in adults are similar to those observed with furosemide, in newborns and children this has yet to be determined and is not likely to be, as the drug declines in usage.

Limited data are available for bumetanide, a relatively newer loop diuretic, in the pediatric age group. Hence, its use is generally reserved for those patients in whom conventional diuretic therapy has failed. Bumetanide differs from furosemide in that it is partially metabolized in the liver and about 50% is excreted unchanged in the urine. Furthermore, in neonates and children, it is many times more potent in potassium loss than furosemide and must be monitored carefully.

Bumetanide and metolazone (see below) may be particularly valuable in children with right heart failure, such as those post repair of tetralogy of Fallot or in children who have undergone the Fontan operation or its variants. Data definitively establishing this utility, however, need to be amplified.

**Thiazide Diuretics**

Hydrochlorothiazide (HCTZ) and chlorothiazide, structural analogues, are the primary thiazide diuretics used in pediatric patients with cardiovascular disease. Their diuretic effect is primarily mediated by inhibition of sodium and chloride transport in the nephron’s distal convoluted tubule. Thiazides are effective until the GFR drops below 50% of normal, at which point a loop diuretic should be utilized instead. Thiazides are used in the chronic, outpatient management of congestive circu-
latory states. In addition, they are employed in the treatment of hypertension, particularly in older children and adolescents.106 Whereas the mechanism of action, diuretic efficacy, and adverse effects of HCTZ and chlorothiazide are similar, their pharmacokinetics differ. HCTZ is more potent. Among its adverse effects are electrolyte imbalance, including hypokalemia, hypercalcemia, and hyperuricemia. Additionally, it may negatively alter the lipid profile and may cause carbohydrate intolerance.

**Metolazone**
Metolazone is a sulfonamide derivative whose site and mechanism of action is similar to that of thiazides. It is used in the short-term treatment of edematous states refractory to loop and thiazide diuretic therapy. Metolazone is commonly administered along with a more distally acting diuretic, since, when given by itself, the unaffected distal tubule compensates for the disabled proximal tubule.107 It is administered once a day or every other day. The major adverse effects are severe electrolyte disturbances (hypokalemia) and significant volume depletion.

**Potassium-Sparing Diuretics**
Spironolactone, the most commonly used potassium-sparing diuretic,108 is usually reserved for long-term therapy because it is administered only orally. It exerts its diuretic effect by competitively inhibiting aldosterone at the distal tubule. It is weaker than either loop or thiazide diuretics and thus is mostly used in combination with either. Its major adverse effects are hyperkalemia and renal dysfunction. Patients with existing renal and/or hepatic dysfunction are at greatest risk. Concomitant potassium supplementation, as well as ACE inhibitor co-administration, should be done with extreme care. Gynecomasia and menstrual abnormalities have been reported in adults. Data in pediatric patients regarding the use of other potassium-sparing diuretics, such as triamterene, eplerenone, and amiloride, are limited, and generalized recommendations cannot be made currently.

Spironolactone also has other nondiuretic benefits for the patient with CHF. The findings of direct myocardial function enhancement, of inhibition of the collagen production and fibrosis stimulated by aldosterone, and of additive effects when combined with ACE inhibition (see below) have focused new attention on the use of spironolactone.109 The landmark Randomized Aldactone Evaluation Study (RALES) was interrupted early, in fact, because the findings of the value of spironolactone were impressive.110,111

**Osmotic Diuretics**
In pediatrics, mannitol is the most commonly used drug in this class. Mannitol’s cardiovascular use is reserved for the acute treatment of severe circulatory congestion in the face of limited renal output (ie, prerenal failure and azotemia). The primary site of action is the proximal tubule, and mannitol will maintain high rates of tubular flow to prevent obstruction. More total salt and water reabsorption occurs in the distal tubule in neonates than in older patients. Hence, mannitol as a proximally acting agent is less effective than more distally acting agents in neonates.97 Adverse effects are hemodynamic: Immediately following its administration, mannitol may temporarily increase intravascular volume and the risk of electrolyte disturbances.

**Nitrovasodilators**
Vasodilator therapy has become central to the management of impaired circulatory status in infants and children. With the tremendous development of the basic science knowledge base in microcirculatory function, particularly the factors involved with control of vasomotor tone, an increasing armamentarium of agents has become available. When vasodilators are combined with other agents, such as the inotropes reviewed above, efficacy is enhanced beyond the use of either class of agents alone.112

For acute usage, particularly in the intensive care unit, the nitrovasodilators have become agents of choice. These drugs have rapid onset of action and exceedingly short duration of action, making them especially suitable for the acutely ill patient. Principally, but not entirely, these are venoactive agents that work through nitric oxide (NO) activation and consequent cyclic guanosine monophosphate (cGMP) mediation of regulatory proteins involved with smooth muscle contraction. In general pediatric usage, nitroprusside is used most frequently, although nitroglycerin is used on occasion in the postoperative cardiac surgery patient.

**Nitroprusside**
This drug has both venous and arteriolar activity and is the most widely used acute intravenous vasodilator in the pediatric population. Similar to nitroglycerin, it was used originally for pediatric patients following cardiac surgery during the immediate postoperative period.113,114 With doses ranging from 1.5 to 12 µg/kg per minute, there is a decline in filling pressures, an increase in cardiac output (CO), and little change in heart rate. Nitroprusside is effective in pediatric patients with left ventricular dysfunction and mitral regurgitation.115 Nitroprusside must be administered parenterally by continuous infusion because it is metabolized so rapidly.

Pulmonary and systemic vascular resistances and atrial pressures are reduced, causing a net increase in CO. Its effects in neonates are comparable to those in older children. One neonatal study documented improved
systemic perfusion in 40% of the patients, and almost all the infants had improved urine output after initiation of therapy. This study also demonstrated safety as well as efficacy in young infants.\(^{116}\)

While most results have been favorable, caution was raised by one study of nitroprusside use in hypoxic neonatal and juvenile lambs. Nitroprusside decreased PVR in the juvenile but not in the neonatal group. Moreover, the newborn lambs were not able to hemodynamically tolerate the nitroprusside-induced decrease in preload.\(^{117}\) These age-related differences in vascular response suggest that nitroprusside should be used with extra caution in neonates.

Nitroprusside’s metabolite, cyanide, is toxic. Symptoms of toxicity include headache, disorientation, fatigue, vomiting, anorexia, tachypnea, and tachycardia. In patients being given long-term or high-dose therapy, the specific meaningfulness of periodic red blood cell cyanide and plasma thiocyanate measurements remain unclear. Clinical evidence of toxicity has not been shown to correlate well with specific cyanide and thiocyanate concentrations,\(^{118}\) so close monitoring of clinical symptoms is important.

Nitroglycerin

In pediatrics, nitroglycerin is most commonly employed following cardiac surgery in the immediate postoperative period, with several studies demonstrating its beneficial effect in this setting.\(^{119,120}\) It is most commonly used in patients with increased preload and symptoms of systemic and/or pulmonary venous congestion. Nitroglycerin has been demonstrated to be beneficial in newborns with low CO due to congenital heart disease, asphyxia, and sepsis. Although nitroglycerin can affect all smooth-muscle sites, its predominant action is to relax venous vascular smooth muscle and therefore to reduce left-ventricular preload. Nitroglycerin reduces pulmonary venous and arterial pressures.

The hemodynamic actions of nitroglycerin appear to be dose-related. At doses < 2 \(\mu \text{g/kg/minute}\), a venodilation effect predominates. Doses from 3 to 5 \(\mu \text{g/kg/minute}\) result in progressive arteriolar dilatation with a decrease in SVR and a resultant rise in CO. Higher-than-conventional doses may cause hypotension and reflex tachycardia. Conventional pediatric doses, such as a mean nitroglycerin dose of 20 \(\mu \text{g/kg/minute}\) as used in one study, may not significantly alter the mean arterial pressure (MAP) in children, but similar doses produce hypotension in adults. In children with pulmonary hypertension, a decrease in PVR is noted.\(^{121}\)

Nitroglycerin can be administered sublingually, intradermally, or intravenously, but not orally, because it undergoes extensive first-pass hepatic metabolism. When given intravenously, it must be given by continuous infusion because of its short serum half-life. Recommendations for chronic management in pediatric patients cannot be made because of insufficient data. Patients must be monitored for (1) the possibility of further reduction of CO secondary to even lower filling pressures than desired, and (2) hypotension accompanied by tachycardia and hypoxemia secondary to overdosage.

Nitric Oxide

Much recent attention has focused on NO and its role in modulating vascular smooth muscle vasomotor tone as noted above in the discussion of therapeutic infused nitrovasodilators. Use of NO itself as a pharmaceutical has been widely accepted in its inhaled form to effect pulmonary vasodilation.\(^{122-124}\) As an inhaled agent with little systemic action, NO causes selective and prolonged reduction in pulmonary artery pressure in a variety of clinical settings with consequent beneficial effects on right ventricular mechanics and relief of cor pulmonale.\(^{125}\) A strong rationale for this therapy has been found for modulating pulmonary vasomotor tone in the newborn with congenital heart or lung disease or a combination of both.\(^{126}\) Use in other forms of pulmonary hypertension and right heart failure has been more limited, but recently a role for inhaled NO in problems such as adult respiratory distress syndrome has been proposed.\(^{127}\)

Peripheral \(\alpha_{1}\) Adrenergic Receptor Blockers

Prazosin

Prazosin is an \(\alpha_{1}\), selective blocker that can cause a reduction in SVR and MAP. Its selectivity for the \(\alpha_{1}\) receptor explains its ability to produce less reflex tachycardia than can nonselective agents. It exerts an effect both on arteriolar and venous capacitance vessels. Prazosin has been used in pediatric patients with CHF due to systolic dysfunction.\(^{128}\) The drug is administered orally, and its peak effect occurs within 2 to 3 hours. Although its serum half-life is 2.5 to 4 hours, prazosin’s duration of action lasts for about 12 hours.

Prazosin is generally tolerated well with only minor adverse effects. However, the “first-dose phenomenon,” characterized by dizziness, hypotension, and syncope, may occur within approximately 0.5 to 1.5 hours after initiation of therapy. It may also occur after an increase in dosage. This effect can be avoided by giving the patient the drug at bedtime. It is unclear whether the tendency in adults who have CHF to develop drug tachyphylaxis applies to children as well.\(^{129}\) There is little pediatric experience with other similar drugs, terazosin or doxazosin, two congeners with long-acting potential.

Phentolamine

Phentolamine is a nonselective \(\alpha\) blocker. Unlike selective \(\alpha\) blockers such as prazosin, phentolamine is more likely to cause tachycardia and arrhythmias by virtue of its \(\alpha_{2}\)-
Effects generally last for 6 to 8 hours. In young infants, peak plasma concentrations are reached within 1 to 2 hours after an oral dose, and therefore, dosage should be reduced in neonates, idiosyncratic adverse effects including significant hypotension, oliguria, and neurologic complications have occurred. Hence, it is obligatory to monitor BP closely during the use of captopril. Increases in BUN and creatinine also must be monitored when using this drug.

Captopril has been used successfully in children with large left-to-right shunts and elevated SVR to reduce the magnitude of the left-to-right shunting. Additionally, in patients with dilated cardiomyopathies or paradoxical hypertension following coarctation surgery, captopril appears to be beneficial.

Patients with ventricular volume loading associated with chronic aortic or mitral regurgitation have also derived benefit from these medications. Recently, clinical practice has focused on the use of captopril and other agents of this group as prophylactic therapies in those at risk for declining ventricular function, such as postcancer chemotherapy patients, or patients who have single ventricle conditions, such as those who have undergone the Fontan operation or its variations. Multicenter clinical trials are underway to objectively verify the value of such prophylaxis, but a preliminary report in single ventricle patients was not encouraging as to specific efficacy.

Captopril, Enalapril, and Lisinopril

The use of these agents has been studied in children of all ages and has proved to be an effective antihypertensive agent. Initial pediatric experience with captopril was for the treatment of systemic hypertension in infants and children. Dose-response studies in older children have shown similar responses to 0.5, 1.0, and 2.0 mg/kg per dose; hence the lowest dose of 0.5 mg/kg is recommended when therapy is initiated in children older than 6 months. If the desired effect is not achieved with that low dose, then the dose should be increased to 1.0 mg/kg; further increase would most likely not result in better control, and another agent should be used.

Captopril is given orally. Although twice-daily dosing has been successful, captopril is generally administered 3 times daily. In premature infants, as high as 60% reductions in BP levels were achieved with doses of 0.3 mg/kg; oliguria was also reported. Normotensive BPs have been achieved in premature and full-term infants with doses as low as 0.01 mg/kg. Captopril's absorption is inhibited by food in the stomach, and therefore the drug should be given on an empty stomach. Peak plasma concentrations are reached within 1 to 2 hours after an oral dose, and effects generally last for 6 to 8 hours. In young infants and newborns, captopril is more potent and its duration of action is longer as compared to older children. Approximately half of the drug is excreted unchanged in the urine. Drug clearance is positively correlated with renal function, and therefore, dosage should be reduced in renal disease.

Adverse effects of captopril described in adults, including hypotension, hyperkalemia, renal insufficiency, and dry cough, are less common in children. However, in neonates, idiosyncratic adverse effects including significant hypotension, oliguria, and neurologic complications have occurred. Hence, it is obligatory to monitor BP closely during the use of captopril. Increases in BUN and creatinine also must be monitored when using this drug.

Captopril has been used successfully in children with large left-to-right shunts and elevated SVR to reduce the magnitude of the left-to-right shunting. Additionally, in patients with dilated cardiomyopathies or paradoxical hypertension following coarctation surgery, captopril appears to be beneficial.

Patients with ventricular volume loading associated with chronic aortic or mitral regurgitation have also derived benefit from these medications. Recently, clinical practice has focused on the use of captopril and other agents of this group as prophylactic therapies in those at risk for declining ventricular function, such as postcancer chemotherapy patients, or patients who have single ventricle conditions, such as those who have undergone the Fontan operation or its variations. Multicenter clinical trials are underway to objectively verify the value of such prophylaxis, but a preliminary report in single ventricle patients was not encouraging as to specific efficacy.

Enalapril, the second commercially available ACE inhibitor in the United States, is also effective in the treatment of children with systemic hypertension and CHF. It is a prodrug that must be de-esterified in the liver to the active form. (Enalaprilat is the only ACE inhibitor available for intravenous administration.) Enalapril differs from captopril in two significant ways: (1) Its molecular structure contains no sulphhydryl group, postulated to be an etiologic factor in the development of some adverse effects; and (2) Its half-life is longer. In general, enalapril's adverse effects are similar to captopril but may occur somewhat less frequently.

Lisinopril, another long-acting ACE inhibitor, was evaluated in 115 hypertensive children (aged 6 to 16 years) and found to lower BP in a dose-dependent manner. A starting dose of 0.07 mg/kg was appropriate, and the drug was well tolerated. Other uses and indications mimic captopril and enalapril as well.

Direct renin inhibitors such as aliskiren have not been well evaluated in children.

Beta-Adrenergic Blockers

While much experience in pediatric patients has been accumulated for beta blockers in the treatment of
hypertension and arrhythmias, only recently were these drugs found to be useful in heart failure as well. First- and second-generation drugs of this group are reviewed under arrhythmia treatment. In several important trials and reports on adult CHF patients, carvedilol, bisoprolol, and metoprolol appear to have important clinical benefit. Their efficacy relates to interference with the deleterious effects of excessive sympathetic activity in CHF, and, in pediatric patients, particularly to those with nonischemic cardiomyopathy.

Bisoprolol and metoprolol are both $\beta_1$-selective blockers. Carvedilol, a nonselective beta blocker, is an $\alpha$-adrenergic antagonist as well, with antioxidant capability.

In pediatrics, a few favorable original studies with small numbers of patients have been supported by the multicenter carvedilol trial, demonstrating the value of this agent in patients deemed severe enough to warrant heart transplantation. As more information has developed, these drugs have secured a place in the management of pediatric patients with CHF, although not as demonstrably as in adults.

### Natriuretic Therapy

The use of brain natriuretic peptide therapy in pediatrics is extremely limited and has thus far primarily involved postcardiac surgery patients. Nesiritide, the intravenous synthetic derivative of brain natriuretic peptide, promotes vasodilation, renal perfusion, natriuresis, and diuresis. Empiric dosing with infusion rates of 0.005 to 0.03 $\mu$g/kg/minute has been suggested after a bolus dose of 1 $\mu$g/kg/minute. Recent adult trials have been suspended particularly in view of important renal function impact, and raise attention to the need for caution and for very close monitoring with the use of this agent.

### Arterial Hypertension

Although it was thought for many years that hypertension in children was primarily secondary to diseases of the kidney, the cardiovascular system, or the endocrine system, it is now known that primary hypertension is a significant problem of children and adolescents, strongly associated with the prevalence of overweight and obese children. Large population studies have helped to establish norms and percentiles for infants, children and adolescents, and there is strong evidence of a relationship between pediatric hypertension and a multiple morbidities in adulthood.

Although lifestyle changes, including nutritional change and a regular exercise program, are the usual initial therapeutic interventions for hypertension in children, there are specific indications for antihypertensive pharmacotherapy in pediatrics. These include symptomatic hypertension, secondary hypertension, hypertensive target-organ damage, persistent hypertension despite nonpharmacologic measures, and the coexistence of diabetes mellitus (types 1 and 2). Many antihypertensive medications have now been studied and used in children and a variety of classes of drugs may be useful. Classes of antihypertensive medications used include calcium-channel blockers, beta blockers, ACE inhibitors, angiotensin receptor blockers and diuretics. There have been a number of new agents developed and used recently within each class.

### Classes of Antihypertensive Medications

#### Calcium Channel Blockers

Calcium channel blockers exert their antihypertensive effect by inhibiting the influx of calcium ions across the cell membranes, resulting in dilation of the peripheral arterioles whose BP requires urgent control. These agents are divided into two groups based on their molecular structure and clinical application (see Chapter 8, Calcium Channel Blockers). Type I agents are characterized by a tertiary amine structure similar to verapamil. They are used primarily to treat cardiac arrhythmias and are discussed in the section entitled “Antiarrhythmic Therapy.” Type II agents have a dihydropyridine nucleus, similar to nifedipine. These agents exhibit less antiarrhythmic activity but are more potent vasodilators and are used in pediatrics to treat hypertension.

The effects of nifedipine, a dihydropyridine compound, were studied in 25 hypertensive children (aged 6 months to 16 years) who had systolic and diastolic BP consistently exceeding the 95th percentile for age and gender. Significant reductions in BPs (mean decrease 148/99 to 128/77 mm Hg after 1 day and to 121/75 mm Hg after 2 weeks) were observed within 24 hours, and the effects were sustained through 3 months of treatment with a dose of 0.25 to 0.50 mg/kg given every 6 to 12 hours. It was apparently safe. The duration of action and the long-term clinical response to nitrendipine was believed to be substantially better than that of nifedipine. Amlodipine, another long-acting dihydropyridine calcium-channel blocker, was evaluated in an international, placebo-controlled study of 268 hypertensive children aged 1–17 and found to be both safe and effective. Headache was the most common adverse effect.

Oral, rapid-acting nifedipine and isradipine and intravenous nicardipine are safe and effective agents for the management of hypertensive crisis in children. For chronic control, extended-release nifedipine and amlopidine are the two most commonly used oral calcium
channel antagonists. For both acute and chronic management of hypertension, calcium channel antagonists are safe and effective in children and are well tolerated with relatively few adverse effects.158

**Nifedipine**

Nifedipine, the most potent vasodilator of the calcium channel blockers, has been used to treat hypertension in children with hypertensive emergencies. Its rapid onset of action and relatively short duration of action make it ideal for this purpose. It has also been used to treat infants with hypertrophic cardiomyopathy, primary pulmonary hypertension, and ventricular septal defect with pulmonary hypertension. It is supplied as an encapsulated liquid that must be swallowed and not taken sublingually, because very little absorption occurs via the latter route. Uchiyama and Sakai suggest that rectal administration of perforated nifedipine capsules may be a reliable way to acutely treat young children with severe hypertension. Pediatric patients appear to tolerate nifedipine better than do adult patients, with infrequent and mild adverse effects. However, cardiovascular collapse and cardiac arrest after ingesting an extraordinary large dose of nifedipine can reflect nifedipine poisoning in which the antihypertensive effect is not maintained.

**Nicardipine**

Nicardipine is a dihydropyridine calcium-channel blocker, has been used to treat hypertension in children with hypertensive emergencies. Its mechanism of action and clinical effects closely resemble those of nifedipine and the other dihydropyridines (amlodipine, felodipine), except that nicardipine is more selective for cerebral and coronary blood vessels. Furthermore, nicardipine does not intrinsically decrease myocardial contractility. It has been shown to be effective in the management of severe hypertension in childhood in the pediatric intensive care unit with close monitoring.

**Isradipine**

Isradipine, a short-acting, second generation calcium channel blocker, is administered orally with a fairly rapid onset of action. It has been shown to be effective in secondary and primary forms of hypertension, and has been used in solution form, allowing for the effective treatment of infants and young children.

**Beta-Blockers**

Beta-blockers act at the β-adrenergic receptor. Although they share this common characteristic, they differ from each other with regard to the presence or absence of β1 selectivity, lipid solubility, intrinsic sympathomimetic activity, membrane stabilization, and potency (see Chapter 5, Alpha- and Beta-Adrenergic Blocking Drugs). These drugs' high therapeutic index has been confirmed by reports in children. The antihypertensive effect is poorly correlated with plasma concentrations and surpasses the anticipated duration of action based on plasma half-life. Hence, even preparations with short half-lives generally can be given on a twice-daily basis, and possibly even once a day. The reported incidence of adverse effects to beta blockers in children is exceptionally low. Administration of any of the β-blocking agents, which can inhibit β1-receptor bronchodilation, to children with obstructive forms of lung disease such as asthma, should be strongly discouraged. CNS adverse effects in children are more likely to present in the form of sleep disturbances as opposed to the depression, dreams, confusion, and agitation seen in adults. Glucose and lipid profile can be adversely affected.

For many years, the most extensive published clinical pediatric experience with beta blockers was with propranolol. Berenson et al randomized 95 patients with persistent hypertension, defined as greater than the 90th percentile for BP over a 4-month interval, to either a drug-treatment group consisting of low-dose propranolol and chlorthalidone therapy or to a control group. Both groups were exposed to an education program oriented toward the treatment of hypertension by diet and exercise. Those in the drug-treatment group, after 30 months of follow-up, had significantly lower mean systolic and diastolic BPs with minimal adverse effects. Griswold et al treated 9 children with hypertension secondary to renal disease associated with high plasma renin levels who had failed pharmacotherapy with diuretics, hydralazine, and methyldopa. One patient developed resting bradycardia. Ruley and Magalnick successfully treated hypertension in a 1-year-old male with Wilms' tumor and elevated plasma renin activity with doses as high as 24 mg/kg/day of propranolol. Boerth reported a need for higher plasma propranolol levels to achieve therapeutic results in those patients with secondary hypertension due to renal parenchymal disease or hypoplastic abdominal aorta than in those patients with essential hypertension (140 versus 111 ng/mL). Mongeau et al conducted a single-blind, 8-month, crossover trial that compared propranolol to the placebo in 10 patients (aged 14 to 17 years) with essential hypertension. Both systolic and diastolic pressures were significantly reduced with propranolol. None of the patients developed adverse effects severe enough to require cessation of propranolol therapy. Three of 10 patients did, however, experience fatigue after exercise, bradycardia, and transient Raynaud's phenomenon.
ics, methylldopa, and hydralazine. There was a mean reduction of BP from 139/94 to 127/84 mm Hg. Two of the 13 patients did not improve with propranolol therapy, and there was no correlation between change in renin levels and change in BP. Propranolol has also been shown to be effective preoperatively in children with coarctation of the aorta.

Gidding et al.174 addressed the question of whether preoperative administration of propranolol could prevent paradoxical hypertension noted in children following surgery for coarctation of the aorta. They found that propranolol effectively decreased postoperative rises in both BP and plasma renin activity. Leenen et al.175 have also confirmed the effective use of propranolol in this regard in a randomized, controlled, double-blind trial.

In previously noted pediatric studies,172,173 β blockade caused a fall in serum renin activity, but there was no relationship between that reduction and an antihypertensive response. Falkner et al176 reported adequate BP control with metoprolol and a blunted change in the systolic pressure and heart rate response to aerobic exercise and mental stress. At maximum exercise, patients were able to increase their heart rate to expected maximal levels, without limitation in endurance capacity (measured by exercise stress testing), suggesting that metoprolol may be useful in diabetics who fail propranolol therapy. In addition, metoprolol had no adverse effect on glucose levels and insulin requirements. A recent study showed both efficacy and safety of extended release metoprolol in children with hypertension.177,178

Labetalol
Labetalol acts as a nonselective beta blocker. It also has α-adrenergic blocking properties and direct vasodilating activity.179 Its β-blocking properties, however, are about 8 times as potent as its α-blocking ability. It is well absorbed after an oral dose and undergoes extensive first-pass hepatic metabolism. The intravenous use of labetalol was recently reported in children. Bunchman et al.4 noted that the intravenous infusion of labetalol in children with severe hypertension or in those with uncontrollable hypertension was effective in controlling BP when oral medication could not be tolerated. Labetalol’s antihypertensive effect was observed within an hour after a starting dose of 0.2 to 1.0 mg/kg. Its effect was sustained with a continuous parenteral infusion of 0.25 to 1.5 mg/kg/hours. Adverse effects were rare, and the response to labetalol was independent of kidney function. Labetalol is particularly useful in treating the hypertensive crisis of chronic renal failure.152

Esmolol
Esmolol, an ultrashort-acting beta blocker, is helpful in slowing an incessant supraventricular tachycardia in children while other long-term agents are being titrated. Hypotension is a serious limitation with esmolol, especially if ventricular dysfunction already exists as a result of an incessant arrhythmia. The pharmacokinetics of esmolol in children have recently been reviewed and the authors suggest using pediatric dosing guidelines.181

Vasodilators

Hydralazine
Hydralazine’s primary action is to relax precapillary arteriolar vascular smooth muscle (see Chapter 16, Nonspecific Antihypertensive Vasodilators). It reduces SVR and, therefore, afterload, which permits increased ventricular muscle fiber shortening during systole. This results in an enhanced stroke volume at any given end-diastolic volume. In infants and children, hydralazine has been shown to be effective in the treatment of ventricular systolic dysfunction.192,183 It may also decrease shunt magnitude and increase systemic output by decreasing SVR to a greater degree than PVR in infants with left-to-right shunts.184,185

Hydralazine can be given both orally and parenterally. After an oral dose, the drug undergoes extensive first-pass metabolism by acetylation, which limits its bioavailability. Hemodynamic effects occur within 30 to 60 minutes and last for as long as 8 hours. Unlike adults to whom hydralazine has been given by continuous infusion, infants and children should be given hydralazine by bolus infusions. Following intravenous administration, hemodynamic responses are apparent after approximately 5 to 10 minutes, peak by approximately 30 minutes, and last for 2 to 4 hours.186 Its rapid onset of action makes intravenous hydralazine useful for treating hypertensive urgencies.

Presently, the incidence of adverse effects in infants and children is not well delineated. The most common adverse effects seen in adults include headache, dizziness, nausea, and vomiting, postural hypotension, and tachycardia. About 10% of adult patients on long-term hydralazine therapy develop a generally reversible lupus-like syndrome. Without clinical suspicion of a lupus-like syndrome, routine monitoring of antinuclear antibody is not justified, because only some of the patients in whom antinuclear antibodies are present will subsequently develop clinical features of lupus. For a given dose, slow acetylators achieve higher plasma concentrations and are at increased risk for adverse effects. It is unclear whether tolerance to long-term hydralazine therapy, as demonstrated in adults, will occur in pediatric patients as well.

Diazoxide
Diazoxide, a nondiuretic thiazide derivative, is a potent arteriolar dilator (see Chapter 16, Nonspecific Antihypertensive Vasodilators). Its antihypertensive effect is rapid in onset, and it has been used safely in children.179 One
may avoid an abrupt decrease in BP and its associated complications (see above) by administering diazoxide as a slow, rather than a rapid, infusion, as was done in one adult study, which demonstrated the efficacy of the slower infusion. Adverse effects of diazoxide include fluid retention and hypertrichosis, especially with frequent administration.

Sodium Nitroprusside
This drug has both venous and arteriolar activity and is the most widely used acute intravenous vasodilator in the pediatric population (see Chapter 14, The Organic Nitrates and Nitroprusside). Similar to nitroglycerin, it was used originally for pediatric patients following cardiac surgery during the immediate postoperative period. With doses ranging from 1.5 to 12 μg/kg per minute, there is a decline in filling pressures, an increase in CO, and no change in heart rate. Nitroprusside is effective in pediatric patients with left ventricular dysfunction or mitral regurgitation. PVR and SVR and atrial pressures are reduced, causing a net increase in CO. Heart rate may be unaffected or increase slightly. Its effects in neonates are comparable to those in older children. One neonatal study showed that 40% had improved systemic perfusion, and almost all the infants had improved urine output after initiation of therapy. Nitroprusside must be administered parenterally by continuous infusion because it is metabolized so rapidly.

Nitroprusside’s safety and efficacy have been demonstrated in neonates. In hypoxemic neonatal and juvenile lambs, however, nitroprusside decreased PVR in the juvenile but not in the neonatal group. Moreover, the newborn lambs were not able to hemodynamically tolerate the nitroprusside-induced decrease in preload. These age-related differences in vascular response suggest that nitroprusside should be used with extra caution in neonates.

Nitroprusside’s metabolite, cyanide, is toxic. Symptoms of toxicity include headache, disorientation, fatigue, vomiting, anorexia, tachypnea, and tachycardia. In patients being given long-term or high-dose therapy, the meaningfulness of periodic red blood cell cyanide and plasma thiocyanate measurements are uncertain; clinical evidence of toxicity has not been shown to correlate well with specific cyanide and thiocyanate concentrations.

Hypertensive Emergencies
Severe, symptomatic hypertension (well above the 99th percentile), accompanied by clinical evidence of end-organ injury, is an emergency and requires immediate pharmacotherapy, generally with an intravenous agent. Signs and symptoms such as retinal hemorrhages or papilledema, seventh nerve palsy, diplopia, symptoms of encephalopathy (headache, vomiting, altered mental status, or seizures), CHF, or renal insufficiency all reflect end-organ injury due to malignant hypertension. The patient’s BP must not be reduced too rapidly, because it may lead to hypotension, obtundation, or other disabling adverse effects. It is recommended that the BP be reduced by ≤ 25% over the first 8 hours after presentation and then gradually normalize the BP over 26 to 48 hours. Severe hypertension with less severe symptoms needs to be treated urgently and may be treated with rapid acting oral agents.

Rapidly acting agents including calcium channel blockers such as nicardipine, nifedipine, and isradipine, beta blockers such as esmolol and labetalol, and direct vasodilators such as hydralazine and nitroprusside are all useful.

Chronic Hypertension Management
Chronic drug therapy in hypertensive children is predicated on the expectation that reduction of high pressure will result in decreased long-term morbidity and mortality, which has been proved with at least some antihypertensive agents in adults. In fact, there is mounting evidence, as the Bogalusa Heart Study suggested, that hypertension in children is linked to end organ damage and the development of essential hypertension later in life. In combination with or after the failure of lifestyle changes, pharmacotherapy of hypertension may be indicated.

For chronic, nonemergent control of BP, a stepwise approach is recommended, beginning at the lowest recommended dose and increasing as needed for control. When the maximum dose of a medication is reached, a drug from a different class is added. An aggressive approach to therapy with multidrug regimens is often necessary for adequate control of secondary hypertension, as it is generally more resistant to therapy than essential hypertension. Again, several classes of medications may be useful, and the selection is usually up to the practitioner. Most frequently used medications include diuretics such as thiazides, loop diuretics, or spironolactone; ACE inhibitors such as enalapril, captopril, and lisinopril; and beta blockers such as metoprolol, propranolol, and atenolol. In recent years, chronic initial antihypertensive drug therapy in children has usually included either an ACE inhibitor or a calcium-channel blocker. Their once-a-day dosages and favorable adverse effect profile have tended to improve adherence, a major issue in childhood and adolescence.

Other, less commonly used agents include angiotensin II inhibitors such as losartan, olmesartan, and central alpha 2-adrenergic agonists, including clonidine and guanabenz. The latter drugs act centrally by stimulating α2-mediated inhibition of sympathetic outflow, which
results in decreased SVR (see Chapter 6, Central and Peripheral Sympatholytics). These drugs are primarily used in the treatment of hypertension. Abrupt discontinuation of therapy may result in rebound hypertension. Other adverse effects are sedation and dry mouth. Published pediatric experience with these agents is limited. Minoxidil results in arteriolar vasodilation without significant venous vasodilation, similar to hydralazine. Its use is primarily reserved for children with severe drug-resistant hypertension. Adverse effects of minoxidil include hypotension, tachycardia, hypertrichosis, and fluid retention.

**Treatment of Lipid Disorders**

Increasingly, evidence has been accumulated that links atherosclerosis in adults with a juvenile onset. In addition, there are primary lipid disorders with marked elevation of cholesterol and its congeners, which exist in childhood in their own right. As a result, increasing attention has been focused on developing strategies of pharmacologic management of lipoprotein metabolism in childhood.

There is considerable experience with antilipid pharmacotherapy in children with familial hypercholesterolemia (FH), the most commonly recognized and best understood disorder of lipoprotein metabolism in childhood. In FH heterozygotes (1 of 500), plasma cholesterol [total and low-density lipoproteins (LDL)] is elevated two- to three-fold while FH homozygotes (1 of 1,000,000) have cholesterol levels that are elevated five- to six-fold. However, most published studies have been small in size, making it difficult to thoroughly assess the potential adverse effects of antilipid drug therapy. Furthermore, therapeutic approaches studied in FH may not have broad-based applicability to other types of childhood dyslipidemias. Additionally, in these studies, therapy for the most part has been oriented toward the reduction of serum total cholesterol and LDL cholesterol without addressing other constituents of the serum lipid profile that may have both prognostic and therapeutic significance.

In children with dyslipidemias and sustained hypercholesterolemia, much evidence has been uncovered to indicate that atherosclerosis develops at an accelerated rate. The treatment of dyslipidemic children relies on the assumption that modifying serum lipoprotein concentrations will reduce the rate of atherogenesis. The use of combined diet–drug intervention has been shown to arrest the progression of arteriographically defined coronary atherosclerosis and to reduce cardiovascular disease risk in middle-aged men. Recently, an impact on vascular change with drug therapy has been demonstrated in children, too.

As in adults, initial medical intervention for dyslipidemias in childhood is generally nonpharmacologic. On average, LDL cholesterol will decrease approximately 10% to 15% with diet therapy. In some children, however, diet therapy alone will not suffice. The National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents selected cut points for initiation of pharmacotherapy that recently have been modified as new information has become available. According to those newest guidelines, in children 10 years and older, drug therapy should be initiated after a 6- to 12-month trial of diet if (1) serum LDL cholesterol is $> 190$ mg/dL or (2) serum LDL cholesterol is $> 160$ mg/dL along with either a positive family history of premature coronary artery disease or two or more other risk factors that remain present after vigorous attempts have been made to control them. In children younger than 10 years, clinical judgment of the physician must dictate treatment.

Another set of recommendations has been issued by the American Academy of Pediatrics Committee on Nutrition. While specific levels for screening algorithms differ to a limited extent, there is consensus agreement that indications for pharmacotherapy include a 190 mg/dL LDL cholesterol value in children 10 years or older who have attempted diet modification or an LDL of $> 160$ mg/dL if there is a family history of premature cardiovascular disease or if there are other risk factors present assuming a strong attempt at dietary control. In addition, there are advocates for beginning treatment at even younger ages, although the value of this approach remains to be tested in large population samples.

Approved medication options for use in the pediatric population are limited. The most widespread experience is with the bile acid sequestrants colestipol and cholestyramine. However, other drugs, including various statins, niacin, and fenofibrate, also reduce the total cholesterol.

**Bile-Acid Binding Resins**

Cholestyramine, Colestipol, and Colesevelam

The NCEP recommends only the use of the bile acid sequestrants. These agents have been used successfully to lower LDL cholesterol in children over long intervals, apparently with relatively few adverse effects. Doses are not related to the body weight of the child but to the postdietary LDL cholesterol levels. These drugs are the safest to use because they are not absorbed systemically. Both cholestyramine and colestipol have been used for up to 8 years in children without evidence of fat-soluble vitamin deficiencies, steatorrhea, calcium, or vitamin D metabolic disturbances, or erythrocyte folic deficiency. However, no placebo-controlled, double-blind, prospective study of the safety and efficacy of these agents, par-
particularly regarding long-term growth and development, has been done.

The dose range frequently recommended is 2 to 16 g/day. Most common adverse effects include flatulence, nausea, and constipation. Approximately a 15% to 20% reduction in LDL cholesterol values can be achieved, on average, over the long term, although greater reductions have been reported in selected circumstances.

**HMG-CoA Reductase Inhibitors (Statins)**

An AHA statement includes the use of HMG-CoA reductase inhibitors in patients greater than 10 years (with the preference for post menarche in females). As noted above, on occasion this may even include younger patients. In the last several years, placebo-controlled double-blind clinical trials have demonstrated reductions in LDL cholesterol in children using statins and diet, both with and without concomitant bile acid sequestrant therapy. Only limited adverse effects have been reported in these studies, involving pravastatin, lovastatin, or simvastatin in doses ranging from 5 to 40 mg/day, depending on the particular study.

Reductions in mean LDL cholesterol ranged from as high as 21% to 36% in one study 211 to 17% to 27% in another, with similar reductions found in other trials as well. As with adults, monitoring of cholecystokinin and liver function studies is required, as well as accurate reporting of muscle cramping, rash, and fatigue. Importantly, statin use in these trials has not had adverse effects on growth or on maturation in males. The caveat against their use in the pubertal female remains in place; however, as there are no data proving safety in this group for either the patient or a prospective fetus, long-term studies are still needed, perhaps spanning decades, for obtaining secure data concerning the impact of such treatment in children on the development of cardiovascular complications in adults with lipid disorders. However, several statins now have pediatric labeling instructions as a result of favorable clinical trial data (see Chapter 20, Lipid-Lowering Drugs).

**Niacin**

Niacin functions by suppressing hepatic production and secretion of LDL and very-LDL. There are descriptions of the use of niacin in childhood, but its clinical utility is limited because of well-documented adverse effects. The most worrisome is its potential hepatotoxicity at therapeutic doses, as suggested by elevation of liver enzymes. Common adverse effects include "niacin flush," which can be prevented by taking aspirin (dose is age-dependent) 20 to 30 minutes prior to the niacin dose. Less commonly, itching, dry skin, headaches, nausea, vomiting, diarrhea, and increased liver function tests may occur. Usually, niacin is recommended to be used in combination with diet therapy plus bile acid sequestrants in doses of 2 to 6 g/day. Unfortunately, in view of the multiplicity of adverse effects, use is relatively limited.

**Cholesterol Absorption Inhibition**

Very recently, this class of therapy has gained ground in a variety of treatment regimens, some combining statins with cholesterol absorption inhibitors. Ezetimibe is the principle agent of this type of treatment. This is reserved under current protocols for those who fail to achieve target reduction on LDL cholesterol with monotherapy. The study by Gagne et al did include patients 12 years and older, but more extensive studies in the younger pediatric population are yet to be reported.

**Treatment of Obesity**

Childhood obesity has become the most common pediatric disorder in the Western world. Treatment of obesity in children includes modifications in diet, increased exercise and the use of drugs. At this juncture, only orlistat (see Chapter 23, Pharmacotherapy of Obesity) is approved for use in overweight adolescents. There are no conclusive studies with metformin or sibutramine in children. Weight loss supplements are also lacking in efficacy and safety studies and thus cannot be recommended.

**Antiarrhythmic Drugs**

Arrhythmias are encountered much less frequently in children than in adults but remain important indications for pharmacotherapy in childhood. Arrhythmia therapy in children differs from that in adults because of the spectrum of arrhythmias most frequently encountered in children and the differences in pharmacokinetics and specific effects of antiarrhythmic drugs between children and adults. In addition, the strategy for fetal arrhythmia drug therapy given via the mother and the cardiac electrophysiologic effects of commonly used psychotropic medications in childhood also make discussion of this topic in childhood unique.

The most frequently encountered arrhythmia requiring treatment in children without congenital structural heart disease is supraventricular tachycardia (SVT). Ventricular tachycardia (VT) is a relatively uncommon occurrence in children, but knowledge about predisposing genetic cardiac channelopathies is accumulating rapidly. After corrective surgery for congenital heart defects, SVT, atrial flutter, atrial fibrillation, and VT can all occur.
Children with complex congenital heart disease are living longer postoperatively with an increasing incidence of arrhythmias with increasing age. Atkins et al recently extensively reviewed evidence-based drug therapy of arrhythmias in children and adults.\textsuperscript{217}

**Overview of Arrhythmia Diagnoses in Children**

**Supraventricular Arrhythmias**

SVT is the most frequent significant arrhythmia of childhood, with an estimated incidence of 1 in 250 to 1 in 1000.\textsuperscript{218} The most common electrophysiologic mechanisms are atrioventricular and atrioventricular nodal reentry. In the hemodynamically unstable patient, electrical cardioversion is indicated. If the patient with SVT is hemodynamically stable after a trial of vagal maneuvers, intravenous adenosine is the drug of choice for acute conversion to sinus rhythm. Adenosine works by blocking conduction in the AV node, breaking the re-entrant circuit. Its very short half-life necessitates that a sufficient dose reach the heart quickly, requiring a rapid intravenous push at a fairly proximal site.\textsuperscript{219} Intravenous procainamide and amiodarone have also been shown in children to be effective and may be used if adenosine is unsuccessful or unavailable. Intravenous verapamil may be used but not in patients younger than 1 year, because of reported cardiovascular collapse. For prevention of subsequent episodes, digoxin, beta blockers (propranolol, atenolol), verapamil, flecainide, and amiodarone may all have a role. In the presence of pre-excitation (Wolff-Parkinson-White syndrome), digoxin should be avoided because it can accelerate conduction along the bypass tract. Transthoracic radiofrequency ablation, however, has become an increasingly popular alternative to chronic pharmacologic therapy.

Atrial flutter and atrial fibrillation occur infrequently in infants and children without structural heart disease, but are increasingly encountered in children with surgical repairs involving extensive atrial suturing and consequent scarring (Mustard, Senning, Fontan, or TAPVR repair). Electrical cardioversion is the definitive therapy and indicated for hemodynamic instability, although care must be taken to follow anticoagulation guidelines\textsuperscript{220} in order to prevent thromboembolic complications. For pharmacologic rate control or conversion to sinus rhythm, several therapies including beta blockers, calcium-channel blockers, digoxin, amiodarone, procainamide, flecainide, and sotalol may all be effective. Therapy is determined by the presence or absence of pre-excitation and the hemodynamic status.

Junctional ectopic tachycardia may be encountered after open-heart surgery and may be treated by intravenous amiodarone, procainamide, or digoxin, along with cooling and decrease or cessation of catecholamine infusions.

**Ventricular Tachycardia**

In children, VT is encountered much less frequently than SVT but does occur in certain settings, including abnormalities of cardiac ion channels (the prolonged QT syndrome, catecholaminergic polymorphic VT, and Brugada syndrome), after cardiac surgery involving ventricular suturing (eg, tetralogy of Fallot repair), arrhythmogenic right ventricular dysplasia, and a variety of cardiomyopathies. Hemodynamically unstable VT warrants electrical cardioversion. In the hemodynamically stable child, effective acute drug therapy for monomorphic VT includes intravenous amiodarone, procainamide, or lidocaine. Polymorphic VT, specifically, torsades de pointes, may be treated by intravenous magnesium, pacing, beta blockers, or isoproterenol. Other polymorphic VT may be treated by intravenous lidocaine, amiodarone, procainamide, sotalol, beta blockers, or phenytoin. Pulseless VT and ventricular fibrillation are electrically cardioverted, but if refractory to electroshock, the arrhythmias can be treated with epinephrine, intravenous amiodarone, lidocaine, procainamide, or magnesium.

Chronic therapy for VT may include beta blockers, mexiletine, amiodarone, or phenytoin, depending upon the substrate. The role of implantation of automatic cardioverter/defibrillator devices in children at risk for VT or fibrillation is increasing.\textsuperscript{221}

**Prolonged QT Syndrome**

Prolonged QT syndrome is characterized by prolongation of the QT interval, predisposing to polymorphic VT (torsades de pointes) and possible sudden death.\textsuperscript{222} The prolonged QT interval is caused by abnormalities of transmembrane sodium and/or potassium currents due to abnormal function of cardiac ion channels. The congenital long QT syndrome is familial in at least 75% of cases. The earliest familial syndromes described included the Romano Ward (autosomal dominant associated with normal hearing) and Jervell and Lange-Nielsen (autosomal recessive with sensorineural deafness) syndromes.\textsuperscript{223} Mutations on specific genes that determine specific abnormalities in proteins that control cardiac ion channel functions and lead to different subtypes of long QT syndrome continue to be identified and have most recently totaled 11. The most common types are LQT1 (KCNQ1), LQT2 (HERG), and LQT3 (SCN5A). Subtypes may correlate with clinical manifestations, prognosis and even determine the most effective pharmacologic therapy.\textsuperscript{219}

Acute therapy is aimed at the prevention of sudden death by terminating VT and its immediate reinitiation, while chronic therapy is targeted at preventing torsade. Beta-blockade continues to be the mainstay of chronic therapy of all subtypes of long QT syndrome, as it has
proven effective in 75% to 80% of patients. Noncardioselective beta blockers such as propranolol have been used for a long time, and nadolol has become increasingly popular due to its prolonged duration of action requiring only once-daily dosing, enhancing adherence. Propranolol is equal to other beta blockers in providing effective treatment for symptoms and ventricular arrhythmias and is similar in terms of incidence of late sudden death. The sudden death risk is not related to the type of other beta blocker used. However, despite full-dose beta blockers, 20% to 25% of patients continue to have syncopal episodes and remain at a high risk for sudden cardiac death. Cardioselective agents such as atenolol have also been used, but there have been recent reports of treatment failures with atenolol. In patients with LQT3, sodium channel agents, such as mexiletine, have been reported to be more effective than beta blockers, and some patients benefit from combined therapy.

Additional therapies have been suggested and studied, including potassium supplementation and spironolactone for long QT2, a subtype involving an abnormality of the rapid inward potassium channel. In vitro, magnesium inhibits early-after depolarizations and may play a role in suppressing reinitiation of torsades de pointes. Since bradycardia or long pauses may potentiate the tachycardia and are important risk factors, ventricular pacing and isoproterenol infusion can be important chronic and acute adjunctive therapies, respectively. Lidocaine infusion has variable results. Experimental data have suggested that calcium-channel blockers may be of some acute benefit, but they are not commonly utilized. For those patients unresponsive to medications, high thoracic left sympathectomy has been used. An international prospective study provided evidence that left cardiac sympathetic denervation is a very effective therapy. Implantation of automatic internal defibrillators have played an increasing role in the treatment of children with near sudden death or break-throughs on beta blocker therapy.

Children with asymptomatic long QT syndrome on EKG should be treated with beta-blockade since cardiac arrest may be the first symptom. This differs from adults where the majority of patients have syncopal episodes before a cardiac arrest. The authors noted that ineffective treatment, particularly for symptoms, was a predictor for later symptoms and sudden death. Also, it has been noted that ineffective treatment with one agent likely predicted ineffective therapy with other pharmacologic agents. Hence, lack of clinical response to even one drug should prompt the clinician to consider alternative therapies, including pacing or left-cardiac sympathetic denervation. Children with syncope and/or symptomatic ventricular tachycardia on beta-blocker therapy should have placement of an automatic internal defibrillator and may be considered for sympathetic denervation. After automatic internal defibrillator implantation, beta-blocker therapy is continued.

Specific Antiarrhythmic Drugs

When selecting an appropriate antiarrhythmic drug, finding pediatric drug-dosing guidelines can be challenging. Antiarrhythmic medications can have different pharmacokinetics and effects in infants and children than they do in adults. Historically, the use of antiarrhythmic medications in children often have been extrapolated from adult studies, although attempts are being made to collect pediatric data. In the following discussion, the Vaughan Williams classification of antiarrhythmics will be used. The electrophysiologic actions of the drugs are summarized in Chapter 17, Antiarrhythmics.

Class IA Agents

Procainamide

Procainamide is approved for use in ventricular tachycardia and has a role in the management of supraventricular tachycardia, atrial flutter, and fibrillation. It prolongs the action potential and QT interval but not as much as quinidine. Also, it has weaker autonomic effects, which include less anticholinergic activity and no α-adrenergic blocking action. Procainamide does act as a mild ganglionic blocker and thereby may cause peripheral vasodilation and a negative chronotropic effect. Animal studies show that unlike quinidine in neonates, higher concentrations of procainamide are necessary to produce effects similar to those on adult myocardium.

Procainamide may be used intravenously. It is rapidly absorbed following oral administration, with peak plasma concentrations achieved in about 75 minutes. Unlike quinidine, only 20% of procainamide is protein bound. Conventional and sustained-release forms are available. More than 50% of the drug is excreted unmetabolized in the urine. The rest undergoes N-acetylation to form N-acetyl procainamide (NAPA), which is then excreted in the urine. The rate of metabolism corresponds to a genetically determined acetylator phenotype. NAPA itself displays class III antiarrhythmic properties. Whereas NAPA’s parent drug exerts its effect on both the duration and the upstroke of the action potential, NAPA’s electrophysiologic effect is limited to its ability to prolong the action potential.

Procainamide has a significantly shorter elimination half-life in children (1.7 hours) than in adults. Its cardiovascular adverse effects in children are similar to quinidine. However, torsades de pointes is less frequent and appears to be dose-related. Gastrointestinal adverse effects occur less often than with quinidine, but can still limit the utility of the drug. Approximately one-third of
patients can develop a lupus-like syndrome with fever, rash, and thrombocytopenia after 6 months of therapy, and up to 70% of patients will develop antinuclear antibodies, conditions that are reversible with cessation of therapy. Slow acetylators carry an increased risk for developing adverse effects from treatment. Amiodarone may increase plasma levels of propranolol.  

Disopyramide
Not only does disopyramide exert class IA antiarrhythmic effects, but it also exhibits a pronounced negative inotropic effect. In fact, it has recently been used successfully in children with hypertrophic obstructive cardiomyopathy to reduce outflow tract gradients. In addition, it exhibits much greater anticholinergic activity than the other class IA agents. It is administered orally, is well absorbed, and is subject to first-pass hepatic metabolism. Apparent age-related differences in the ability of pediatric patients to maintain therapeutic disopyramide serum levels have been noted. Whereas older children may achieve satisfactory levels after being given 5 to 15 mg/kg/day, children younger than 2 years may require as much as 30 mg/kg/day to obtain the same levels.  

The cardiovascular adverse effects are similar to quinidine. It also may precipitate CHF due to its negative inotropic actions. Gastrointestinal adverse effects occur less frequently than with the other class IA agents. Anticholinergic adverse effects do occur and the drug does not increase serum digoxin levels. 

Class IB Agents
Lidocaine
Lidocaine is useful in the treatment of ventricular tachyarrhythmias by suppressing delayed after depolarizations, but has no use in the management of SVTs. Canine studies reveal that neonatal fibers require greater lidocaine concentrations to achieve the same effects on the action potential as that seen in adult dogs. Lidocaine is less effective in reducing conduction velocity in young, as compared to adult, Purkinje fibers, and the time constant of recovery from rate-dependent conduction delay in intact newborn canine heart is notably shorter than in the adult. Lidocaine is not administered orally as it undergoes extensive first-pass hepatic metabolism. Its half-life, which is related to hepatic blood flow, is approximately 3.2 hours in neonate versus 1.8 in adults. Adverse effects appear to be dose-related and may occur at plasma levels as low as 5 μg/mL. Most commonly, CNS symptoms (confusion, dizziness, and seizures) occur and can be avoided by reducing the infusion rate and by monitoring drug serum levels. With serum levels exceeding 9 μg/mL, even more serious reactions have been seen, including, hypotension, low cardiac output, muscle twitching, and respiratory arrest. Lidocaine may exacerbate pre-existing electrophysiologic abnormalities (AV block, sinus node dysfunction).

Mexiletine
Mexiletine has a role in the chronic oral treatment of ventricular tachycardia that had previously responded to intravenous lidocaine, as well as certain subtypes of long QT syndrome. Principal adverse effects are gastrointestinal and central nervous system-related. Also in this class, phenytoin has been used as an antiarrhythmic agent for chronic therapy of ventricular arrhythmias after cardiac surgery and for treating digoxin-induced arrhythmias.

Class IC Agents
Flecainide
Flecainide has been used in children to treat SVT, atrial flutter, and ventricular arrhythmias. Some of flecainide electrophysiologic effects appear to be less pronounced in the neonatal as compared to the adult myocardium. The adult CAST trial, however, raised concern about the safety of flecainide and prompted the review of the use of flecainide in children. The pediatric patient with ventricular arrhythmias and structural heart disease most closely parallels the profile implicated in the CAST trial, namely the adult with ventricular arrhythmias after myocardial infarction. In their comprehensive review of the use of flecainide in children, Perry and Garson concluded that in pediatric patients with SVT (excluding atrial flutter) and normal hearts, flecainide appeared to be both effective and safe (no deaths with usual oral dosing and less than 1% serious proarrhythmia). In patients with atrial flutter or ventricular arrhythmias with structurally abnormal hearts, flecainide may not be safe. However, for those patients with ventricular arrhythmias and structurally normal hearts, the safety of flecainide has yet to be established.  

The elimination half-life of flecainide manifests age-dependence. Although children between 1 and 12 years have a mean elimination half-life of 8 hours, pediatric patients outside of that age range have a longer elimination half-life of 11 to 12 hours. The therapeutic flecainide dose is 100 to 200 mg/m2/day or 1 to 8 mg/kg/day. The risk of toxicity is increased in patients who require high doses of flecainide because of persistently low plasma trough levels, and in those patients whose diet changes so that it includes fewer milk products, which can result in increased flecainide absorption.

Propafenone
In addition to its possessing the electrophysiologic properties of flecainide, propafenone exerts a mild beta-blocking and calcium-channel blocking effects. In children, intravenous propafenone has been used to treat postoperative junctional ectopic tachycardia and congenital junctional ectopic tachycardia. It appears to be effec-
tive for treating children with SVTs, particularly those arising from an ectopic site.\textsuperscript{259} It can be given orally or intravenously. In a report by Janousek et al,\textsuperscript{260} the use of oral propafenone (mean dose 353 mg/m\textsuperscript{2}/day divided 3 times daily) effectively controlled SVTs in 41 of 47 (87\%) patients studied, most of whom were infants. This report helps give dosing guidelines (200 to 600 mg/m\textsuperscript{2}/day divided into 3 doses) for oral propafenone use. Furthermore, the authors suggest that for monitoring drug effect, measuring QRS duration is preferred over measuring drug plasma levels. Because of propafenone’s interaction with digoxin, it has been recommended that the digoxin maintenance dosage should be halved when initiating propafenone therapy in a child already taking digoxin.\textsuperscript{261,262}

Class II Agents
Beta-Adrenergic Blockers
Beta blockers have been used for years in children to treat supraventricular arrhythmias and ventricular arrhythmias. Propranolol can significantly inhibit sinoatrial (SA) node automaticity in children with normal SA node function and has had little effect, if any, on sinoatrial conduction.\textsuperscript{263} The usefulness of \(\beta\) blockade in the treatment of children with supraventricular tachycardias has been elucidated in several studies reviewed by Kornbluth and Frishman\textsuperscript{264} and are briefly summarized here.

In one study,\textsuperscript{265} in 3 of 6 children with SVT in whom digoxin treatment failed, propranolol (1 to 3 mg/kg/day) restored normal sinus rhythm. Another report\textsuperscript{266} again demonstrated the usefulness of digoxin plus propranolol in suppressing SVT in a 4-month-old girl but also illustrated propranolol’s adverse effects of bronchospasm and sleep disturbances that necessitated its discontinuation. The substitution of propranolol with metoprolol (2 mg/kg/day) yielded effective arrhythmia suppression, which was devoid of adverse effects over the next 7 months. Pickoff et al\textsuperscript{267} described 5 of 5 patients studied who had SVT inadequately controlled by digitalis and were free of arrhythmias for up to 2 years with propranolol dosed at 7 to 14 mg/kg/day, maintaining peak serum drug levels between 118 and 250 ng/mL. Dworkin et al\textsuperscript{268} reported beneficial effect in 7 of 9 children who failed to respond to other therapy (digoxin and/or quinidine and/or cardioversion) but who did respond to propranolol in doses of 0.5 to 4.0 mg/kg/day. The adverse effects that led to dosage reduction were sinus bradycardia, feeding difficulties, and worsening of ketotic hypoglycemia. Finally, Walters et al\textsuperscript{269} described 5 patients with chronic SVT who were refractory to digitalis alone but were successfully treated, without adverse effects, using the combination of digitalis and propranolol doses of 20 to 120 mg/d.

The efficacy of \(\beta\) blockade for the treatment of VT has also been documented. Propranolol has been used for the acute termination of ventricular tachycardia and chronically for the prevention of its recurrence. For chronic management, for the most part, \(\beta\)-blocking agents have not been effective when given alone but have been effective when combined with either another drug such as procainamide\textsuperscript{271} or another therapeutic modality, such as electrical pacing.\textsuperscript{272} Ayabe and Chemmongkol\textsuperscript{273} however, reported both successful acute treatment and chronic suppression of VT after 1.5 years follow-up in an infant born to a heroin addict, with continued doses of 1 mg/kg propranolol used alone.

Because of its once-a-day and twice-a-day dosing, atenolol, a \(\beta\)-selective blocker, has gained popularity for the treatment of older children and adolescents with arrhythmias, but a high incidence of adverse effects limits its usefulness. Nadolol is a nonselective beta blocker (similar to propranolol) that may also be given once daily with high effectiveness.

Esmolol, an ultrashort-acting beta blocker, is helpful in slowing an incessant SVT in children while other long-term agents are being titrated. Hypotension is a serious limitation with esmolol, especially if ventricular dysfunction already exists as a result of an incessant arrhythmia. The pharmacokinetics of esmolol in children have recently been reviewed and the authors suggest using pediatric dosing guidelines.\textsuperscript{181}

Class III Agents
Amiodarone
As in adults, amiodarone exhibits a broad spectrum of antiarrhythmic efficacy that includes the termination of SVTs and VTs. Its use, however, is limited due to its multiple, serious adverse effects, including a tendency to be proarrhythmic. Chen et al\textsuperscript{274} recently reported the successful treatment of SVT-induced cardiomyopathy in a neonate with amiodarone. Shuler et al\textsuperscript{275} reported on oral amiodarone’s safety and efficacy in 17 infants. Oral amiodarone was successful in relieving arrhythmias in 10 of 17 patients (59\%). In 3 infants with primary atrial tachycardias, the combination of amiodarone with a class IC antiarrhythmic agent was effective. In two infants, amiodarone was found to be proarrhythmic as they developed “incessant episodes” of re-entrant supraventricular tachycardia soon after the initiation of treatment. Those who “failed” amiodarone therapy were considered to have re-entrant SVTs and were sent for ablative therapy. Perry et al\textsuperscript{276} reported on the use of intravenous bolus amiodarone for life-threatening tachyarrhythmias in 10 pediatric patients. The drug was well-tolerated, devoid of significant adverse effects, and was effective in terminating rapid tachyarrhythmias in 6 of 10 patients. Among those who responded was one patient with postoperative junctional ectopic tachycardia.\textsuperscript{277}

Recently, Etheridge et al reported on 50 infants treated with amiodarone for supraventricular arrhythmias.\textsuperscript{278}
Amiodarone was felt to be highly effective with a low incidence of adverse effects. The QTc interval increased during drug loading, but no ventricular arrhythmias were encountered. There were increases in alanine and aspartate aminotransferases and in thyroid-stimulating hormone, but no clinical abnormalities in liver or thyroid function.

Other Class III Agents
Sotalol is a class III agent that is used frequently for atrial flutter and fibrillation (SVTs that are refractory to first line medications and ventricular arrhythmia). It acts as a nonselective beta blocker at low doses, but exhibits class III activity at medium-high levels. Negative inotropic effect is limiting in children with ventricular dysfunction.278

Ibutilide is a class III antiarrhythmic drug with an FDA indication for the rapid conversion of atrial fibrillation and atrial flutter to sinus rhythm. The dosage is 0.01 mg/kg intravenously over 10 minutes. The safety and efficacy of ibutilide in children has not been established.218 Dofetilide is a similar agent that can be used orally, but there is no published experience with the drug in children.

Intravenous bretylium use is reserved for patients with recurrent or refractory ventricular fibrillation. Significant hypotension may follow its administration because of the drug’s antiadrenergic properties.

Class IV Agents
Class IV antiarrhythmic drugs exert their electrophysiologic effects by blockade of the slow calcium channels.

Verapamil
Verapamil has been used in the initial treatment of SVT in older children. While the drug lengthens the action potential of mature Purkinje fibers, it shortens it in the neonatal myocardium.279 Furthermore, verapamil’s negative inotropic effect is greater on neonatal than on adult ventricular myocardium,240,241 and the drug should not be used in conjunction with beta blockers.242 Pediatric pharmacokinetic studies have shown that verapamil can have slower and faster elimination half-lives than in adults.243,244 Although as many as 44% of children develop adverse effects while on chronic oral verapamil therapy, less than 10% of those reactions are severe enough to necessitate discontinuation of the drug.245 Verapamil is contraindicated in infants younger than 1 year, however, because it may reduce cardiac output and produce hypotension and cardiac arrest.246,247

Miscellaneous Antiarrhythmics
Adenosine
Adenosine has emerged as the drug of choice for the acute termination of SVT in the hemodynamically stable infant or child in whom the use of nonpharmacologic vagal maneuvers have failed.248-250 It is an endogenous nucleoside with a very short half-life (10 seconds). Its net electrophysiologic effect is to slow the SA node firing rate and to block AV nodal conduction. It has a rapid onset of action and minimal effects on cardiac contractility. In a recent report, Ralston et al251 used intravenous adenosine in 24 patients and achieved the desired AV block in 21 (88%). The investigators demonstrated both the diagnostic and therapeutic utilities of causing AV block with intravenous adenosine. In 11 patients, AV block terminated the re-entrant tachycardia; in the remaining 10 patients, AV block allowed for proper diagnosis of the enduring atrial arrhythmias.

In a review of use of adenosine in children in the emergency room, the most effective dose was found to be between 0.1 and 0.3 mg/kg (for children greater or equal to 50 kg, 6 mg, increasing to 12 mg if unsuccessful) by rapid intravenous push. No major adverse effects, including bronchospasm and sinus arrest, were reported. Minor adverse effects, including nausea, vomiting, headache, flushing, and chest pain, were found to occur with an incidence of 22%.292 Adenosine has been demonstrated to be safe and highly effective in the management of SVT in infants and children.293

Digoxin
Digoxin is described earlier in this chapter. It is commonly used for the long-term therapy of SVT. In atrial flutter and fibrillation, it is used to lessen the ventricular response.

Fetal Arrhythmias
Currently, the most common indication for cardiovascular drug therapy for the fetus is for intrauterine SVT.25 In 1969, SVT was first implicated as a cause of fetal heart failure.294 In 1980, first report of in utero treatment of SVT appeared.295 Soon after, in the mid-1980s, with the advent of new fetal echocardiographic techniques that facilitated the detection and diagnosis of fetal arrhythmias, the treatment of fetal arrhythmias became more common.296,297

The mother will be affected by any therapy of the fetus, and maternal drug toxicity often limits the effective employment of commonly used antiarrhythmic agents for treating fetal arrhythmias. Correspondingly, difficulties in controlling fetal arrhythmias stem from difficulties in maintaining adequately high drug concentrations in the mother to provide an effective concentration in the fetus. Some newer, technically more demanding approaches for fetal drug delivery, which bypass the placenta, have been used but may confer greater risk to the fetus.

The majority of those fetuses found to have an arrhythmia have unsustained, isolated ectopy, and this rhythm constitutes about 80% of all fetal arrhythmias detected.
by echocardiography. Most of these unsustained, isolated ectopies are premature atrial contractions, isolated ventricular ectopy, and variable AV block. These arrhythmias are of little clinical significance because only 1% of fetuses will have underlying structural congenital heart disease and only 0.5% will go on to develop sustained supraventricular tachycardia. In the absence of structural heart disease, the arrhythmias are generally benign and do not necessitate drug therapy.

As mentioned above, SVT, usually generated by a re-entrant mechanism, is by far the most commonly treated fetal arrhythmia. Recently, Toro et al. postulated that atrial septal aneurysms, found in 78% of those fetuses with persistent arrhythmia, may serve as a nidus for premature atrial contractions and subsequent supraventricular tachycardias. For the viable, near-term, nonhydropic fetus developing a sustained tachyarrhythmia, delivery is the treatment. For the immature fetus, however, who exhibits pulmonary immaturity or who displays signs of CHF, pharmacotherapy should be initiated. Atrial flutter or fibrillation with variable AV block and ventricular response is less commonly treated. Digoxin is the drug of choice for the treatment of fetal SVT. It may be more effective to load the mother with digoxin intravenously rather than orally.

In the hydropic fetus, who may display increased resistance to drug therapy, it may be necessary to administer digoxin directly, that is, either intraperitoneally or via the umbilical vein. For the fetal SVT patient refractory to digoxin alone, a class IA antiarrhythmic agent such as quinidine or procainamide may be added to the maternally administered regimen. Although verapamil has been used, Klitzner and Friedman advocate against this in view of Klitzner et al.’s more recent findings, which demonstrate the fetus’ greater dependence on calcium influx to support myocardial contractility than later in life.

Bradycardias account for about only 5% of all fetal arrhythmias. Etiologies include sinus bradycardia, nonconducted premature atrial contractions, and complete heart block. In and of itself, sustained fetal bradycardia is not an indication for therapeutic intervention, and the fetus should be monitored for fetal distress. In combination with fetal distress, such as hydrops fetalis, however, sustained bradycardia may herald demise. Sustained bradycardia in a fetus with structural heart disease renders the fetus a dismal prognosis. The fetus should be delivered early and paced. Unfortunately, in utero pacing is not yet a widely available therapeutic option.

**Arrhythmias and Psychotropic Drugs in Children**

Psychotropic drugs are used with increasing frequency in children with a variety of diagnoses, including attention deficit disorder, hyperactivity, depression, and bipolar disorder. Due to reports of arrhythmias and sudden death related to the cardiac and, specifically, the cardiac electrophysiologic effects of these medications, in 1999 the AHA issued recommendations for cardiac monitoring of children being treated with certain drugs of this type, based upon knowledge of their cardiac electrophysiologic effects. Between 1999 and 2003, a number of cases of sudden death were reported in children with a variety of “cardiac conditions” in Canada who were on methylphenidate, amphetamines, or Adderall. Although the sale of Adderall was initially suspended, no causal relationship was established. Still, a block box warning was added to stimulant packaging in the United States, warning of the risk of sudden death in children with “serious heart problems” using stimulants. In 2008, the AHA issued a policy statement, addressing recommendations for assessment of patients for potential use of stimulants, recommendations for administration of medications and monitoring of patients and suggestions for future studies. It was recommended that an EKG be obtained before starting stimulants, in that it was “reasonable and useful.” Subsequently, the American Academy of Pediatrics, in agreement with the American Academy of Child and Adolescent Psychiatry and other groups, issued a policy statement, stating that a targeted history and physical examination was sufficient, without a routine electrocardiogram or pediatric cardiology consultation.

Tricyclic antidepressants can cause prolonged QTc, QRS, and PR intervals. Phenothiazines, butyrophenones, and diphenylbutylpiperidines have all been reported to prolong the QTc. Phenothiazines and tricyclic antidepressants have also been reported to cause sinus tachycardia. Clinical and electrocardiographic monitoring have been recommended for these medications.

**Special Pharmacologic Approaches**

**Patent Ductus Arteriosus**

Pharmacologic manipulation of the ductus arteriosus has become central to the treatment of neonates with congenital heart disease and to the management of premature newborns, even those with structurally normal hearts.

The ductus arteriosus is a physiologically vital channel required for normal development of fetal circulation. It is found normally in all mammalian fetuses. As lung blood flow in the fetus only amounts to less than 10% of the right ventricular output, and the right ventricle ejects approximately 65% of the combined ventricular output, the ductus arteriosus carries 55% to 60% of the...
combined ventricular output of the fetus. After birth, as the transition from fetal to normal postnatal circulation develops, the ductus arteriosus closes, first functionally then anatomically. Functional closure occurs by 24, 48, and 96 hours in 10%, 82%, and 100%, respectively, of term infants. Anatomic closure is usually finished by 2 to 3 weeks. In about 0.04% of term infants, however, the ductus fails to close and remains patent.312-314

A variety of factors are contributory to the initial closure process. These include oxygen, calcium, endogenous catecholamines, and other vasoactive compounds. The most important substances involved, however, are the prostaglandins: prostacyclin produced by the ductus arteriosus and prostaglandin E2. While prostacyclin is produced more vigorously, prostaglandin E2 is much more potent as a ductus relaxer.314 Because prostaglandin E2 metabolism by the lung is limited in the fetus, and the placenta also is a source of this hormone, relatively high circulating levels are maintained. After birth, prostaglandin E2 levels decline substantially and ductal relaxation is less well maintained allowing oxygen and other vasoconstrictors to become dominant.

The effects and counter-effects of these substances differ at different postnatal gestational ages, another factor relevant for clinical pharmacotherapeutics. In less-mature infants, the ductus is more sensitive to dilating prostaglandins. In as many as 40% of infants born weighing less than 2000 g, and as many as 80% of infants weighing less than 1200 g, the ductus remains patent after birth.315 In addition, even in term infants, any lowering of arterial PO2, such as with pulmonary disease or asphyxia, can result in delayed normal closure.316

These physiologic relationships underlie the development of pharmacologic strategies to modulate tone of the ductus. There are two distinct strategies necessitated by either the importance to augment or to reduce pulmonary blood flow in the newborn infant.

Indomethacin, as an example of a cyclooxygenase inhibitor, is currently the most widely used medication to effect closure of the ductus.317 Indomethacin is most useful in the preterm infant in whom a PDA may complicate other problems of prematurity by causing circulatory overload and even CHF. Dosage varies based on weight and age and regimens vary from center to center. Table 32-3 outlines a typical regimen.317

Indomethacin also has vasoconstrictive action in other vascular beds. In humans, these include renal and cerebral artery vasoconstriction. Gut perfusion may also be affected. In view of this activity, the preferred route of administration is by slow intravenous infusion. In particular, this approach reduces cerebral blood flow alteration.318 A similar salutary effect on renal blood flow also results from continuous infusion. While control of fluid volume including the use of diuretics had been advocated in the past, currently vigorous diuresis, such as with furosemide, is no longer thought to be useful because furosemide may enhance release of prostaglandin E1, helping to promote ductal dilation. The patent ductus arteriosus, even when treated with cyclooxygenase inhibition, can redilate, and this reopening has been linked to increasing dilator prostaglandin levels.319

Complications from indomethacin not only affect renal, cerebral, and mesenteric blood flow as noted above, but they also affect platelet and neutrophil function. In addition, bilirubin metabolism must be monitored, as indomethacin can displace bilirubin from albumin-binding sites and may influence serum bilirubin levels. Some interest has been shown in the use of other prostaglandin synthesis inhibitors, such as ibuprofen, mefenamic acid, and others,311 but use of these agents is not widespread in the United States.

Pharmacologic manipulation of the ductus to maintain patency, instead of promoting closure, has become a mainstay of the management of the newborn with certain forms of congenital heart disease. In this circumstance, the aim of therapy is to overcome the physiologic cascade that normally results in a decline in circulating dilating prostaglandins shortly after term birth. Prostaglandin E1 has become the agent of choice for this purpose. Dosages of 0.05 to 0.1 mg/kg/minute are usual, and the drug must

### Table 32-3. Indomethacin Dosing Regimen (mg)

<table>
<thead>
<tr>
<th>Age and Weight</th>
<th>0 h</th>
<th>12 h</th>
<th>24–36 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 48 h, all weights</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>2–7 d, &lt; 1250 g</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>2–7 d, &gt;1250 g</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>&gt;7 d, all weights</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Most infants should receive the third dose 24 h after the first dose; infants with poor renal function, most commonly those weighing < 1000 g, should be given the third dose 36 h after the first dose. Use the same schedule for the second course unless it is begun within 24 h of the last dose, in which case 0.1 mg/kg x 3 is used. An alternate schedule for infants < 1000 g, especially if treatment is initiated after 3 to 4 days of life, is to give 0.1 mg/kg q24h x 7 d.

be given by continuous intravenous infusion because more than 80% is metabolized on transhepatic and transpulmonary passage.

Adverse effects include apnea, bradycardia, rash, seizures, hypotension, and hyperthermia. Maintenance intravenous infusion can be extended for a prolonged period until surgery is possible for more permanent palliation. However, oral prostaglandin E₁ administration is not efficacious for long-term treatment, because the drug has a very short half-life and absorption from the gastrointestinal tract can be unpredictable. If prolonged intravenous therapy is required (usually in the preterm or low-birth-weight infant), electrolyte depletion, metabolic alkalosis, and delayed wound healing can complicate management. In addition, during prolonged prostaglandin E₁ usage, the unique x-ray finding of periosteal calcification and cortical hyperostosis involving long bones, ribs, and clavicles can develop. Fortunately, this appears to be a reversible phenomenon once prostaglandin E₁ is discontinued.

**Pulmonary Hypertension**

All children with idiopathic pulmonary hypertension require urgent treatment. The treatment algorithm is similar to that used in adults. Pharmacotherapy includes calcium-channel antagonists, prostacyclin, endotherlin receptor antagonists, and sildenafil. Most children will require combination therapy and some will need an urgent septostomy.

In the neonatal unit, the pathophysiology of pulmonary hypertension often differs from that seen in older children and adults (see Chapter 25, Prostacyclins, Endothelin Inhibitors, and Phosphodiesterase-5 Inhibitors in Pulmonary Hypertension; however, the basic principles of management are similar. Treatments include nitrix oxide, intravenous prostacyclin and its analogs, and the oral medications described above.

**Cyanotic Spells**

Certain constellations of congenital heart defects involving dynamic right ventricular outflow obstruction, can predispose infants and young children to episodes of arterial desaturation called “hypoxemic attacks” or “cyanotic spells.” Conditions including this type of dynamic, muscular subpulmonary stenosis are some forms of Tetralogy of Fallot and less commonly, tricuspid atresia. When the subpulmonary muscle contracts, resistance to right ventricular outflow increases and the relatively unsaturated blood in the right ventricle is ejected right to left through an associated ventricular septal defect into the left ventricle and the aorta, thus lowering the arterial oxygen saturation.

The initial trigger for an episode of sudden extreme cyanosis cannot always be conclusively identified, but the mechanism frequently involves decreased systemic vascular resistance, excessive endogenous catecholamine release, or both. Changes in cardiac rhythm, such as tachyarrhythmias, and peripheral vascular pooling, such as occurs with prolonged recumbent position, can also precipitate an event. Similarly, sudden or sharp pain or prolonged agitation can also lead to a hypercyanotic episode, as well as use of medications with a positive inotropic effect such as digoxin or isoproterenol.

If an acute intervention is required to ameliorate a cyanotic “spell,” morphine sulfate (0.1–1.5 mg/kg IM or IV) has been demonstrated over many years to be an effective remedy. Morphine has primary sedating effects to interfere with catecholamine production and secondary effects to slow heart rate and respiratory rate, thus favorably effecting right ventricular filling. This drug, when used in combination with implementing a “knee-chest” position to augment SVR, is often effective in improving oxygenation. Administration of 100% oxygen, used to increase the SVR, can also be helpful. If morphine, 100% oxygen, and knee- chest are not successful, pharmacologic increase of the SVR is required. For this purpose, infusion of phenylephrine, an α-agonist, at 2 to 10 mg/kg/minute is of value. When a hypercyanotic spell is persistent despite these maneuvers, general anesthesia may be required with emergency surgical augmentation of pulmonary blood to follow.

While definitive therapy for tetralogy of Fallot is surgical repair, pharmacologic management of the acute hypercyanotic episode can be critically important to allow the child to reach surgery. Long-term pharmacologic palliation of hypercyanotic spells in patients with tetralogy of Fallot and its variations is decreasingly used, coincident with advances in surgical techniques and perioperative management. Combined surgical and interventional cardiology approaches have made treatment available to many more children with even-marked pulmonary arterial bed anomalies at earlier ages. However, there still is an occasional indication for extended medical management. Because positive inotropy may result in exacerbation of a hypercontractile right ventricular outflow tract (“infundibulum”) and promote a hypercyanotic spell, positive inotropes should be avoided and agents that decrease contractility can be used to prevent spells. Beta-blockers, specifically propranolol, are particularly useful in this context. Several major studies documented the usefulness of propranolol for long-term palliation (several months’ duration), confirming suggestions first raised 15 years earlier. Potential complications, including bronchospasm, hypoglycemia, and bradycardia, must be monitored for once this therapy is initiated. Most clinicians continue beta-blocker therapy until shortly before surgery, but there
is controversy in this regard because beta blockers may adversely affect myocardial recovery postcardiopulmonary bypass.

**Conclusion**

Cardiovascular drugs evaluated in adults for clinical approval are frequently used to treat disorders in children with few therapeutic guidelines. Although most of the experiences with pediatric drug use are favorable, carefully done clinical trials need to be conducted to help guide physicians in the future drug management of cardiovascular disorders in children.

*Note: References for this chapter can be found here: www.cvpct3.com*
Pharmacotherapeutic advances in both the prevention and treatment of cerebrovascular disease have provided more favorable clinical outcomes. Primary prevention of stroke remains the optimal therapeutic strategy and includes treatment of systemic hypertension and hypercholesterolemia. For the treatment of an acute ischemic stroke, the early use of thrombolytic agents can reduce the degree of brain damage while improving functional outcomes. However, trials evaluating various classes of other neuroprotective agents have not shown benefit to date. For the prevention of second stroke, the use of antiplatelet drugs, statins, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers with a diuretic have shown benefit in reducing new events. In patients with underlying heart disease and/or atrial fibrillation, warfarin appears to be the drug of choice in preventing stroke. However, newer anticoagulants have shown promise as potential alternatives to warfarin. Early treatment of hemorrhagic stroke with calcium channel blockers can improve the functional outcome. Innovative therapies are now available for the treatment of migraine headache and vascular dementia.

In this chapter the pathophysiology of cerebrovascular disease is discussed and the various pharmacotherapies to prevent and treat cerebrovascular disease are reviewed.

**Anatomy and Physiology**

Cerebrovascular disorders comprise diseases of the circulation supplying the brain. Circulation to each cerebral hemisphere is provided by the right and left carotid arteries. The carotid arteries bifurcate into the internal and external carotid arteries in the neck before the internal carotid artery penetrates the skull. This is the most common site for the formation of atheromatous disease. The internal carotid artery bifurcates intracranially into the anterior cerebral artery supplying the midline structures and the middle cerebral artery, which extend over the convexities of the frontal, temporal, and parietal lobes. The vertebral arteries supply the inferior portion of the brainstem and cerebellum and form the basilar artery, which supplies the upper brainstem and cerebellum as well as the occipital lobe, posterior parietal lobe, and thalamus through its terminal branches, the posterior cerebral arteries.

There is extensive collateral circulation to the cerebral hemispheres through the Circle of Willis at the base of the brain. The two anterior cerebral arteries connect through the anterior communicating artery so that one carotid artery can supply blood to both cerebral hemispheres. The basilar artery circulation connects to the carotid circulation through the posterior communicating arteries, so that the carotid arteries can feed the basilar circulation or the basilar artery can feed the carotid circulation. There are also extensive sources of collateral flow from the external carotid arteries to the cerebral hemispheres through anastomoses with the ophthalmic arteries and meningeal arteries. Therefore, an occlusion of a major artery can be tolerated in patients who have normal collateral channels.

The pathophysiology of ischemic cerebrovascular disease is closely related to ischemic cardiovascular disease, but the properties of the organ involved are considerably different. The myocardium is homogeneous and performs a single function. The brain consists of a variety of structures with different metabolic demands, sensitivities to ischemic insult, and chemical constituents that can act as neurotoxic agents.

The cerebral cortex consists primarily of neuron cell bodies (gray matter) with a high metabolic demand and an appropriately high rate of normal blood flow.
Immediately below the cortical mantle is the centrum semiovale containing myelinated axons (white matter), which are electrically excitable tissues but have a lower metabolic demand and requirement for blood flow (10ml/100gm/min). Surrounding the axons are support tissues, the glia, which also have a lower metabolic rate than excitatory neurons. In the center of the cerebral hemispheres are gray matter structures, the basal ganglia (caudate, putamen, and globus pallidus), and the thalamus, along with the primary descending white matter tracts from the cerebral hemispheres, the internal capsule.

Pathophysiology of Ischemic Stroke

Ischemic infarction accounts for about 85% of strokes (Table 33-1). The etiology of ischemic stroke is cardioembolic 20%, large-vessel atheroembolic 20%, small-vessel intracranial thrombosis 20%, unusual causes 5%, and cryptogenic 30%, in which a definite cause cannot be identified, although most of these are probably cardioembolic or from small-vessel disease. The sources of ischemic stroke are summarized in Figures 33-1 and 33-2.

The cerebral cortex is supplied by extensive collateral circulation. Most ischemic events leading to the infarction of the cerebral cortex are embolic, with thrombus occluding the trunk or distal branches of the middle and anterior cerebral arteries beyond the Circle of Willis. The sources of these emboli are mainly thrombi from the left atrium in patients with atrial fibrillation or valvular heart disease, thrombi from an akinetic ventricular wall with myocardial infarction (MI) or cardiomyopathy, or atheromatous emboli from the cervical carotid artery bifurcation or ascending aorta.

Cortical infarction can be identified by imaging procedures of the brain, such as computerized axial tomography (CAT Scan) or magnetic resonance imaging (MRI). When a cortical infarction is identified, a cardiogenic source is suspected, which may be identified by electrocardiography and echocardiography, often by the transesophageal route, to visualize the left atrial appendage. Occult sources of cerebral emboli, such as right-to-left shunts through a patent foramen ovale, an atrial septal defect, or an atrial septal aneurysm, can be visualized with contrast enhancement during transesophageal echocardiography.

The subcortical white matter and basal ganglia are supplied by small end arteries and arterioles and do not have extensive collateral circulation. Ischemia leading to infarction in these regions is usually produced by thrombosis of small end arteries and arterioles that have thickened proliferative walls caused by diabetes mellitus and hypertension. Small white matter infarcts secondary to intracranial small vessel disease are often referred to as lacunar strokes because they leave small “holes” in the brain.

Occasionally, hemodynamic changes can induce brain ischemia and infarction, either during cardiogenic hypoperfusion (valvular heart disease, arrhythmia) or when
there is large-vessel occlusive disease without good collateral circulation. These infarcts are usually in watershed areas between the distal branches of the arteries to the cortex, which both supply the same area, such as the junction of the middle and posterior cerebral artery territories or the middle and anterior cerebral artery territories. The basal ganglia and hippocampus on the mesial surface of the temporal lobe are also selectively vulnerable regions of brain that are subject to ischemic infarction during global ischemia that does not permanently affect other regions of the brain.

Ischemic cerebrovascular disease can also be induced by spasm of vessels. This has been observed directly in transient ischemia of the retina. Vasospasm is implicated in migraine attacks, which can sometimes lead to cerebral ischemia. Vasospasm is also a complication of subarachnoid hemorrhage. Ischemic cerebrovascular disease can also be caused by inflammatory diseases. Systemic collagen vascular disease can produce a vasculitis that directly affects cerebral vessels or produce a hypercoagulable state through antiphospholipid antibodies or the lupus anticoagulant. A primary granulomatous angiitis of the central nervous system also causes cerebral ischemia. Hematologic disorders, such as protein C, protein S, and antithrombin III deficiencies, as well as sickle cell disease can lead to stroke.

Pathophysiology of Hemorrhagic Stroke

Intracranial hemorrhage accounts for about 10% of strokes (Table 33-1). There are two main types of intracranial hemorrhage: intracerebral (75%) and subarachnoid (25%). Small intracranial arteries and arterioles can develop a weakness in the media secondary to hypertension, which can lead to aneurysm formation (Charcot-Bouchard aneurysms). This may result in intracerebral hemorrhage, usually in the region of the basal ganglia. Hemorrhage into the cortex is often associated with amyloid deposition in cortical arteries and cerebral amyloid angiopathy and frequently accompanies Alzheimer’s disease. Lobar cortical hemorrhage is also seen with hemorrhage into a prior embolic infarction (hemorrhagic infarct) or with septic emboli from endocarditis. Platelet abnormalities, including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, and thrombocytopenia, can also lead to cerebral hemorrhage, sometimes in addition to cerebral infarction when there is a concurrent consumption coagulopathy.

The major arteries supplying the brain from the Circle of Willis are not inside the brain parenchyma but lie in the subarachnoid space between the arachnoid and the dura. “Berry” aneurysms form primarily at the bifurcations of vessels from the Circle of Willis from congenital weakness of the vessel walls at these locations. The primary sites are at the origin of the anterior communicating artery and the posterior communicating arteries. Bleeding from these aneurysms results in subarachnoid hemorrhage. Arteriovenous malformation, in which arteries feed directly into veins without flow through a capillary bed, is another cause of subarachnoid hemorrhage.

Drug Therapy of Ischemic Cerebrovascular Disease

The treatment of cerebrovascular disease must be directed at both the vascular pathology causing ischemia and the diseased organ, the brain.

Prevention of Ischemic Stroke

The modalities for prevention of occlusive cerebrovascular disease are similar to those for coronary artery occlusive disease. Primary prevention of ischemic stroke is aimed at patients with risk factors for cerebrovascular disease who are not yet symptomatic. Secondary prevention is aimed at patients who have become symptomatic with transient episodes of cerebral ischemia lasting up to 24 hours; transient monocular blindness (amaurosis fugax); reversible ischemic neurologic deficits lasting more than 24 hours; or mild stroke with no significant disability. Aneurysmal subarachnoid hemorrhage, although very insensitive, can identify patients with pre-existing vascular occlusive disease in the carotid arteries prior to the onset of symptoms.

Control of Risk Factors

The most significant risk factor for causing cerebrovascular disease is systemic hypertension. Occlusive vascular disease of intracranial arteries and small arteries produced by hypertension accounts for almost 50% of
The risk of stroke over a 10-year follow-up period. The impact of blood pressure control on stroke prevention in elderly subjects, treatment of combined systolic and diastolic hypertension has also been shown to reduce the risk of stroke.

A large meta-analysis of antihypertensive drug trials involving over 40,000 participants was performed to detect differences in benefit from blood pressure reduction between sexes. A strong and statistically significant reduction in the relative risk of total and fatal strokes was found in both men and women. Absolute risk reduction appeared to be dependent on baseline risk more than any other factor, and thus, the authors stressed a need to accurately predict individual patient cardiovascular risk in order to institute effective therapy. The trials in this meta-analysis used thiazide diuretics and beta-blocking agents as principal therapies for reducing blood pressure.

The Hypertension Optimal Treatment (HOT) randomized trial used the calcium channel blocker felodipine. Nearly 20,000 participants were followed for an average of 3.8 years and were assigned to a target diastolic pressure using felodipine as initial therapy, with the addition of up to 4 other agents to achieve target diastolic blood pressures. The lowest risk of stroke was observed at systolic pressures less than 142 mmHg and diastolic pressures below 80 mmHg. To achieve the maximal benefit in diabetics, more aggressive control of systolic blood pressure was required. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) recommends a combination of lifestyle changes and drug treatment to avoid hypertension-related strokes.

A case-controlled study compared the control of hypertension in 595 patients who suffered a stroke to the control of hypertension in 2,966 aged-matched, randomly selected stroke-free patients. Blood pressure was adequately controlled in 78% of 460 ischemic stroke cases and 85% of 95 hemorrhagic stroke cases. The authors estimated that 27% of the ischemic strokes and 57% of the hemorrhagic strokes among treated hypertensive patients were attributable to uncontrolled blood pressure and that uncontrolled blood pressure accounted for 32% of the overall number of strokes.

Treatment of isolated systolic hypertension has been shown to reduce the risk of stroke in the elderly. The Systolic Hypertension in Europe Trial (Syst-Eur) showed a significant reduction in the incidence of both lacunar and hemorrhagic stroke in elderly patients treated with a thiazide class diuretic and additional atenolol 25 mg or 0.05 mg reserpine as needed to reduce systolic blood pressure by at least 20 mmHg to below 160 mmHg. The Systolic Hypertension in Europe Trial (Syst-Eur) showed a significant reduction in the incidence of stroke in elderly patients treated with the long-acting calcium-channel blocker nitrendipine.

However, caution must be applied in treating elderly patients, since aggressive lowering of diastolic blood pressure below 65 mmHg may actually increase the risk of stroke. The risk of stroke also increased with elevated diastolic blood pressure and the lowest risk for stroke for elderly patients was in the range of 140/80 mmHg.

In the treatment of hypertension, the overall reduction in blood pressure appears to provide the greatest benefit in the prevention of stroke and cognitive decline. Diuretics and calcium antagonists have been shown to be of benefit in reducing the risk of stroke; however, the

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**Table 33-2. Pharmacotherapy of Ischemic Cerebrovascular Disease**

<table>
<thead>
<tr>
<th>Primary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of hypertension</td>
</tr>
<tr>
<td>Therapy of patients with atherosclerotic disease:</td>
</tr>
<tr>
<td>Platelet antiaggregants, HMG-CoA reductase inhibitors and other serum lipid lowering agents</td>
</tr>
<tr>
<td>Anticoagulation with warfarin in patients with cardioembolic source (atrial fibrillation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Prevention (Patients with transient cerebral ischemic attack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet antiaggregation for atherothrombotic disease: aspirin, dipyridamole, ticlopidine, clopidogrel</td>
</tr>
<tr>
<td>Cardiogenic embolism: warfarin</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with diuretics</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
</tr>
</tbody>
</table>

**Treatment of Ischemic Stroke**

| Neuroprotective agents: investigational calcium channel blockers, NMDA receptor antagonists, lazaroids, AMPA receptor antagonists, glutamate release inhibitors, free radical scavengers |
| Anticoagulation: antiplatelet drugs, heparin, low-molecular-weight heparin, warfarin, Corticosteroids, antioxidants for cerebral edema |
| Antihypertensives |
| Anticonvulsants for seizures |
| Thrombolytics: tissue plasminogen activator |

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strokes. Early diagnosis and control of mild to moderate hypertension in young adults can significantly reduce the risk of stroke over a 10-year follow-up period. The impact of blood pressure control on stroke prevention increases over time. Unlike coronary artery disease (CAD), where some antihypertensive agents may be more effective in preventing ischemic heart disease than others, it is the absolute quantitative reduction in blood pressure that accounts for the benefit, regardless of the agent employed. In elderly subjects, treatment of combined systolic and diastolic and isolated systolic hypertension has also been shown to reduce the risk of stroke.

A large meta-analysis of antihypertensive drug trials involving over 40,000 participants was performed to detect differences in benefit from blood pressure reduction between sexes. A strong and statistically significant reduction in the relative risk of total and fatal strokes was found in both men and women. Absolute risk reduction
use of beta blockers in the elderly may not be as beneficial as other antihypertensive therapies in preventing stroke. ACE inhibitors have also been shown to be of benefit in reducing the risk of stroke in high-risk patients, including ramipril in the Heart Outcomes Prevention Trial (HOPE),44 the combination of perindopril and indapamide in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS),46,47 and Hypertension in the Very Elderly Trial (HYVET) studies.48 In addition, the combination of indapamide and perindopril was associated with reduced risks of dementia and cognitive decline.49,50

Angiotensin II receptor blockers have also been shown to be of benefit in stroke prevention as demonstrated with losartan in the Losartan Intervention for Endpoint Reduction in Hypertension trial (LIFE),51 the combination of perindopril and indapamide in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS),46,47 and Hypertension in the Very Elderly Trial (HYVET) studies.48 In addition, the combination of indapamide and perindopril was associated with reduced risks of dementia and cognitive decline.49,50

Diabetes is also a significant risk factor for intracranial vascular disease.61 Although it has never been directly demonstrated that strict control of blood sugar is effective in the primary prevention of cerebrovascular disease, it has been documented to be effective in the prevention of diabetic retinopathy, which occurs on a similar basis to small artery occlusive disease.62 It was demonstrated in a subgroup analysis with pioglitazone that treatment with this drug in the PROactive Trial reduced the risk of recurrent stroke in high-risk patients with type 2 diabetes mellitus.63 It has also been shown that high blood glucose at the time of stroke is deleterious to the preservation of neurons in the ischemic area,64 so that strict control of glucose in diabetics may reduce the severity of infarction once cerebral ischemia occurs.

Little information is available on significant risk factors for stroke in younger patients. An epidemiological study of people younger than age 45 was conducted and identified non-traumatic arterial dissection, rather than premature atherosclerosis or hypertension, as a likely cause of large-vessel occlusive stroke in these patients.57 Other causes include cardioembolic strokes from a patent foramen ovale,58 the use of phenylpropanolamine,59,60 hypercoagulable states such as anticardiolipin antibody syndrome, and pregnancy-related stroke. More data will be needed on stroke etiology in this age group before ideal therapies can be developed.

Table 33-3 Antithrombotic Therapy for Stroke Prevention

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommended Therapy</th>
<th>Acceptable Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA or stroke</td>
<td>A 50-325 mg/d</td>
<td>A-D 25-200 mg BID, C 75 mg</td>
</tr>
<tr>
<td>TIA or stroke during aspirin therapy or contraindication to aspirin</td>
<td>C 75 mg/d</td>
<td>W INR 2-3, A-D 25-200 mg BID</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>W INR 2-3</td>
<td>A 50-325 mg; Dab 150 mg BID</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>W INR 2-3</td>
<td>A 50-325 mg (if W is contraindicated)</td>
</tr>
<tr>
<td>Valvular AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>W INR 2.5-3.5</td>
<td>A 50-325 mg</td>
</tr>
<tr>
<td>Asymptomatic Carotid Stenosis</td>
<td>A 50-325 mg/d</td>
<td>C 75 mg/d</td>
</tr>
<tr>
<td>Asymptomatic People &gt;60 years of age</td>
<td>No therapy</td>
<td>A 50-325 mg/d, C 75 mg/d</td>
</tr>
</tbody>
</table>

A, aspirin; C, clopidogrel; A-D, aspirin-dipyridamole combination; d, day; AF, atrial fibrillation; Dab, dabigatran

3-hydroxy-3-methylglutaryl co-reductase (HMG-CoA) inhibitor simvastatin showed a significant 33% reduction of stroke. Additionally, the Cholesterol and Recurrent Events (CARE) trial of over 4,000 post-MI patients with average cholesterol levels demonstrated a significant risk reduction in stroke among men and women treated with pravastatin. The Scandinavian Simvastatin Survival Study (4S) studied 4,444 patients with CAD and high cholesterol. A post hoc analysis of the data showed significant reduction in transient ischemic attack (TIA) and stroke by 30%, but for stroke alone it was not statistically significant.

Several meta-analyses have been conducted on clinical trials of cholesterol reduction with HMG-CoA reductase inhibitors to determine their effect on stroke. A strong and statistically significant effect on stroke reduction among secondary prevention trials was noted in all five analyses, although only a mild and nonsignificant trend towards reduction was observed in primary or mixed primary-secondary trials. Interestingly, among those trials that studied both fatal and nonfatal subgroups, a trend towards an increase in fatal stroke was observed on treatment. It has been suggested that perhaps non lipid-lowering properties of statins such as plaque stabilization, fibrinolytic effects, and alteration of endothelial function may have a greater effect on stroke incidence than their effect on cholesterol.

Analysis of stroke prevention in the Long-Term Intervention with Pravastatin in Ischemic Disease Study (LIPID) demonstrated a 23% risk reduction for ischemic stroke and a 19% risk reduction for overall stroke including hemorrhage. There was no increase in the risk of hemorrhage with pravastatin. Analysis of the etiology of stroke suggested that the risk reduction was due primarily to prevention of cardioembolic events from atrial fibrillation and ventricular thrombus secondary to myocardial infarction (MI) rather than from reduction in atherothrombotic strokes.

Cholesterol reduction with high-dose atorvastatin has been shown to reduce the rate of recurrent stroke, in addition to patients with stable CAD and those having diabetes mellitus. Therefore, all patients with symptoms of cerebrovascular disease or who are at risk for cerebrovascular disease are generally treated with cholesterol-lowering medications (see Chapter 20, Lipid-Lowering Drugs). However, in patients with a previous history of cerebral hemorrhage, statins are probably contraindicated.

Dietary factors may also play a factor in the risk of stroke. High dietary content of beta carotene, an antioxidant, has also been shown to be associated with a reduced risk of stroke. However, in clinical trials, beta carotene and the antioxidant alpha-tocopherol have no effect on the risk of stroke. Plasma homocysteine levels have been found to be elevated to 20 to 40 umol/L in patients with cerebrovascular disease. Homocysteine levels can be reduced by treatment with folic acid 200 µg/day; however, there have been no trials to document that a reduction in homocysteine with folic acid treatment lowers the risk of stroke.

Despite the many treatments that exist for the prevention of stroke, much information on its exact etiology and risk factors are still lacking. With that in mind, the Prospective Studies Collaboration of 45 prospective trials involving over 450,000 patients was conducted to clearly delineate the relation of cholesterol, blood pressure, and stroke. Unfortunately, it was unclear in many of these studies if stroke events were either fatal or nonfatal. Therefore, although no association was observed between serum cholesterol level and stroke, the author suggested that a positive relationship with ischemic stroke and a negative relationship with hemorrhagic stroke and increasing cholesterol levels may have been obscured. It has been suggested by several previous observational studies that a J shaped curve exists for the relationship of cholesterol and stroke mortality, where ischemic stroke increases at high cholesterol levels and hemorrhagic stroke risk increases at low cholesterol levels.

Low cholesterol may also be a risk factor for ischemic stroke. In a study of Japanese men, patients with stroke from large vessel atherosclerotic disease had an increased serum total cholesterol (mean 200 mg/dL), but patients with lacunar type stroke from small vessel disease had a low serum total cholesterol (mean 177 mg/dL).

Finally, menopause can be considered a risk factor for vascular disease. Post-menopausal women who take estrogen replacement therapy have lower rates of CAD than women without replacement therapy. To see whether hormone replacement could reduce the risk of stroke, the Heart and Estrogen-Progestin Replacement Study (HERS) was undertaken to study potential cardiac benefits of this therapy in postmenopausal women with previous MI. After 4 years of follow-up in nearly 2,800 women, no significant differences in rates of MI, CAD-related death, stroke, or TIA's were found. This was despite an 11% net decrease in low-density lipoprotein cholesterol and 10% increase in high-density lipoprotein cholesterol.

In a primary prevention study, the Women’s Health Initiative (WHI), there was also a significant reduction in plasma cholesterol with estrogen and estrogen plus progesterone replacement therapy; however, an increased risk of cerebrovascular events was seen with active replacement treatment compared to the placebo.

**Platelet Antiaggregation Therapy**

See Chapter 18, Antiplatelet and Other Antithrombotic Drugs.
Aspirin

Platelet antiaggregant therapy has been shown to be an effective method in preventing stroke in patients presenting with TIA. Aspirin irreversibly inhibits platelet aggregation by preventing the formation of the aggregating agent thromboxane from arachidonic acid by the enzyme cyclooxygenase.

In 1978, the Canadian Cooperative Study Group trial was one of the earliest studies to show the effectiveness of aspirin. It reported a 50% reduction of stroke in males with TIA at a dose of 650 mg orally twice daily. However, the reduction in risk of stroke for females was not significant. This led to trials of lower doses of aspirin on the presumption that the higher dose of aspirin was also inhibiting the formation of prostacyclin, another product of cyclooxygenase present in arterial walls that prevents thrombosis.

The proper dosage of aspirin for secondary prevention of stroke remains controversial. Several studies, including the United Kingdom Transient Ischemic Attack (UK-TIA), Dutch TIA trial, and the Swedish Aspirin Low-Dose Trial (SALT), showed equivalent efficacy of both low and higher dose aspirin in terms of vascular benefit. However, the studies indicated decreased incidence of adverse effects (ie, bleeding) with the lower doses; therefore, lower doses are preferred.

Aspirin ranging from 283 to 1200 mg/day also failed to show an advantage over a dose of 30 mg/day. In 1998, both the US Food and Drug Administration (FDA) and the American College of Chest Physicians published guidelines for the use of aspirin at a dose of 50 to 325 mg per day for secondary stroke prevention. On the other hand, a comparison of studies using aspirin at doses below 975 mg/day with studies using doses of aspirin greater than 975 mg/day showed a significantly greater reduction in the incidence of stroke at the higher dosage groups in patients with transient ischemic attacks.

The role of aspirin for the prevention of stroke in women is under contention. Although the Canadian Cooperative Study Group concluded no significant beneficial effect was found among females, a later meta-analysis of studies employing a higher dose of aspirin showed a beneficial effect in women as well as men. This suggests that the number of women in the sample of the Canadian Cooperative Study was too small to show significant results. Additionally, both a recent review and a meta-analysis have shown an equal benefit for both men and women for the secondary prevention of stroke.

Aspirin is often used to prevent cerebral vascular events in patients with asymptomatic carotid artery stenosis identified by the presence of a cervical vascular bruit on auscultation or by Doppler ultrasound techniques. However, in patients with TIAs who have a carotid stenosis greater than 60%, surgical therapy is generally recommended.

There are many other guidelines for the use of aspirin. Aspirin has not been shown useful for primary prevention of stroke in patients with acute MI because the absolute risk reduction is only on the order of 0.5-2% per year. Warfarin is often the drug of choice to prevent a stroke immediately following an acute MI. However, aspirin is recommended to prevent recurrent MI, so many patients still are prescribed aspirin.

With regard to the primary prevention of stroke, studies that employed aspirin for the primary prevention of CAD were examined. In one study, patients with coronary disease treated with aspirin did have a significant relative reduction in the incidence of stroke, indicating that aspirin may be useful for the primary prevention of stroke in patients with atherosclerotic vascular disease. However, in more recent studies, there was no significant reduction in the incidence of stroke, and perhaps a slight increase because of hemorrhagic stroke. Therefore, aspirin cannot be advocated for the primary prevention of stroke in patients without risk factors.

Only the HOT trial studied the effects of aspirin in hypertensive patients. This trial used aspirin at 75 mg per day concurrently with antihypertensive therapy. The risk of acute MI was reduced, but there was no effect on stroke. Therefore, the authors recommended aspirin only with antihypertensive therapy for primary prevention of MI in hypertensive patients.

Aspirin has been tried as an agent, much like intravenous thrombolytics, to minimize damage from an acute ischemic stroke event as well as to prevent recurrent strokes. Two large multicenter trials, the Chinese Acute Stroke Trial (CAST) and International Stroke Trial (IST), together included over 40,000 participants suffering from acute ischemic stroke who were treated with medium dose aspirin (160 to 300 mg per day) within 48 hours of stroke onset. Both trials observed a significant decrease in recurrent ischemic events and a nonsignificant trend towards an increase in cerebral hemorrhage. Each trial additionally demonstrated a trend towards reduction of death and dependency. The data from these two trials suggest that aspirin should be started as early as possible after an acute ischemic stroke not only to prevent stroke recurrence but also to decrease overall mortality.

A combined analysis of these two trials demonstrated that a significantly greater number of patients acutely treated with aspirin returned to a near normal functional recovery compared to untreated patients at 3 months after stroke onset. There was a reduction in stroke or death of 0.9%. Recurrent stroke was reduced by 33%. Therefore, acute aspirin therapy is recommended for patients with stroke who have no contraindications for aspirin therapy and do not require anticoagulation.

Ticlopidine

Another platelet antiaggregant drug, ticlopidine, was
developed for patients with gastrointestinal disease who could not tolerate aspirin and for women in which aspirin may not have been adequate protection. Ticlopidine inhibits platelet aggregation by blocking the adenosine diphosphate (ADP) receptor, preventing platelet aggregation to a greater spectrum of in vitro stimuli than aspirin and prolonging the bleeding time in vivo to a greater extent.\textsuperscript{127} Ticlopidine was shown to be more effective than aspirin in preventing stroke in patients with TIA with a risk reduction of 48% after 1 year and 25% after 5 years.\textsuperscript{128} Subgroup analysis showed that aspirin and ticlopidine were both equivalently effective in men and in patients with carotid artery disease, but ticlopidine was more effective than aspirin in women, in patients with intracranial small-vessel disease, and in blacks.\textsuperscript{129} However, a further study of ticlopidine compared to aspirin for prevention of secondary stroke in black patients showed no significant difference with a trend showing that aspirin may have been superior.\textsuperscript{130} When compared with indobufen, in patients with previous TIA, amaurosis fugax, or minor stroke, ticlopidine proved superior in prevention of death and nonfatal events.\textsuperscript{131} Therefore, ticlopidine can be used as a first-line drug for secondary stroke prevention as well as in patients who cannot tolerate the adverse effects of aspirin or in whom aspirin is not working. Ticlopidine has also been shown to be effective in tertiary prevention of recurrent stroke in patients who have already had a stroke with a 33% risk reduction after 1 year and a 25% risk reduction after 3 years compared with the placebo.\textsuperscript{132}

The major complication of aspirin therapy is gastrointestinal hemorrhage, which can be monitored by stool guaiac testing and following serum hemoglobin. Ticlopidine must be monitored more carefully, since 2% of patients encounter significant neutropenia during the first 3 months of therapy. A white blood count must be followed every 2 weeks for the first 3 months of therapy and the drug discontinued if the neutrophil count is progressively dropping below 1200/mm\textsuperscript{3} or falls below 800/mm\textsuperscript{3}. Thrombocytopenia can also occur to a lesser extent and must also be monitored. In addition, hepatitis has been encountered, so liver function tests must be examined on a regular basis. Almost all adverse effects of ticlopidine occur within the first 3 months of therapy\textsuperscript{128} and must be considered before use. However, life-threatening thrombotic thrombocytopenic purpura has been reported with an incidence of 1 in 8000.\textsuperscript{133} Therefore, ticlopidine is currently rarely used since the availability of clopidogrel, a new platelet antiaggregant with the same mechanism of action.

**Clopidogrel**

Clopidogrel is a thienopyridine compound structurally related to ticlopidine. After oral administration, clopidogrel is rapidly absorbed and metabolically activated by the liver. It works by blocking the ADP receptor, thereby irreversibly inhibiting the binding of fibrinogen to the platelet receptor (glycoprotein IIb/IIIa).\textsuperscript{134} In 1996, a large international trial, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE), was conducted to assess the effect of clopidogrel on participants with either recent ischemic stroke, recent MI, or symptomatic peripheral vascular disease as compared to aspirin. For the 19,185 participants studied over 1.91 years, the relative risk reduction over aspirin of primary ischemic events was 8.7% and achieved statistical significance. In the peripheral artery disease subgroup, the drug showed a significant beneficial effect in the reduction of vascular-related events over the aspirin group as compared to the recent stroke and MI groups. This suggests that the benefit of clopidogrel may not be identical across the 3 subgroups.\textsuperscript{135} A later analysis of the CAPRIE findings indicated that subgroup outcome heterogeneity was due to chance.\textsuperscript{136} In contrast to aspirin, efficacy was superior, and there were fewer findings of abnormal liver function or gastrointestinal hemorrhage.

As for clopidogrel versus ticlopidine, efficacy appears to be comparable; however, clopidogrel has both an easier once a day dosing regimen as well as an improved safety profile when compared to the potentially serious complication of bone marrow suppression caused by ticlopidine. A recent report has identified a 4-per-million risk of thrombotic thrombocytopenic purpura in participants taking clopidogrel, which is slightly higher than the natural incidence of the disorder, and has not been considered a contraindication to use.\textsuperscript{137} However, a recent review of the CAPRIE trial demonstrated no evidence that clopidogrel has a better effect than aspirin on stroke and death rates in secondary prevention.\textsuperscript{136}

The combination of clopidogrel with aspirin has been found to be more effective than aspirin alone in preventing recurrence in participants with acute coronary syndrome.\textsuperscript{138} It was also suggested that the combination of clopidogrel and aspirin was more effective in preventing asymptomatic cerebral embolization than aspirin alone.\textsuperscript{139} However, this combination has not been shown to reduce recurrent stroke when compared to clopidogrel alone\textsuperscript{140} or aspirin alone.\textsuperscript{141} A phase 2 trial of immediate treatment of stroke participants within 24 hours has shown preliminary data that the combination of clopidogrel and aspirin may be superior to aspirin in the acute setting.\textsuperscript{142} However, the rate of significant hemorrhage with the combination of aspirin and clopidogrel was 2% higher than aspirin or clopidogrel alone, so that overall events were significantly higher with combination therapy.\textsuperscript{134,140,141} Therefore, the combination of clopidogrel with aspirin is not recommended for treatment of stroke patients.

**Dipyridamole**

Dipyridamole prevents platelet aggregation by inhibition of phosphodiesterase.\textsuperscript{144} Dipyridamole has an established
use for prevention of embolic events from prosthetic cardiac valve replacements. In 1969, a trial of dipyridamole showed that it had no effect in preventing stroke in participants with TIA. In more recent trials, when used in combination with low-dose aspirin (25 mg twice daily), dipyridamole has been shown to reduce the risk of stroke by 37% in participants with prior ischemic stroke or TIA, which is a substantially larger benefit than either low-dose aspirin or dipyridamole alone, with a 23% relative risk reduction compared to aspirin.

These trials, as well as two meta-analyses of secondary preventative trials using aspirin and dipyridamole suggest that dipyridamole has an efficacy similar to that of low-dose aspirin in reducing the risk of stroke and death, and the combination of the two agents is additive. This combination is approved for clinical use and its efficacy has recently been confirmed by another randomized trial. However, a trial comparing combination of low-dose aspirin/time release dipyridamole combination to clopidogrel showed no difference in efficacy for preventing recurrent ischemic stroke. Therefore, either clopidogrel or aspirin extended-release dipyridamole combination therapy can be used when aspirin is not sufficient in patients at high risk for cerebrovascular disease.

New Antiplatelet Drugs

Sarpogrelate is an antiplatelet agent having a selective antagonist effect on 5-HT\textsubscript{2A} receptors. In the Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS), aspirin was found to be superior to sarpogrelate except in diabetic participants.

Triflusal is an antiplatelet drug structurally related to aspirin that exerts its antithrombotic actions by working on platelet aggregation targets and vascular inflammation. In two recent secondary prevention trials, it was shown to have similar actions to aspirin in preventing recurrent stroke. Other antiplatelet drugs being evaluated for secondary prevention of noncardioembolic ischemic stroke include cilostazol, new P\textsubscript{2}Y\textsubscript{12} ADP receptor antagonists including prasugrel, cangrelor and AZD6140, the thromboxane receptor antagonist terutroban, and the thrombin receptor PAR-1 antagonist SCH530348.

Anticoagulation Therapy

See Chapter 18, Antiplatelet and Other Antithrombotic Drugs.

Warfarin

Anticoagulation with warfarin has long been established for prevention of stroke in patients with atrial fibrillation and mitral stenosis. The Stroke Prevention in Atrial Fibrillation Trial (SPAF) also demonstrated a beneficial effect of aspirin prophylaxis 325 mg per day for participants younger than 75 years who did not have associated cardiovascular risk factors such as ventricular hypertrophy. For patients older than 75, warfarin is superior to aspirin in preventing ischemic stroke, but in the SPAF trial, the risk of hemorrhage in these elderly participants negated the beneficial effect of anticoagulation. However, the level of anticoagulation in this trial was higher than in the other trials as measured by the international normalized ratio (INR). In another trial, fixed minidose warfarin and aspirin, alone and in combination, were compared to the currently recommended warfarin only therapy (INR 2.0–3.0) for atrial fibrillation participants, but no advantage with either treatment was found. In another trial, a lower degree of anticoagulation with INR of 1.7 to 2.0 has been demonstrated to be effective. Considering all available evidence, anticoagulation of elderly or high-risk patients to establish an INR in the range of 2.0 to 2.5 is usually sufficient to prevent stroke without an inordinate risk of hemorrhage.

Warfarin has often been recommended for primary prevention of stroke in patients with nonvalvular atrial fibrillation. Clinical guidelines for primary prevention of stroke in patients with atrial fibrillation suggest that warfarin should be used in patients with risk factors for stroke: increasing age, hypertension, diabetes mellitus, congestive heart failure, and previous TIA; for those patients without risk factors, aspirin at 325 mg per day is used. In patients who cannot tolerate warfarin therapy, the combination of aspirin and clopidogrel was superior to aspirin alone for prevention of stroke in atrial fibrillation but not as effective as warfarin. Warfarin may also protect against MI in patients with atrial fibrillation receiving stroke prophylaxis.

Stroke prevention with warfarin is possible in many forms of cardiac disease. Patients with cardiac valve replacement are routinely treated with warfarin for prevention of embolic stroke. Warfarin has also been beneficial in preventing stroke during the first 3 months after MI, although aspirin is more commonly used for long-term prophylaxis. A meta-analysis of 5 major trials that used warfarin in post-MI participants revealed that warfarin reduced the risk of stroke by 64%, but the benefit was unclear in participants older than 75. Current guidelines suggest warfarin should be used to prevent stroke after MI in patients with atrial fibrillation, left ventricle thrombi, or compromised left ventricular function.

A major trial, WARCEF (Warfarin vs Aspirin in Patients with Reduced Cardiac Ejection Fraction), is under way to compare aspirin and warfarin to prevent stroke and death in patients with reduced left ventricular function who are in sinus rhythm.

In participants with atherothrombotic stroke or small vessel lacunar stroke that is not cardioembolic, warfarin has not been found to have any greater efficacy than aspirin.
Cardiovascular Pharmacotherapeutics

In a retrospective review, anticoagulation with warfarin has been shown to be superior to aspirin for prevention of stroke in participants with TIA or prior stroke who have large-vessel intracranial vascular occlusive disease. However, a randomized trial of aspirin compared to warfarin for prevention of recurrent stroke in participants with intracranial stenosis was terminated prematurely because of an increased mortality rate in the warfarin-treated group that was not due to cerebral hemorrhage, while a significant reduction in ischemic stroke was not realized. Warfarin may have some efficacy in patients with atherosclerosis of the thoracic aorta determined by echocardiography, but this seems to be limited to patients in which mobile thrombus on the surface of the plaque is visualized, which is a rare occurrence.

New Anticoagulants

New anticoagulants are in development that may be more convenient to use than warfarin in stroke prevention. Two direct thrombin inhibitors have been studied in participants with atrial fibrillation and have shown comparability to warfarin for stroke prevention with a potential safety advantage in bleeding. Ximelagatran is not being tested further because of hepatotoxicity. Dabigatran was recently approved for clinical use. Oral factor Xa inhibitors are also being studied in clinical trials (see Chapter 18, Antiplatelet and Other Antithrombotic Drugs). These drugs do not manifest all the drug–drug interactions of warfarin, and do not require anticoagulation monitoring.

Treatment of Ischemic Stroke

The first step in the treatment of ischemic stroke is to recognize and control any associated life-threatening medical conditions. Occasionally, patients with massive hemispheric strokes or brainstem strokes have difficulty maintaining adequate respiration, and intubation is necessary, but pulmonary complications such as aspiration pneumonia can be prevented in most patients by keeping the patient NPO (nothing by mouth). An electrocardiogram and cardiac monitoring are necessary to rule out a concomitant MI or arrhythmia. Sudden death has been reported in patients with large strokes involving the insula and amygdala in the medial temporal lobe, probably secondary to cardiac dysfunction induced by systemic catecholamine release. Patients with infarction in this brain region should be carefully monitored.

Extremely high blood pressure (ie, 220/130 mmHg) should be gradually lowered to a moderate range (ie, 180/100 mmHg). Lowering the blood pressure too drastically may worsen ischemic infarction. Therefore, intravenous labetalol, clevidipine, or nicardipine are used to titrate a gradual reduction of blood pressure rather than nitrous oxide–donating agents. Most stroke patients have some acute elevation of blood pressure that does not need to be treated because it resolves spontaneously within a

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Table 33-4. Stroke and Oral Anticoagulants Following Myocardial Infarction*

<table>
<thead>
<tr>
<th>Study</th>
<th>WARIS170</th>
<th>Sixty Plus†170a</th>
<th>ASPECT171</th>
<th>Aggregate</th>
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<tbody>
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<td>Target INR</td>
<td>2.8-4.8</td>
<td>2.7-4.5</td>
<td>2.8-4.8</td>
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</tr>
<tr>
<td>Event Rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke*</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo %/yr</td>
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<td>1.3</td>
<td>1.0</td>
<td>1.5</td>
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<tr>
<td>Anticoagulants %/yr</td>
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<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
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<tr>
<td>CNS Hemorrhage</td>
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<td></td>
<td></td>
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<tr>
<td>Placebo %/yr</td>
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<td>0.04</td>
</tr>
<tr>
<td>Anticoagulants %/yr</td>
<td>0.3</td>
<td>0.9</td>
<td>0.3</td>
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</tr>
</tbody>
</table>

*Unspecified strokes in Sixty Plus study and ASPECT are included with ischemic strokes; † = patients in the Sixty Plus study had been treated with anticoagulants for a mean of 6 years between the qualifying myocardial infarction and study entry.

few days. Hypotension from shock or gastrointestinal bleeding must be addressed. Control of blood glucose to 120 mg/dl or below may be beneficial in reducing the morbidity and mortality from stroke. In patients who are not ambulatory, prophylaxis for deep vein thrombosis should be administered, preferably with low-molecular-weight heparins.

The next step is to determine the etiology of the stroke: large-vessel atheroembolic or occlusive disease, small-vessel occlusive disease, or cardiogenic embolism. For most patients with an ischemic stroke, anticoagulation is not necessary and early treatment with aspirin should be initiated. Acute antiplatelet therapy with the glycoprotein IIb/IIIa receptor antibody abciximab was associated with an unacceptable high rate of cerebral hemorrhage and is not recommended for clinical use.

**Treatment of Vascular Occlusive Stroke**

Patients with both large- and small-vessel athero-occlusive disease are usually treated acutely with aspirin for prevention of recurrent stroke. When symptoms are fluctuating or gradually progressive, indicating a vulnerable region of ischemia that has not yet infarcted, anticoagulation with heparin is sometimes initiated. In fact, up to 40% of patients continue to have deterioration of neurologic function during the 4 days following initial ischemic stroke. Suggested causes of this deterioration include cerebral edema, changes in cellular metabolism, thrombus extension, and decay of the ischemic penumbra.

The theory behind heparin use is to prevent thrombus extension. The partial thromboplastin time (PTT) is usually maintained in the range of 50 to 60 seconds, or 1.5 to 2.0 times the patient’s baseline PTT. When the PTT is spuriously elevated, as in the anticardiolipin syndrome, the clotting time can be used to monitor the anticoagulant activity. The usual starting dose is 1000 U/hr and a bolus injection of 5000 U is usually not given because of the risk of intracranial hemorrhage, particularly in elderly patients. Heparin therapy is usually continued for 7 to 10 days. Depending on the etiology of the stroke, either warfarin or platelet antiaggregant therapy is started prior to discontinuing the heparin for chronic maintenance of stroke prophylaxis. The results from a study that compared warfarin to aspirin for the prevention of recurrent ischemic stroke showed no difference between treatments.

Early trials of heparin anticoagulation for evolving stroke were based on studies that were not controlled in a double-blind comparison protocol. Although it has not been definitively established that heparin was successful in this situation, it seems to be of more value in large vessel occlusive disease of the internal carotid or basilar artery than in small-vessel occlusive disease. In two studies, acute heparinization of all participants with ischemic stroke regardless of subtype did not show a significant benefit. A randomized controlled trial of low-molecular-weight heparin (danaparoid) for the treatment of acute ischemic stroke demonstrated that despite an early benefit from therapy, no improvement in outcome was observed after 3 months. There was some beneficial effect in patients with large vessel occlusive diseases. In contrast, a report from Kay et al demonstrated the efficacy of low-molecular-weight heparin in acute ischemic stroke when used within 48 hours of the onset of symptoms. The IST, a study using aspirin and subcutaneous heparin for acute ischemic stroke, demonstrated that heparin conferred no benefit at 6 months time. Treatment with tinzaparin, a low-molecular-weight heparin, within 48 hours of an acute ischemic stroke did not improve functional outcome compared with aspirin after 10 days of therapy.

Ischemic stroke is sometimes associated with increased blood viscosity. Hemodilution with low-molecular-weight dextran and hydroxyethyl starch has been attempted but has not been shown to significantly improve outcome in controlled trials.

**Thrombolytic Therapy**

Acute coronary artery occlusive disease had been routinely treated with thrombolytic therapy until the advent of acute therapy with coronary stents. In the brain, thromboembolic phenomena are the major cause of ischemic stroke. It is theorized that rapid thrombolysis may restore blood circulation to the affected brain tissue, preventing further loss of function.

**Streptokinase**

Three major trials have studied the effects of streptokinase in the setting of acute ischemic stroke. The Multicenter Acute Stroke Trial-Italy (MAST-I) was a trial of streptokinase used within 6 hours of symptoms which was stopped during randomization due to safety concerns. The Multicenter Acute Stroke Trial-Europe (MAST-E) was of similar design and was terminated early due to an increase in mortality and cerebral hemorrhage. Also terminated early, the Australian Streptokinase Trial (ASK) was designed to give intravenous (IV) streptokinase within 4 hours of onset. After 3 months, there was no difference in outcome between treatment and placebo groups, but mortality and hemorrhagic transformation were significantly higher with streptokinase.

However, patients treated within 3 hours of stroke onset had less disability than those treated later and no increase in mortality over the placebo. Because of this...
unfavorable experience, streptokinase currently has no role in treatment of ischemic stroke.  

**Tissue Plasminogen Activator**

Currently, the FDA has licensed the use of tissue plasminogen activator (tPA) for the treatment of stroke within 3 hours of onset. This recommendation followed the results of the National Institute of Neurological Disorders and Stroke (NINDS) study in 1995. Eligible participants had clear clinical evidence of acute stroke and no evidence of hemorrhage by computed tomography (CT) of the brain. This trial of intravenous recombinant tPA 0.9 mg/kg administered within 3 hours demonstrated an absolute 11% to 13% improvement in disability at 3 months as measured by Rankin scale, Barthel index, Glasgow outcome scale, and the NIH Stroke Scale.

Equally important, there was no associated increase in mortality, although intracranial bleeding was more prevalent on treatment. During the first year following FDA approval, an open-label study examined the use of tPA on participants who fit the NINDS criteria for ischemic stroke. The study demonstrated similar results to NINDS and thus supports the use of tPA in acute ischemic stroke. Kwiatkowski et al now report longer-term outcomes with the use of tPA within the same time limits.

A second large trial, the European Cooperative Acute Stroke Study (ECASS), used recombinant tPA within 6 hours of onset of ischemic stroke. No statistically significant benefit in function was found at 3 months and there was a trend towards increased mortality and hemorrhagic transformation. However, many participants included in the study were not appropriate for treatment, and when these participants were excluded from the analysis, a significant benefit with tPA could be demonstrated. The ECASS study was repeated with adherence to strict NIH entry criteria, but still using a 6-hour window, and similar results were obtained. The data from these trials support the use of tPA under limited conditions and in patients who meet the most stringent criteria within 3 hours of onset.

There is further evidence that early administration of thrombolytic therapy is more effective than delayed administration. Administration of rt-PA between 3 and 5 hours after ischemic stroke conferred no benefit because of hemorrhagic complications. A secondary analysis of the NIH tPA trial determined that administration of tPA had most significant effect when administered 90 minutes prior to the onset of stroke. After 90 minutes, administration of tPA may not have been significantly better than the placebo because participants in the treated group had milder neurological deficits than the placebo group, making them more likely to experience spontaneous recovery. However, recent studies have demonstrated some continued efficacy of administering tPA intravenously up to 4.5 hours after onset of stroke without significantly increasing the risk of bleeding, though the efficacy for successful outcome was lower than when tPA is administered within the 3-hour window. An experience is developing using thrombolytic therapy in participants who wake up with stroke; however, additional study is needed.

Thrombolytic therapy must be used judiciously because there is significant risk of adverse outcome from hemorrhagic complications, particularly brain hemorrhage. Thrombolytic therapy can be administered safely in patients over 80 with no increase in complication rate as long as the NIH guidelines for administration are carefully followed. A review of administration of rt-PA in 389 patients documented that at 30 days after onset of stroke, 35% of patients had a favorable outcome and 43% were functionally independent. However, the mortality rate was 13%. The incidence of intracranial hemorrhage was 3.3%, resulting in 7 deaths. Favorable outcomes were associated with less severity of stroke, those younger than 85 years, lower mean arterial blood pressure and absence of changes of early infarction on computerized tomography of the brain. However, this review surveyed participants primarily treated in academic centers.

A review of the use of tPA in a community setting determined that only 1.8% of patients admitted with ischemic stroke received tPA. The in-hospital mortality rate was 15.1% for patients receiving tPA, significantly higher than the rate of 5.1% in untreated patients. The increase in mortality was mainly due to intracranial hemorrhage, which occurred in 11 of the 70 treated patients.

Thrombolytic therapy has established benefit in treatment of ischemic stroke when administered appropriately. Strict adherence to established guidelines for administration should be followed. Caution should be used in administering tPA 90 minutes after the onset of stroke. Thrombolytic therapy should be avoided in participants over 85, participants with elevated mean systolic blood pressure greater than 140 mmHg, patients with reduced level of consciousness indicating large hemispheric stroke, and patients with early changes of infarction on CAT scan of the brain.

**Pro-urokinase**

Recombinant prourokinase (rpro-UK) has been tested in a limited manner for treatment of acute ischemic stroke. It had been successfully used for acute thrombosis of a cerebral vessel during angiography or in an acute basilar artery thrombosis prior to irreversible infarction. This information spurred broader clinical trials of rpro-UK. A recent placebo-controlled trial, Prolyse in Acute Cerebral Thromboembolism (PROACT), studied participants with angiographically defined middle cerebral artery lesions who received 6 mg rpro-UK and heparin intra-arterially. Recanalization of occluded arteries was associated with therapy, and a trend towards improved neurologic out-
come and mortality was observed at 90 days. Although an increase in cerebral hemorrhage was observed with treatment, the frequency appeared to be related to the dosage of heparin, and no statistically significant difference between treated and placebo groups was ultimately seen at 24 hours or 90 days.227 Prou-UK is currently not available for use, and intra-arterial thrombolytic therapy is performed using tPA, with similar efficacy,226 although a randomized, double-blind clinical trial has not been performed.

Thrombolytic Studies in Progress

Thrombolytic therapy alone is being compared to the combination of thrombolytic therapy and the use of intra-arterial devices. Newer thrombolytics are undergoing phase 2 and 3 studies for acute stroke that include desmoteplase, alteplase, and tenecteplase.136 These newer agents may provide more rapid recanalization and a lesser risk of hemorrhage.

Ancrod

Ancrod is a fibrinogen-depleting agent derived from snake venom. It was shown to be of benefit in patients if infused within 3 hours of stroke onset.227 In a randomized, controlled study of 500 participants, 42.2% of participants receiving ancrod had a favorable outcome compared to 34.4% in the placebo group at 90 days. There was no difference in mortality in treated and untreated participants. The risk of intracranial hemorrhage was 5.2% in treated participants compared to 2.0% for untreated participants. However, ancrod is administered over 72 hours, and the treatment regimen requires constant monitoring of plasma fibrinogen to maintain levels between 1.18 and 2.03 umol/L.

Treatment of Cardioembolic Stroke

Anticoagulation is indicated to prevent recurrent stroke or systemic thromboembolism in patients with a definite cardiogenic source of embolization, such as atrial fibrillation.136 The timing of the initiation of heparin therapy is controversial. Stroke patients with atrial fibrillation are at about a 4% risk of re-embolization during the first week after the initial stroke.228 However, they are at about an 8% risk of serious hemorrhage into the infarcted area associated with clinical deterioration, and the severity is exacerbated by acute heparin therapy.228 The degree and frequency of hemorrhagic complications is directly proportional to the size of the infarct.229

When there is any focal neurologic deficit, it is currently recommended to delay heparin therapy for 48 hours, since most of the hemorrhagic complications occur within this time frame. A CAT scan of the brain is repeated, and if the infarct is not large (ie, involving more than one lobe of the brain), and there is no hemorrhage, heparinization can be started. If the infarct is large, or there is evidence of hemorrhage, heparinization is delayed for several days but can still be instituted while there is residual chronic hemorrhage on the CAT scan.230

Heparin therapy can be initiated if the clinical deficits have resolved or are very mild and the CAT scan is negative for hemorrhage. However, it must be remembered that the CAT scan may not show evidence of infarction for up to 24 hours after stroke, even when a sizable region of ischemia exists. Therefore, the absence of an infarct on an early CAT scan does not necessarily mean that immediate anticoagulation can be given safely.

In instances where there is a large thrombus in the left atrium seen by echocardiography or a mechanical valve replacement, heparin can be administered acutely because the risk of re-embolization is higher than the risk of hemorrhagic complications. Heparin is not used in embolic endocarditis because the risk of hemorrhage from mycotic aneurysms is too high and anticoagulation has not been found to be beneficial.231

Warfarin therapy is usually started a few days after heparin therapy and is gradually regulated to maintain the INR in a therapeutic range of 2.0 to 3.0 for atrial fibrillation and 3.0 to 3.5 for valvular heart disease. When a steady state has been established, usually in 3 to 5 days, heparin can be discontinued.

The low-molecular-weight heparin, enoxaparin, administered 1 mg/kg twice a day subcutaneously, can be employed as a bridging anticoagulant while the warfarin dosage is being established.232 Significantly fewer participants experienced worsening of their neurological condition and there were significantly fewer adverse events compared to intravenous heparin.232 Length of stay was reduced by 3.6 days. Therefore, use of low-molecular-weight heparin may have greater efficacy and less risk than anticoagulation with intravenous heparin in prevention of recurrent cardioembolic stroke.

Treatment of Complications of Ischemic Stroke

Cerebral Edema

Patients with large cerebral infarctions often become somnolent 24 to 48 hours after stroke. This usually occurs with occlusion of an internal carotid artery or embolic occlusion of the middle cerebral artery. Two factors contribute to this delayed alteration in level of consciousness: (1) A depression of blood flow to the entire brain, including the contralateral cerebral hemisphere, can occur; this is referred to as diaschisis,233 a condition that reverses spontaneously; and (2) when there is reperfusion of a large infarcted area, cerebral edema can occur.234

There are two types of cerebral edema, cytotoxic and vasogenic. Cytotoxic edema occurs acutely with ischemic stroke, secondary to swelling of neurons and glia.234 However, the total brain volume decreases during this phase. Vasogenic edema, with fluid accumulation in the extracellular space, occurs 24 to 48 hours after infarction.234 Often,
cerebral edema resolves without any exacerbation of the ultimate outcome, and antiedema treatment with corticosteroids has been found to be of no significant value when administered to all patients with ischemic stroke.235

When the degree of somnolence caused by edema is so great that the airway is threatened or the patient is in danger of brain herniation, dexamethasone 4 mg IV every 6 hours can be administered,236 although it is usually preferable to employ osmotic diuretics or hypertonic saline to reduce cerebral edema. In acute situations; where the patient has developed acute pupillary abnormalities and is in imminent danger of herniation, the osmotic diuretic mannitol, 100 g IV over 4 hours237 or glycerol, 50 g in 500 mL of 5% glucose,238 can be administered. Mannitol can be used only within the first 24 hours before a rebound effect occurs, but glycerol, either IV or orally by nasogastric tube, can be employed on a chronic basis. A hypertonic solution of 3% saline can also be effective in reducing cerebral edema without the risk of rebound.239

Epileptic Seizures
Ischemic brain injury can produce an irritative epileptic focus in about 10% of stroke patients.240 When seizures develop acutely but are self-contained, a loading dose of phenytoin, 1000 mg IV (15 mg/kg), is given in saline at a rate of 50 mg/minute. Chronic therapy is maintained with phenytoin, 100 mg by mouth or IV three or four times a day, to maintain a serum level of 10 to 20 mg/L plasma. Continuous seizures can be treated with benzodiazepines acutely (diazepam 5 to 10 mg IV or the longer-acting lorazepam 1 to 2 mg IV), until phenytoin can take effect.241 Phenobarbital is sometimes necessary to control protracted generalized seizures or focal seizures that do not respond to phenytoin.240 Up to 300 mg (5 mg/kg) can be administered IV acutely without the necessity for endotracheal intubation and the serum level maintained at 20 to 40/100ml with doses of 30 mg PO or IV three or four times a day. If seizures continue, general anesthesia with barbiturates or volatile gases is sometimes necessary.

Vascular Dementia
Ischemic vascular dementia is a common, long-term complication of stroke. Dementia is defined as deterioration from a known or estimated prior level of intellectual function sufficient to interfere broadly with the conduct of the patient’s customary affairs of life. Ischemic vascular or multi-infarct dementia is essentially defined as dementia associated with evidence of two or more ischemic strokes by history, neurologic signs, and/or neuroimaging studies or the occurrence of a single stroke with a clearly documented temporal relationship to the onset of dementia. In addition, arterial stiffness and increased pulsatile flow may be associated with cognitive decline.242 The diagnosis of vascular dementia is suggested in a demented patient having evidence of multiple infarcts in brain regions known to affect cognition; a history of multiple transient ischemic attacks; and a history of vascular disease risk factors (eg, systemic hypertension, previous coronary bypass surgery, heart disease, or diabetes mellitus). Ischemic vascular dementia can be seen in patients with existing Alzheimer’s type dementia.243

There is no definitive medical or surgical treatment for vascular dementia. Modalities to prevent ischemic stroke, as described previously, would reduce the incidence of vascular dementia, especially the control of elevated blood pressure.244-246 Once vascular dementia occurs, continued control of risk factors for stroke may be useful. Of interest, patients with known vascular dementia may improve when systolic blood pressure is maintained at the 135-150 mmHg range with daily adjunctive aspirin (325 mg) rather than lowering pressure below these values.247-248

Pharmacologic strategies being evaluated for protecting the brain from ischemia include many of those interventions described previously for preventing ischemic complications of acute stroke and include pentoxifylline, a hemorheological agent,249 and propentofylline, an adenosine uptake phosphodiesterase inhibitors.250 Nimodipine has been used with some success.251 The acetyl cholinesterase inhibitor donepezil252 and a modulator of nicotine receptors galantamine were efficacious on all key areas of cognitive and noncognitive abilities in participants with vascular dementia.253-254 A previous trial with bromocriptine, a dopamine enhancer, was negative.255

Cerebral Neuroprotection
Innovative clinical strategies are being developed to protect neurons from ischemic damage (Table 33-5 and Figure 33-3) and are being utilized with and without thrombolysis in patients with stroke.256 The final common pathway for ischemic neuronal death appears to be influx of calcium. Calcium enters cells from stimulation of the N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acids glutamate and aspartate, which are released during cerebral ischemia.257 This influx of calcium is not inhibited by calcium channel blockers and is believed to be the main source of calcium responsible for ischemic neuronal death.258 Noncompetitive NMDA receptor antagonists (aptiganel, dextorphan, ramacemide, magnesium) are currently in clinical trials but are difficult to manage because of their psychotic effects.259 A competitive NMDA receptor antagonist, selfotel, has not been effective in improving ischemic stroke.260 The glycine site inhibitor gavestinel has not been shown to be effective for ischemic stroke in an international trial.261 and the results of the North American Trial were similar in showing no benefit of this therapy.262 Inhibition of the initial ischemic release of glutamate is also being evaluated with the sodium channel blocker riluzole, the anticonvulsant lamotrigine, and BW619C89.263
The calcium influx from NMDA receptor stimulation causes delayed neuronal death occurring at about 8 hours after the onset of ischemia. The initiating event for the excitotoxic ischemic cascade induced by glutamate appears to be the influx of sodium induced by stimulation of the AMPA (kainic acid) glutamate receptor site. Siesjo has hypothesized inhibition of the AMPA site by phosphonates such as APV and quinoxaline diones such as NBQX. In animal models, NMDA receptor antagonists have been more effective in reducing infarct volume in models of focal ischemia that are analogous to arterial occlusive disease. AMPA receptor antagonists have been more effective in reducing infarct volume in models of global ischemia analogous to cardiac arrest or hypovolemic shock. The mechanisms for cerebral neuroprotection are summarized in Figure 33-4.

Table 33-5. Neuroprotective Agents Studied in Clinical Trials

<table>
<thead>
<tr>
<th>Category</th>
</tr>
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<tbody>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>Calcium-channel blockers (nimodipine, nicardipine)</td>
</tr>
<tr>
<td>Glucose-insulin-potassium</td>
</tr>
<tr>
<td>NMDA receptor antagonists (selfotel, dextorphan, cerestat, eliprodil, caffeine, magnesium, lamotrigine, glycine site antagonists)</td>
</tr>
<tr>
<td>Lubeluzole</td>
</tr>
<tr>
<td>Membrane stabilizers (citicoline)</td>
</tr>
<tr>
<td>Free radical scavengers (tirilazad, hypothermia, NXY-059 [disufenton])</td>
</tr>
<tr>
<td>Anti-inflammatory approaches (anti-ICAM-1 antibody, tacrolimus, corticosteroids)</td>
</tr>
<tr>
<td>GM-1 ganglioside</td>
</tr>
<tr>
<td>Glycine site inhibitor (gavestinel)</td>
</tr>
<tr>
<td>GABA agonists (clomethiazole)</td>
</tr>
<tr>
<td>Statins (anti-inflammatory effect)</td>
</tr>
<tr>
<td>Fosphenytoin</td>
</tr>
<tr>
<td>Nootropic agents (piracetam)</td>
</tr>
<tr>
<td>Glutamate release inhibitors (BW619C89)</td>
</tr>
<tr>
<td>AMPA receptor antagonists (YM 872)</td>
</tr>
<tr>
<td>Adenosine agonists</td>
</tr>
<tr>
<td>Kappa-selective opioid antagonists (nalmefene)</td>
</tr>
<tr>
<td>Calpain inhibitors</td>
</tr>
<tr>
<td>Basic fibroblast growth factor</td>
</tr>
<tr>
<td>Selective serotonin agonists (BAYx3702, repinotan, piclozotan)</td>
</tr>
<tr>
<td>Combined cytoprotective strategies</td>
</tr>
<tr>
<td>Cytoprotection plus thrombolysis</td>
</tr>
</tbody>
</table>

Free radicals have also been implicated in ischemic neuronal damage, particularly in animal models involving reperfusion. A steroid derivative, tirilazad mesylate, with antioxidant properties, has been employed in clinical trials, but no definitive benefits have been demonstrated as yet for ischemic stroke. A series of studies with disufenton (NXY-059), a free radical trapping agent, also provided no benefit in acute ischemic stroke.

Lubeluzole is a novel benzothiazole compound that has emerged as a neuroprotective agent in animal models of focal ischemia. Blockade of sodium channels may be one of the mechanisms contributing to its neuroprotective effect. Lubeluzole also inhibits glutamate release after ischemia and reduces potassium-induced increases in intracellular calcium. Finally it prevents glutamate-mediated increases in nitric oxide production by inhibiting the activity of nitric oxide synthase. A phase 2 clinical trial of lubeluzole in acute ischemic stroke suggested that lubeluzole lowered mortality and disability in some participants. However, a phase 2 trial of lubeluzole did not demonstrate a significant benefit. A trial of lubeluzole versus the placebo in combination with intravenous recombinant tPA therapy (LUB-USA-6) was interrupted.

The anticonvulsants clomethiazole and vigabatrin are gamma aminobutyric acid agonists recently shown to be neuroprotective in animal models of focal and global ischemia. The results of a phase 3 trial of 1,360 participants randomized to receive either the placebo or 75 mg/kg of clomethiazole intravenously over 24 hours, beginning within 12 hours of stroke onset, were reported. The difference between clomethiazole and the placebo on the primary endpoint (percentage of participants scoring > 60 on the Barthel Index at 3 months post stroke) was not statistically significant. Prespecific subgroup analysis
revealed a positive effect of clomethiazole in participants with larger strokes; confirmation of these results awaits completion of an ongoing phase 3 trial in North America.

Piracetam, a gamma aminobutyric acid derivative, was shown to be neuroprotective in two pilot trials of acute ischemic stroke. Although its mechanism of action is not entirely clear, it is thought that its neuroprotective properties are mediated through restoration of cell membrane fluidity and, thus, maintenance of membrane-bound cell functions. However a recent randomized, placebo-controlled trial of 927 participants given piracetam intravenously within 12 hours of stroke onset demonstrated no difference in mortality or neurologic outcomes at 12 weeks post stroke. Further studies are under way to evaluate several other potential neuroprotective strategies. Citicoline is an endogenous substance that regulates the rate-limiting step involved in phosphatidylcholine synthesis and reduces production of free fatty acids, which may cause neurotoxicity through lipid peroxidation. Preliminary results of a recent trial suggest that citicoline might reduce the size of brain infarct in stroke when compared to the placebo. A large trial (The International Citicoline Trial on Acute Stroke [ICTUS]) is now in progress. Enlimomab is a murine anti-intracellular adhesion molecule-I monoclonal antibody that has been shown to inhibit neutrophil adhesion, migration, and cytotoxicity. However, preliminary studies with enlimomab have shown considerable toxicity with the drug and no apparent clinical benefit. The opioid antagonist nalmeprine failed to show any treatment benefit.

Transplantation of cultured neuronal cells is an exciting new strategy for reversal of motor deficits in stroke patients. A preliminary study demonstrated improvement in motor function in 6 of 12 participants with no significant adverse effects.

Treatment of Migraine

The pathophysiology of migraine is largely unknown despite its wide prevalence. Many potential factors are likely to be involved. There is much evidence indicating that neuronal hyperactivity causing secretion of vasoactive factors plays a role. Serotonin, calcitonin gene-related peptide, and sensory nerve peptides are all proposed to be involved. The trigeminal nerve system ultimately becomes activated and alters extracranial and meningeal vascular function, thus causing pain. In classic migraine, there are prodromal symptoms such as scintillating scotomas and nausea during the vasoconstrictive phase that lasts several minutes. This is followed by throbbing hemicranial headache during a longer vasodilatory phase. Common migraine, only headache occurs. In complicated migraine, focal neurologic deficits such as hemiparesis developed from cerebral ischemia, which can last for several hours to days or occasionally be permanent.

Sumatriptan is used to treat acute migraine attacks. Sumatriptan, a serotonin agonist working at the 5HT receptor, has been shown to be effective in aborting migraine attacks when given subcutaneously, orally, intranasally, and rectally. However, headache recurrence within 24 hours is a common problem. Newer oral triptan agents have been developed with faster onset of action and fewer adverse effects. In addition, the oral calcitonin gene-related peptide (CGRP) receptor antagonist telcagepant, has been shown to be effective for the acute treatment of migraine. Intravenous telcagepant (BIBN 4096) has also been shown to be effective.

Ergot alkaloids, which inhibit serotonin receptors, can be used to prevent onset of headache during the prodromal phase. Ergots can be compounded with phenobarbital to provide symptomatic relief. Routes of administration include oral, sublingual, subcutaneous, rectal, nasal, and parenteral. Ergot alkaloids and sumatriptan are to be avoided in patients with complicated...
migraine or CAD. Symptomatic relief of pain can be obtained with combinations of aspirin or acetaminophen with caffeine and barbiturates. Antiemetics such as metoclopramide, 5 to 10 mg orally, intramuscularly or per rectum are often used for nausea and vomiting. Sodium bicarbonate has also been useful, with verapamil 120 to 240 mg per day the most effective, but hypotension is again a complication. Calcium channel blockers have also been employed but have systemic adverse effects such as alopecia and hypotension. They have numerous contraindications and appear to be effective in only 50% to 60% of patients. Calcium channel blockers have also been useful, with verapamil 120 to 240 mg per day the most effective, but hypotension is again a complicating factor. In addition, inhibition of platelet aggregation with aspirin to reduce serotonin release from platelets has had limited success. Amitriptyline and the antiepileptic valproic acid show some use, but both have potentially severe adverse effects. The antiepileptic drug topiramate has been approved by the FDA for clinical use in migraine prevention. A most successful prophylactic agent has been the serotonin antagonist methysergide, but this can be administered only in the most extreme conditions and for limited time periods because of the complication of retroperitoneal fibrosis.

Cluster headache is a variation of migraine that predominately effects middle-aged men and has a cyclic temporal pattern. Headache paroxysms last from minutes up to 3 hours and are associated with symptoms such as rhinorrhea, lacrimation, conjunctival injection, and unilateral facial pain. Previously assumed to be mediated by histamine, they are now thought to have several possible etiologies, probably related to a diffuse cerebrovascular dysfunction. Much like migraine, treatment can be divided into preventative and abortive therapies. Primary treatment for treatment of acute attack is inhaled 100% oxygen at 8 liters per minute for 10 minutes. This is effective in over 80% of patients. Ergotamine, dihydroergotamine, and sumatriptan all appear nearly as effective as oxygen. Corticosteroids and intranasal capsicain have also been helpful. Narcotics and analgesics have limited value. Prophylaxis of cluster headaches has been effective with ergotamine, verapamil, lithium, and methysergide.

**Drug Therapy of Hemorrhagic Cerebrovascular Disease**

**Intracerebral Hemorrhage**

Primary intracerebral hemorrhage (ICH), particularly in the region of the basal ganglia, can often be life-threatening, causing herniation of cerebral structures with secondary hemorrhage into the pons resulting in brain death. Therapeutic efforts are aimed at stopping the bleeding, reducing hematoma growth and reducing intracranial pressure (Table 33-6). Most ICH is associated with hypertension. Bleeding stops when the tamponade effect of increased intracranial pressure balances the blood pressure. Therefore, hypertension should be treated more aggressively in ICH than ischemic stroke to reach a normotensive range for the particular patient based on the premorbid blood pressure. Since there is surrounding ischemia from pressure effects of the hemorrhage, the blood pressure still needs to be reduced gradually. Sublingual nifedipine should be avoided and nitroprusside only used when the blood pressure is over 220/140 because these agents can precipitously decrease the patient's blood pressure. Generally, intravenous labetalol, clevidipine, and nicardipine at dosages to titrate a gradual blood pressure reduction are used.

Massive ICH carries a poor prognosis regardless of therapeutic attempts, either medical or surgical. However, a recent study of recombinant Factor VIIA use to reduce the propagation of hemorrhage to prevent deterioration showed potential benefit despite an increase in the thromboembolic complications. If the patient survives the initial hemorrhage, edema develops around the clot. While treatment with corticosteroids has not been shown to be of any benefit when administered to all patients with ICH, these are still often employed to prevent subsequent brain herniation and maintain the highest possible level of consciousness. An initial dose of 10 to 12 mg IV is given, followed by 4 mg IV every 6 hours. The osmotic diuretic mannitol is given intravenously 100 g over 4 hours, to try to prevent acute herniation with increased intracranial pressure. Hypertonic 3% saline is also frequently used. Hyperventilation with a respirator after endotracheal intubation can also reduce intracranial pressure. Barbiturate coma has been investigated for reducing intracranial pressure, but is not commonly used in ICH. The role of surgery is controversial except in large cerebellar hemorrhages, where surgical removal has been

**Table 33-6: Pharmacotherapy of Hemorrhagic Cerebrovascular Disease**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drug</th>
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<tbody>
<tr>
<td><strong>Intracerebral Hemorrhage</strong></td>
<td>Antihypertensive Treatment</td>
</tr>
<tr>
<td></td>
<td>Antiedema agents: Corticosteroids, Mannitol, Glycerol, Recombinant Factor VIIA (investigational)</td>
</tr>
<tr>
<td><strong>Subarachnoid Hemorrhage</strong></td>
<td>Antihypertensives</td>
</tr>
<tr>
<td></td>
<td>Antispasmodic Therapy: nimodipine, hypertensives with plasma volume expansion</td>
</tr>
<tr>
<td></td>
<td>Antifibrinolysins</td>
</tr>
<tr>
<td></td>
<td>Free radical scavengers: still investigational</td>
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</tbody>
</table>
effective. A recent meta-analysis of 4 surgical trials indicated no evidence of any benefit from surgical treatment of ICH.

Intraventricular extension of cerebral hemorrhage is associated with a poor prognosis. Recent studies have demonstrated that infusion of urokinase into the ventricular system hastens the disappearance of ventricular blood. However, secondary hemorrhage can occur. A controlled trial is being initiated to determine if intraventricular or intrahemorrhage infusion of urokinase or tPA results in improved outcome compared to ventricular drainage alone.

ICH can occur in patients with atrial fibrillation or cardiac valve replacements who require continuous anticoagulant therapy. Discontinuation of warfarin therapy for 1 to 2 weeks has been demonstrated to have a low probability of subsequent embolic infarction, but anticoagulation can be restarted safely within one week after the event.

**Management of Subarachnoid Hemorrhage**

Subarachnoid hemorrhage (SAH) is usually associated with rupture of an intracranial aneurysm. The mortality rate is 50%, and many deaths occur before the victim ever reaches the hospital. Initial efforts should be aimed at stopping the bleeding by lowering the blood pressure to normotensive levels. The major complications of SAH are recurrent hemorrhage and vasospasm with resulting cerebral ischemia. Therapy to prevent rebleeding is often (although not uniformly) surgical, but pharmacological therapy is necessary in the acute setting and to maintain the patient until surgery is performed.

Angiographically demonstrable vasospasm usually occurs within 4 to 7 days following hemorrhage and can induce focal cerebral infarction and stroke. However, reduction in blood flow appears to occur acutely before spasm can be visualized. The calcium-channel blocker nimodipine increases cerebral blood flow following SAH while lowering systemic blood pressure as well. Nimodipine administered 60 mg by mouth every 4 hours for 21 days after SAH reduces the incidence of cerebral infarction by 34% and poor outcome by 40%, with no increased incidence of rebleeding. Oral nimodipine is now standard therapy for patients with SAH and is started acutely once the diagnosis has been made. Nimodipine is continued after surgical therapy to prevent postoperative ischemia due to vasospasm. In some instances, increasing the blood pressure with pressor agents and plasma expansion with low-molecular-weight dextran have been used to increase blood supply to ischemic regions after aneurysms have been clipped. Hypervolemic therapy with isotonic crystalloid has not reduced symptomatic vasospasm following aneurysm clipping.

The free radical scavenger tirilazad mesylate given intravenously, 2 mg/kg, has also been shown to provide a positive trend for improved outcome compared to vehicle in a phase 2 trial. Tirilazad is a 21-aminosteroid similar structurally to methylprednisone, which has been employed empirically for patients with SAH for many years. Whether there is any benefit of tirilazad over corticosteroid therapy has not been determined.

The cerebrospinal fluid contains fibrinolysins. Agents that inhibit fibrinolysis, epsilon amino caproic acid and tranexamic acid, have been employed to help prevent recurrent bleeding of aneurysms from dissolution of clot formed when the initial bleeding ceases. Epsilon amino caproic acid, 24 to 36 g IV per day administered by constant infusion, reduced the 7-day mortality rate, predominantly by reducing recurrent hemorrhage from 22.6% to 12.1%. Treatment with tranexamic acid reduced the 7-day mortality rate to 8.1%. However, these agents were associated with long-term complications of venous thrombosis and cerebral ischemia. Since the advent of nimodipine therapy, these antifibrinolysins are now rarely employed. A study showed no additive improvement when anti-fibrinolytic therapy was combined with calcium channel blockade. However, intracisternal irrigation with urokinase may be effective in preventing symptomatic vasospasm. Infusion of tPA into the clot may also be successful.

**Conclusion**

The goal of therapy for stroke is immediate treatment; consider a cerebral vascular accident as a brain attack analogous to a heart attack. For an ischemic stroke, it is imperative to re-establish perfusion acutely with thrombolytic agents, and in the future we may see increased use of neuroprotective agents to protect neurons from the ischemic cascade induced by calcium influx and the use of free radical scavengers to prevent reperfusion injury. The therapeutic window is brief, and rapid emergency response is necessary for any treatment to be effective. Early treatment of hemorrhagic stroke, particularly subarachnoid hemorrhage, may also improve the ultimate outcome.

Prevention of stroke is still the optimal therapeutic strategy. Early identification of patients at high risk for stroke and treatment of hypertension, hypercholesterolemia, and the use of platelet antiaggregants hold promise that the incidence of stroke can continue to be reduced.

*Note: References for this chapter can be found here: www.cvpct3.com*
Despite intensive investigation over the past several decades, there remains a limited number of clinically useful agents available for the treatment of peripheral vascular disorders. In particular, it has been most difficult to find effective drugs for the symptomatic relief of peripheral arterial disease (PAD). The treatment of PAD has focused on exercise training, modification of risk factors for atherosclerosis, and revascularization for critical limb ischemia (CLI). In contrast, treatment of Raynaud’s syndrome has primarily focused on symptomatic relief, with no therapy aimed at altering the underlying problem. The prevention and treatment of deep vein thrombosis (DVT) has evolved with the development and refinement of antithrombotic and thrombolytic therapy. The treatment of vasculitides, particularly those affecting the large vessels, involves suppression of the inflammatory response.

This chapter reviews the pharmacotherapeutic armamentarium available in the treatment of these peripheral vascular disorders (PVD). Emphasis is placed on agents used clinically, but investigational agents and emerging therapies are also covered.

**Peripheral Arterial Disease**

The manifestations of PAD, typically due to arteriosclerosis obliterans, vary from asymptomatic to chronic CLI, as well as acute limb ischemia. However, the most common classical symptomatic manifestation of PAD has been reported to be intermittent claudication (IC), although atypical leg symptoms have been shown to be more common. Treatment for patients with PAD should focus on relieving symptoms, delaying or preventing disease progression, and reducing morbidity and mortality.

There are few agents available for the management of symptomatic PAD. There are a far greater number of agents useful in the treatment of risk factors for atherosclerosis. In addition, there is evidence that an angiotensin-converting enzyme (ACE) inhibitor, ramipril, reduced cardiovascular events in a high-risk group of patients, many with PAD. This cardioprotective benefit was beyond that anticipated simply from a blood pressure–lowering effect. Despite considerable interest in developing new and effective agents for the symptomatic treatment of claudication, few agents have demonstrated a clear benefit (Table 34-1). In contrast, the effectiveness of exercise training in the treatment of IC is well established. A meta-analysis found that exercise training improved treadmill walking distances with an increase in initial claudicant distance (ICD) of 139 m and absolute claudicant distance (ACD) of 179 m compared with controls. Furthermore, exercise has been shown to improve cardiopulmonary function and functional status during daily activities, with enhanced community-based ambulation and quality of life.

A randomized controlled trial involving 156 participants with IC was recently conducted to determine the effect of supervised treadmill exercise and lower extremity resistance training on the functional performance. It was shown that those in the supervised treadmill exercise group increased their 6-minute walk distance (6MWD) by 35.9 m (95% confidence interval, 15.3 m to 56.5 m; \( P < .001 \)) compared with the control group at 6-month follow-up. To a lesser extent, those in the resistance training group increased their 6MWD by 12.4 m (95% confidence interval, -8.4 m to 33.3 m, \( P = .24 \)) compared with the control group. The treadmill group also had significantly improved brachial artery flow-mediated dilation, maximal treadmill walking time and quality of life, whereas the lower extremity resistance training group had significantly improved maximal treadmill walking time and quality of life.
Pentoxifylline was the first agent approved—and is one of only two agents currently approved—by the US Food and Drug Administration (FDA) for the symptomatic treatment of IC. It is a xanthine derivative that inhibits 3,5-monophosphate diesterase, leading to increased cyclic adenosine monophosphate (cAMP). The proposed mechanism of action involves decreased whole-blood viscosity, in part due to increased erythrocyte deformability, decreased platelet activity, and decreased fibrinogen levels.

Over the past several decades, numerous small studies have evaluated the effect of pentoxifylline for the treatment of IC with conflicting results. Attempts to analyze the aggregate data concluded that a reliable conclusion regarding the drug’s efficacy could not be reached due to inadequate data. However, two meta-analyses concluded that pentoxifylline had a modest effect on treadmill walking distance with increases of approximately 20 to 30 minutes in ICD and 45 to 48 m in ACD compared with the placebo.5,9

The clinical relevance of an effect of this magnitude on walking distance has been questioned, but others conclude that it is highly relevant. This treadmill distance is equivalent to walking 90 m (or greater than one city block) on level ground, which may minimize the disability in these patients, enabling engagement in personal and social activities as well as employment.9 However, there is limited (or discouraging) information regarding the impact of pentoxifylline on functional status or quality of life.

Perhaps the greatest benefit with pentoxifylline may be found in those with moderate disease and long duration.10 It has been suggested that pentoxifylline may alter the natural history of PAD. Continuous use of pentoxifylline for 4 months was associated with a reduced number of diagnostic and therapeutic procedures within the first year in a small group of participants with IC.11 The use of pentoxifylline was not associated with a greater cost of PAD-related care and, in fact, was possibly associated with a reduction in hospital costs.12 The drug has also been used with mechanical compression in the management of venous ulcers and may be effective for patients not receiving compression for this indication.13
The dose of pentoxifylline is 400 mg given 3 times daily, preferably with meals. The most common adverse effects are gastrointestinal (GI) in origin, including dyspepsia, nausea, and vomiting. Pentoxifylline is well tolerated despite these potential adverse effects, as only 3% of patients are unable to tolerate it. Although there is still uncertainty (and considerable skepticism) regarding the clinical utility of this agent, some vascular clinicians may give a 6- to 12-week trial of pentoxifylline to assess its efficacy after other measures (including exercise) have failed to diminish symptoms. The American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines for PAD suggest that pentoxifylline (400 mg 3 times per day) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with IC since the clinical effectiveness of pentoxifylline as a therapy for IC is marginal and not well established.14

Cilostazol

Cilostazol is the second agent approved by the FDA for the symptomatic treatment of IC. Cilostazol is a type III phosphodiesterase (PDE) inhibitor that blocks proteolysis and leads to an increase in intracellular cAMP levels. The proposed mechanisms of therapeutic action are vasodilation, due to direct smooth muscle relaxation and perhaps enhanced effect of prostacyclin, and inhibition of platelet function.15 In addition, cilostazol appears to favorably influence serum lipids and to have smooth muscle antiproliferative properties.16,17

An extensive number of randomized controlled trials have been performed to evaluate the efficacy of cilostazol in the treatment of IC of varying severity. A randomized, double-blind, placebo-controlled trial involving 239 participants with mild to moderate IC found that cilostazol, at a dose of 100 mg twice daily for 16 weeks, improved walking distance.18 Cilostazol increased ACD by 62 m (32%) and ICD by 28 m (27%) compared with the placebo (P < .05) on a variable-grade treadmill protocol. Another trial of cilostazol involving 81 participants with moderately severe IC found significant improvements in ICD (35%) and ACD (41%) on a fixed-incline treadmill protocol.19

Several other studies have reported a beneficial effect of cilostazol on walking distance, including a larger trial involving 698 participants that compared the effectiveness of cilostazol to that of the placebo and pentoxifylline.20-22 Cilostazol increased ACD significantly more than pentoxifylline or the placebo after 24 weeks of therapy (107 m with cilostazol versus 64 m with pentoxifylline and 65 m with the placebo).21 The withdrawal of treatment with cilostazol, by crossing over to the placebo, worsened the walking distance in participants with IC who benefited from therapy.22

Concomitant with the improved treadmill performance was a subjective improvement in walking performance and functional status. There was significant improvement in the physical component scale score of the Medical Outcome Scale Health Survey (SF-36) and walking speed and specific measures of walking difficulty on the Walking Impairment Questionnaire, although there was no change in the perceived walking distance.18 Using a global therapeutic assessment, more participants and investigators subjectively judged the IC symptoms to be improved with cilostazol. More participants receiving cilostazol rated their outcome as “better” or “much better” compared with pretreatment.15 Several trials demonstrated an approximate 9% increase in ankle brachial index (ABI) with cilostazol; however, the clinical significance of this finding remains uncertain.16,18

The recommended dose of cilostazol is 50 to 150 mg twice daily, with 100 mg twice daily being used most commonly. One study found that 50 mg of cilostazol given twice daily also improved walking distance; however, a dose response was observed, as the standard dose of 100 mg twice daily seemed to provide greater efficacy.20 Cilostazol is metabolized by cytochrome P450 isoenzymes, especially CYP3A4 and CYP2C19 but does not inhibit their action. It is excreted primarily (~75%) by the kidney; thus plasma levels are increased in renal insufficiency. The plasma levels of cilostazol are also increased by other drugs that utilize or inhibit the P450 isoenzymes, including erythromycin, omeprazole, diltiazem, and ketoconazole as well as grapefruit juice. The ACC/AHA Practice Guidelines for PAD recommend that a therapeutic trial of cilostazol (in the dose of 100 mg orally 2 times per day) should be considered in patients with lifestyle-limiting IC (in the absence of heart failure) (Level of Evidence: A).14

Most vascular clinicians have found cilostazol to be useful in the treatment of patients with IC.21-25 Despite these clear benefits, the use of cilostazol requires some consideration, careful instructions, and close monitoring. Adverse effects are reported frequently, including GI complaints, headaches, and palpitations (in over 25% of patients). Patients need to be carefully instructed to anticipate adverse effects, which are often transient and will dissipate with continued use. The use of analgesics is often helpful to palliate symptoms such as headache. Despite the high rate of adverse effects, the rates of withdrawal among patients taking cilostazol were similar to those among patients receiving the placebo or pentoxifylline.19,22

Since cilostazol is a PDE inhibitor, it is contraindicated in patients with congestive heart failure of any severity as a result of detrimental effects observed with other agents in this category (such as milrinone and vesnarinone) in patients with New York Heart Association class III to IV heart failure. It is recommended that patients be screened for history and signs or symptoms of congestive heart
failure prior to initiating therapy. Such concerns have led some to recommend regular reassessment of the risk-benefit ratio based upon interval ischemic events and close monitoring for tachycardia during initiation of therapy.\textsuperscript{26} There are limited long-term data available regarding safety; however, experience in the 8 US/UK phase 3 trials involving over 2,000 participants found no increased risk of death or ischemic cardiovascular events during the study period. Death due to cardiovascular causes occurred in 0.6% of participants treated with cilostazol and 0.5% of participants treated with the placebo. Pending more definitive information, the FDA has mandated a black-box warning that cilostazol should not be used in patients with heart failure.

NM-702

NM-702 is a novel agent which selectively inhibits PDE isoforms III and IV as well as thromboxane A2 synthesis. It was evaluated in a phase 3 randomized, controlled, double-blind study involving 391 participants with IC.\textsuperscript{27} After 24 weeks of treatment, participants who received NM-702 showed statistically significant improvement in peak walking time and IC onset time compared to participants who received the placebo. It was reasonably well tolerated and no unanticipated safety concerns were established. NM-702 appears to have a good potential to provide an additional therapeutic option for patients with IC if further studies confirm its safety and efficacy.

**Antiplatelet Drugs**

Platelets are well known to participate in the development and progression of atherosclerosis and its complications. Activated platelets release a number of vasoactive mediators that may also participate in the pathogenesis of limb ischemia. Inhibition of platelet function provides a potential site for the treatment of IC. Furthermore, the increase in cardiovascular events among individuals with PAD warrants some form of antiplatelet therapy (Table 34-2), given the well-established benefit of this category of agents in prevention of coronary events.\textsuperscript{28}

Current available antiplatelet agents in routine use include aspirin, dipyridamole, and the adenosine di-phosphatase (ADP) receptor antagonists, ticlopidine and clopidogrel (see Chapter 18, Antiplatelets and Antithrombotics). There remains some uncertainty as to the best agent to use to prevent events in those with PAD, particularly with coexistent diabetes mellitus. A large multicenter, randomized, double-blind, placebo-controlled trial was conducted to determine whether aspirin and antioxidant therapy, combined or alone, are more effective than the placebo in reducing the development of cardiovascular events in participants with diabetes mellitus and asymptomatic PAD (those with ABI < 0.99). The study found no evidence of benefit from either aspirin or antioxidant treatment on the composite endpoints of cardiovascular events and cardiovascular mortality in diabetic patients with asymptomatic PAD.\textsuperscript{29}

**Aspirin**

Aspirin, the traditional antiplatelet agent, inhibits cyclooxygenase, thereby preventing the formation of thromboxane A2 and thromboxane-dependent platelet activation. The benefit of antiplatelet therapy (primarily aspirin) in the prevention of cardiovascular events in patients with atherosclerotic vascular disease has been demonstrated in the meta-analysis of studies conducted by the Antiplatelet Trialists’ Collaboration.\textsuperscript{30} Analysis of the subgroup of participants with IC demonstrated an 18% reduction in cardiovascular events; however, this failed to reach statistical significance. This has led to various recommendations regarding the use of antiplatelet therapy in patients with PAD. The American College of Chest Physicians’ recommended dose of aspirin is 81 to 325 mg daily as life-long therapy in those with PAD in the absence of contraindications.\textsuperscript{28} An FDA expert panel found insufficient evidence to approve the labeling of aspirin as indicated for patients with PAD.\textsuperscript{31} Furthermore, there is a controversy with the use of aspirin in patients with PAD, as a recent meta-analysis found a statistically nonsignificant decrease in overall cardiovascular events with aspirin alone (or with dipyridamole) in PAD.\textsuperscript{32} In addition, in a large primary prevention trial, aspirin failed to demonstrate a benefit in reducing cardiovascular events in participants with diabetes mellitus and asymptomatic PAD.\textsuperscript{29}

There is no evidence to support the use of aspirin for the symptomatic treatment of IC, but some suggest it may alter the natural history. The Antiplatelet Trialists’ Collaboration found that antiplatelet therapy containing aspirin reduced the risk of graft or vessel occlusion by 43% in those with PAD undergoing revascularization.\textsuperscript{33} In the US Physician Health Study, aspirin (325 mg every other day) failed to prevent the development of IC but decreased the need for peripheral artery surgery.\textsuperscript{34}

Aspirin plus dipyridamole may have a modest effect in the treatment of IC. One study involving 54 participants with IC found that the combination of these two drugs improved both resting limb blood flow and ICD compared with aspirin alone.\textsuperscript{35} Two other studies involving 296 and 240 participants with IC found that aspirin plus dipyridamole improved ABI and delayed progression of disease, as assessed by serial angiograms.\textsuperscript{36,37} Neither study reported the effect on walking distance or functional status. Thus, aspirin, particularly in combination with dipyridamole, may alter the natural history of lower extremity arterial insufficiency, although larger-scale trials supporting this are still lacking.
A Cochrane database review has also shown the benefits of antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. The long-term (6 weeks to 2 years) administration of antiplatelet agents started prior to surgery, resulting in improved graft patency. People who received aspirin alone or with dipyridamole showed reduced occlusion of grafts at one year (odds ratio 0.6, range 0.45 to 0.8) compared with no treatment (6 trials, 966 participants). People receiving an artificial graft were more likely to benefit than those treated with a venous graft. 38

Ticlopidine
Ticlopidine is an ADP–receptor antagonist that prevents ADP-mediated platelet activation and aggregation by inhibiting glycoprotein IIb/IIIa expression on the platelet surface. In 151 participants with IC, ticlopidine was reported to significantly improve walking distance with an increase in both ICD and ACD compared with the placebo. 39 In contrast, another randomized trial involving 169 participants failed to find an effect of ticlopidine on treadmill walking distance. 40 Perhaps a more important finding has been a significant reduction in the combined cardiovascular endpoints in participants with IC who were treated with ticlopidine. 41 Ticlopidine is dosed at 250 mg twice daily. Adverse effects include bleeding, dyspepsia, diarrhea, nausea, anorexia, rash, and dizziness. The potential for developing severe leukopenia and thrombocytopenia requires regular monitoring of the cell count for at least several months.

Clopidogrel
Clopidogrel is in the same class of agents as ticlopidine, but has largely replaced ticlopidine because of the lower frequency of adverse effects, including leukopenia and thrombocytopenia. Clopidogrel is given at a dose of 75 mg once daily. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study demonstrated a benefit of clopidogrel over aspirin in preventing “vascular” events in 19,185 participants with atherosclerotic vascular disease, with a relative risk reduction of 8.7%. 42 The overall incidence of the composite endpoint of ischemic stroke, myocardial infarction (MI), or vascular death was 5.32% per year in the clopidogrel group compared to 5.83% per year in the aspirin group. Subgroup analysis demonstrated that this effect of clopidogrel was most pronounced among the subset of participants with established PAD, with a 23.8% relative risk reduction. Despite the possibility that this may have been due to chance, this finding has led many to consider clopidogrel as the preferred antiplatelet agent in patients with PAD. 26

Currently, clopidogrel is the only antiplatelet agent that is FDA-approved for reduction of thrombotic events in patients with established PAD, and the American College of Chest Physicians guidelines state that for reducing ischemic complications, clopidogrel may be superior to aspirin. There has been further investigation to determine if a single or dual antiplatelet therapy including clopidogrel is best, but this remains unresolved without overwhelming support for dual antiplatelet therapy. A post-hoc subgroup analysis of another large cilostazol

<table>
<thead>
<tr>
<th>Problem</th>
<th>Agent</th>
<th>Clinical Effect</th>
</tr>
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<tbody>
<tr>
<td>Chronic arterial ischemia</td>
<td>Aspirin</td>
<td>Reduce cardiovascular morbidity and mortality*</td>
</tr>
<tr>
<td></td>
<td>Aspirin plus dipyridamole</td>
<td>? Modify the natural history of limb disease</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>? Superiority to aspirin</td>
</tr>
<tr>
<td>Acute arterial occlusion</td>
<td>Heparin</td>
<td>Prevents thrombus propagation</td>
</tr>
<tr>
<td></td>
<td>Thrombolysis</td>
<td>Facilitate recanalization and minimize need for surgery</td>
</tr>
<tr>
<td>Revascularization surgery</td>
<td>Aspirin</td>
<td>Reduce cardiovascular events</td>
</tr>
<tr>
<td>Infrainguinal bypass with prosthetic</td>
<td>Aspirin plus dipyridamole</td>
<td>May provide additional benefit</td>
</tr>
<tr>
<td>Infrainguinal bypass with high-risk thrombosis</td>
<td>Warfarin ± aspirin</td>
<td>Protect against graft thrombosis</td>
</tr>
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*Concern has arisen with use in diabetes mellitus with asymptomatic PAD.

Data from Geerts WH et al. 179

Table 34-2. Antithrombotic Therapy in Peripheral Arterial Disease
trial included participants with established documented atherothrombotic disease (prior MI, prior ischemic stroke, or symptomatic PAD). A total of 9,478 participants fulfilled the criteria and were enrolled for this analysis. Out of these, 2,838 participants had symptomatic PAD (defined as current IC with ABI < 0.85 or a history of IC with a previous related intervention). The enrolled participants were randomized in a double-blind fashion to clopidogrel plus aspirin or the placebo plus aspirin, and were followed for a median period of 27.6 months. The overall rate of cardiovascular death, MI or stroke in this cohort was 8.8% in the placebo plus aspirin arm and 7.3% in the clopidogrel plus aspirin arm (HR 0.83, 95% confidence interval, 0.72 to 0.96, \( P = 0.01 \)). However, unlike the prior CAPRIE trial, the risk reduction in the PAD subgroup did not reach statistical significance (HR 0.869, 95% confidence interval, 0.67 to 1.12, \( P = 0.285 \)).43

The aggregate data on the use of antiplatelet agents for the symptomatic treatment of IC indicate that they result in, at best, minimal improvement. However, due to the cardioprotective benefit of these drugs, antiplatelet therapy should be part of the medical regimen of nearly every patient with PAD provided that there are no absolute contraindications.26 The ACC/AHA Practice Guidelines for PAD recommend that antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD.14

Newer Antiplatelet Agents

Despite recent advances, cardiovascular disease remains a leading cause of morbidity and mortality. The limitations of the existing antiplatelet drugs have provided opportunities for the development of new agents (see Chapter 18, Antiplatelets and and Other Antithrombotic Drugs). Attempts to replace aspirin with other inhibitors of the thromboxane A2-mediated pathway of platelet aggregation have not yet been successful. Instead, attention has focused on novel ADP receptor antagonists (P2Y12 antagonists) and on drugs that target protease activated receptor (PAR)-1, the major thrombin receptor on platelets.

Prasugrel, a novel P2Y12 antagonist, is a new member of the thienopyridine class of oral antiplatelet agents.44 It is rapidly converted \textit{in vivo} to an active metabolite (R-138727) that binds specifically and irreversibly to the platelet P2Y\textsubscript{12} purinergic receptor leading to a more predictable inhibition of ADP-mediated platelet activation and aggregation.45 It has a rapid onset and offset of action and is approximately 10- and 100-fold more potent at inhibiting \textit{ex vivo} platelet aggregation and \textit{in vivo} thrombus formation than clopidogrel and ticlopidine, respectively.

Prasugrel, co-administered with aspirin, has been evaluated for the reduction of atherothrombotic events in participants with acute coronary syndrome managed with percutaneous coronary intervention in a Phase 3 clinical trial.46 This study demonstrated that the inhibition of ADP-induced platelet aggregation achieved with prasugrel is more effective at preventing ischemic events than is the platelet inhibition conferred by clopidogrel. This trial has prompted further trials using prasugrel in other atherothrombotic diseases, such as cerebrovascular diseases and PAD. In an initial study, the effect of prasugrel was compared with clopidogrel in rat models of cerebral and peripheral arterial occlusive diseases.47 Prasugrel was shown to be more potent than clopidogrel in preventing the progression of thrombotic lesions in the cerebral and peripheral vessels. Further studies are needed in humans to clarify its use in patients with PAD.

Other newer antiplatelet agents target the PAR-1, the major thrombin receptor on platelets. Among this group, an oral non-thienopyridine agent which binds reversibly to the platelet P2Y\textsubscript{12} receptor, and cangrelor, an intravenously administered analog of ticagrelor, have shown promising results in the studies involving the acute coronary syndromes.48 Further studies are needed to test their efficacy in other vascular diseases. Although these new P2Y12 antagonists have the potential to be more efficacious than clopidogrel because they produce more profound inhibition of ADP-induced aggregation, caution is needed as there may be issues with an increased risk of major bleeding.49

The other novel antiplatelet agents target the PAR-1, the major thrombin receptor on platelets. Among this group, an oral agent (SCH-530348) has shown encouraging results in the treatment and prevention of atherothrombosis.50 In preclinical studies, SCH-530348 demonstrated no effect on bleed time or coagulation parameters. In a phase 2 clinical trial of participants undergoing percutaneous coronary intervention, SCH-530348 added to standard therapy with aspirin and clopidogrel did not increase major or minor bleeding. The distinct mechanism of action of SCH-530348 allows for cardiovascular protection without the liability of increased bleeding associated with other antiplatelet therapies.

Statins

The statins are reversible inhibitors of the enzyme HMG-CoA reductase, thus inhibiting an early rate-limiting step in cholesterol biosynthesis; therefore, they are effective in lowering blood cholesterol levels (see Chapter 20, Lipid-Lowering Drugs). Interestingly, they have been shown to have beneficial effects on atherosclerosis beyond those related to cholesterol lowering. Statins stabilize atherosclerotic plaques, reduce oxidative stress, and decrease vascular inflammation. In vascular endothelium, statins increase concentrations of nitric oxide with resulting vasodilation and antithrombotic and antiproliferative effects.51 These beneficial properties may contribute to the clinical effects observed in those with established cardio-
nary heart disease as well as in those at high-risk, including those with PAD. Primary prevention studies, such as the Heart Protection Study, have shown that in subsets with PAD, aggressive lowering of low-density lipoprotein cholesterol (LDL-C) was associated with a marked reduction in cardiovascular events, whether or not there was evidence of coronary disease at baseline. Furthermore, there was no apparent threshold cholesterol value below which statin therapy was not associated with a benefit.

A subsequent study of 515 participants with severe PAD showed that statin therapy was associated with a substantially improved intermediate-term survival of participants with severe PAD and a high inflammatory activity (elevated hs-C reactive protein levels) but not in those with low inflammatory activity. In another large prospective cohort study, it was shown that statin therapy was associated with almost a 60% reduction in cardiovascular mortality in participants with PAD defined by ABI < 0.9. The risk reduction in this study was unaffected by baseline levels of C-reactive protein and D-dimer.

Interestingly, it has been shown that statins not only lower the risk of cardiovascular events but may also improve the symptoms associated with PAD. In a study involving 392 participants with PAD (ABI < 0.9), it was shown that those taking statins had better 6MWD (1,276 versus 1,218 feet, \( P = .045 \)); faster walking velocity (0.93 versus 0.89 m/s, \( P = .006 \)); and a superior performance score (10.2 versus 9.4, \( P < .001 \)) than those not taking statins after adjusting for all the confounders. In another study, atorvastatin was shown to improve pain-free walking distance and community-based physical activity after 12 months of treatment in 354 participants with IC.

There is also evidence that statins reduce surgical mortality and improve graft patency and limb salvage.

The current recommendation of the Adult Treatment Panel III Guidelines is to treat a patient with PAD as a coronary equivalent aiming for LDL-C levels < 100 mg/dl. However, a more aggressive LDL-C target of < 70 mg/dl should be considered to maximally reduce the atheroma burden and the related events in those with PAD and other high-risk features (such as uncontrolled risk factors). The common adverse effects associated with the use of statins include myalgias and myositis, neuropathy, hepatotoxicity, renal impairment, and cognitive impairment. Some of these, such as rhabdomyolysis and hepatotoxicity, can be fatal, although rarely.

**Carnitine**

Carnitine is an important cofactor for skeletal muscle metabolism during exercise (see Chapter 30, Alternative and Complementary Medicine for Preventing and Treating Cardiovascular Disease). An impairment in muscle energetics and abnormalities in carnitine metabolism, with a deficiency of carnitine, is seen in skeletal muscle in severe PAD. L-carnitine and its analogues are believed to act by replenishing the deficient carnitine and normalizing energy metabolism in ischemic muscle and may subsequently improve exercise capacity in patients with IC. One randomized, placebo-controlled trial found that L-carnitine, 2 g orally twice per day, improved absolute walking distance.

Propionyl-L-carnitine (PLC) is a naturally occurring analogue of carnitine that has been evaluated in the treatment of IC. A double-blind, placebo-controlled trial involving 245 participants with IC found a modest increase in ACD of 139 m (73%) in participants receiving PLC compared with 90 m (46%) in those receiving the placebo. There was a doubling in the ICD compared with the placebo, which failed to reach significance. A follow-up report to this trial noted a subjective improvement in functional status and quality of life among individuals with the most severely impaired walking capacity.

Another study involving 485 participants with IC identified a potential target population, those with an ACD of < 250 m, that may benefit from PLC therapy. In this group, there was an improvement in walking distances with PLC with an increase in ACD of 98% (155 m) compared with 54% (95 m) in the placebo group (\( P < .05 \)). The optimal dose of PLC is still under investigation, but the maximal benefit appears to occur at 2 g per day. Adverse effects reported with the use of PLC include occasional headache and GI symptoms. PLC may improve exercise performance and functional status; however, further clarification is required. This agent is not approved for the treatment of IC in the United States. However, an application for approval has been submitted to the FDA and is under review.

**Prostaglandins**

Prostaglandins of the E series and PGI\(_2\), are generated by the endothelium to maintain the microcirculation and to counteract the vasoconstrictive and proaggregatory actions of thromboxane A\(_2\). Because of their potent vasodilator and antiplatelet properties, these agents (especially PGE\(_1\) and PGL\(_2\)) have been evaluated in PAD. Although prostaglandins have primarily been evaluated for the treatment of CLI, they have also been tested for IC. In a randomized, placebo-controlled trial, 1,560 participants with CLI were treated with daily intravenous infusions of PGE\(_1\) for up to 28 days. This regimen resulted in improved tissue perfusion with diminished ongoing ischemia and reduced need for amputation at hospital discharge. There was a significant reduction in the combined endpoint (including death, major amputation, persistent CLI, MI, and stroke) at hospital discharge, although this difference was no longer significant at 6
months. Thus prostaglandins, particularly PGE₃, may play an important role in the treatment of CLI to allow healing of ulcers or limb salvage attempts in patients who are not candidates for surgery. These agents may be administered daily by intravenous infusion for up to 28 days in the management of CLI.

Several small studies have also suggested a benefit of PGE, in the treatment of IC with a moderate improvement in treadmill walking distance and an improvement in the quality of life. A surprising finding in one study was a marked beneficial effect when PGE infusion was added to an exercise program. The beneficial effects of PGE were also demonstrated in a recent single-blind controlled trial involving 123 participants with IC who were randomized in two groups. The first group received PGE while the second one received a pentoxifylline-buflomedil combination by venous infusion. After 4 weeks of treatment, there was an increase of about 370% in pain-free walking distance and 260% in the maximum walking distance in participants treated with PGE; the other group showed an increase of 110% and 118% respectively.

There has also been interest in the use of oral agents for long-term treatment of IC. A trial evaluated the effect of an oral PG₃ analogue, beraprost sodium (40 g 3 times daily for 6 months), on treadmill walking distance in 549 participants with severe IC. There was an improvement in ICD of 81.5% and ACD of 60.1% in the beraprost sodium group compared with respective increase of 52.5% and 35.0% in the placebo group. The difference between the beraprost sodium and the placebo groups was 36 m for the increase in ICD and 70 m for the increase in ACD at 6 months compared with baseline. Another trial involving 897 participants with IC found that beraprost was not effective at improving symptoms of IC, with no change in walking distances or quality of life compared with the placebo after 1 year of treatment.

Treprostinil and iloprost are also being investigated in participants with PVD.

Therapy with prostaglandins is often complicated by the development of hypotension, flushing, nausea, diarrhea, abdominal pain, and vomiting. It is important that these adverse effects be carefully assessed in order to be able to take precautionary measures where possible.

Vasodilators

In theory, vasodilators may be beneficial in the treatment of IC by improving blood flow in muscle and decreasing tissue ischemia. However, there have been no adequate controlled studies to demonstrate the efficacy of vasodilators in the treatment of IC. Vasodilator drugs such as papaverine were the first medications studied for the treatment of IC, but several controlled trials have failed to show any beneficial effects of the drugs of this class.

The lack of benefit may be explained by failure of these agents to dilate a fixed lesion in the peripheral vessels that limits blood flow in PAD and near maximal dilation of resistance vessels in ischemic limbs. On the contrary, in theory these may decrease resistance in other vessels leading to a “steal” of blood flow away from the underperfused muscle. In addition, they can lower systemic pressure leading to a further reduction in perfusion pressure. As a result, most vascular specialists agree that there is no role for vasodilators in the treatment of PAD.

A single trial suggested a benefit of verapamil in the treatment of IC, with an improvement in ICD and ACD of 29% and 49%, respectively, although this represented a small increase in walking distance and testing was performed on level ground. Nevertheless, the current data do not support the use of vasodilators for IC.

L-Arginine

Nitric oxide is a critical vasoregulatory mediator released from the endothelium, participating in control of vascular tone and regulation of blood flow. Nitric oxide is generated during the conversion of L-arginine to L-citrulline by the action of nitric oxide synthase. Nitric oxide has multiple actions that may be beneficial in the treatment of limb ischemia, including vasodilation, antiplatelet actions, and antiproliferative actions. L-arginine and nutritional supplements that enhance nitric oxide generation have been gaining interest as a potential therapy for PAD. Experimentally, L-arginine administered intravenously increased limb perfusion and nutritive capillary flow in ischemic limbs as determined by positron emission tomography. A trial involving 39 participants with IC found that both L-arginine and PGE improved walking distance compared with the placebo. In this study, 8 g of L-arginine administered by daily infusion for 3 weeks increased ICD by 147 m (230%) and ACD by 216 m (155%). These effects lasted for 6 weeks after the discontinuation of therapy and were associated with improved endothelium-dependent vasodilation, supporting enhanced nitric oxide generation. Similar improvements in walking distance have been reported with a nutritional supplement designed to enhance nitric oxide metabolism.

Another placebo-controlled trial examined the efficacy of a food bar that contained 3.3 g of L-arginine (as well as antioxidant vitamins and minerals, folic acid, and B-complex vitamins). After 2 weeks, there was modest improvement in pain-free and maximal walking distance in participants who ingested 2 bars per day. However, more prolonged use of L-arginine was not associated with a sustained beneficial effect on walking performance, and to the contrary, was associated with less of an improvement compared with the placebo.
Growth Factors

Angiogenesis is an exciting adjunct for this disease process, but it is no substitute for risk factor reduction (weight loss; smoking cessation; exercise; and control of hypertension, diabetes mellitus, and dyslipidemia) or revascularization. While enhancing angiogenesis, this will likely improve the symptoms of some patients with PAD, it has never been shown to improve limb salvage or exercise tolerance as the proven therapies listed above have.

The use of growth factors to stimulate the growth of new blood vessels, in an approach known as therapeutic angiogenesis, is an area of research that has gained widespread attention for the treatment of vascular disease. These agents have included vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hypoxia-inducible factor-1α (HIF1α) and hepatocyte growth factor (HGF) in the peripheral circulations.76-79

VEGF has been found to augment collateral development and improve tissue perfusion in experimental models of hind-limb ischemia.80 In patients with CLI, VEGF was found to stimulate the development of new vessels associated with ulcer healing and limb salvage.81 In this uncontrolled study, intramuscular gene transfer of naked DNA encoding human VEGF was performed in 10 limbs of 9 participants with nonhealing ulcers or ischemic leg rest pain.81 New visible collateral vessels were documented by computed tomographic angiography in 7 limbs, improved distal flow was seen by magnetic resonance angiography in 8 limbs, and marked improvement was observed by clinical assessment in 4 of 7 limbs with ulcers. The only reported complication was transient peripheral edema attributed to enhanced vascular permeability by the growth factor.82 This typically responded to a brief course of oral diuretic therapy. In a trial involving 105 participants with IC, VEGF administration was not associated with an improvement in exercise performance or quality of life.83

Similarly, bFGF has been shown to improve limb blood flow in experimental models and humans with IC.84 In a phase 1 trial, 19 participants with IC were randomized to receive by intra-arterial infusion 1 of 3 doses of bFGF or the placebo. Intra-arterial bFGF was safe and well tolerated without any detected retinal neovascularization during the 1-year follow-up. There was an improvement in resting calf blood flow measured by plethysmography in the two higher doses of bFGF at 1 month by 66% and 6 months by 153%.84

The use of recombinant FGF-2 has been evaluated in the phase II Therapeutic Angiogenesis with FGF-2 for Intermittent Claudication study in participants with PAD and IC. There was an improvement in the ACD at 90 days with a single infusion of recombinant FGF-2 compared with the placebo.85 Unfortunately, this benefit was no longer seen at 180 days, and there was no additional benefit of repeat infusions.

The use of both HIF1α and HGF as gene therapies has been tested for safety in participants with PAD with CLI. HIF1α therapy was evaluated in a phase 1 trial involving 34 participants with CLI and no revascularization options. At the end of one year, 42% of participants had complete resolution of rest pain and 30% had complete ulcer healing. The therapy was well tolerated as no participants developed any serious adverse events attributable to the study treatment.78

HGF therapy was evaluated for safety and efficacy in 104 participants with CLI. A statistically significant improvement in the transcutaneous oxygen pressure measurements was found at 6 months in participants who received high dose HGF therapy. The therapy was well tolerated, with most adverse events attributable to disease progression or comorbid conditions rather than the study drug itself.79

Other approaches to therapeutic angiogenesis include autologous transplantation of bone marrow and peripheral blood mononuclear cells.86-87 An interesting study enrolled 29 participants with CLI, the majority facing amputation as the only therapeutic option, to explore the utility of autologous peripheral blood mononuclear cells transplantation.88 The peripheral blood mononuclear cells were injected into the ischemic leg spaced several cm apart and repeated approximately one month later with assessment for up to 12 months after treatment. Maximum walking distance, healing of ischemic ulcers, and ankle-brachial blood pressure ratios were increased, whereas rest pain and amputation were decreased, with 21 of 29 participants manifesting improvement in at least one of these categories.

Endothelial cell therapy is also under study in patients. Although intriguing as potential therapeutic targets, these agents are still in the early stages of development. Therapeutic angiogenesis seems to be the promising hope for participants with advanced vascular diseases not responding to the conventional treatment.

Thrombolics

Thrombolytic agents, including streptokinase, urokinase, and tissue plasminogen activator (t-PA), have been evaluated in the management of acute arterial occlusion of the limbs (see Chapter 19, Thrombolytic Agents). As a group, these agents have been shown to be effective in dissolving thrombus and improving recanalization on angiography. They appear to reduce the need for surgical procedures and improve amputation-free survival.

Randomized trials have compared surgical thrombectomy and thrombolytic therapy in participants with acute arterial occlusion. For example, in a randomized
multicenter trial, catheter-guided intra-arterial recombinant urokinase was compared with vascular surgery for the management of acute arterial occlusion of the legs.\textsuperscript{90} The amputation-free survival rates among participants treated with urokinase were similar to those observed among participants treated with surgery at both 6 months and 1 year (71.8 versus 74.8\% at 6 months and 65.0 versus 69.9\% at 1 year).\textsuperscript{91}

A comparison of agents is limited and primarily involves open trials. In one such trial, intra-arterial recombinant t-PA (rt-PA) was superior to either intravenous rt-PA or intra-arterial streptokinase, resulting in a rate of thrombolysis of 100\%, compared to 45\% and 80\% for intravenous rt-PA or intra-arterial streptokinase, respectively.\textsuperscript{90} In another trial, rt-PA achieved more rapid thrombolysis than urokinase; however, there was no significant difference between treatments in success at 30 days.\textsuperscript{91}

It is not possible, based upon the available data, to make an absolute recommendation on the selection of a specific agent or dose; however, the current clinical practice has favored the use of rt-PA.\textsuperscript{92,93} The preferred route of administration is catheter-guided intra-arterial or intrathrombus infusion rather than the intravenous administration. Although variable dosing schemes are available, a commonly used regimen for rt-PA is 1 mg/hour or 0.05 mg/kg/hour. The common adverse effects relate to hemorrhagic complications.

Surgical revascularization is still indicated for profound limb-threatening ischemia, with emergent thromboembolectomy for proximal emboli. However, thrombolysis should be considered for acute limb ischemia due to thrombosis or embolus presenting within 24 to 48 hours of onset. It is now an acceptable part of a treatment strategy designed to gradually restore blood flow to minimize reperfusion injury.\textsuperscript{92} However, successful thrombolysis will often reveal an underlying lesion that requires correction by either a percutaneous or surgical approach. Furthermore, emboli that may consist of old thrombus and atherosclerotic plaque may be less amenable to thrombolysis.

**Other Agents**

**Alpha Tocopherol**

Alpha tocopherol, the most active form of vitamin E, is a lipid-soluble antioxidant that participates in the defense against oxygen-derived free radicals (see Chapter 30, Alternative and Complementary Medicine for Preventing and Treating Cardiovascular Disease). Vitamin E has been advocated for the treatment of IC since the 1950s, when several small studies suggested some improvement.\textsuperscript{94,95} Since that time, the data supporting the use of vitamin E have been limited. In a large cancer prevention study, alpha tocopherol (50 mg daily) did not prevent the development of IC in male smokers, as assessed by the Rose questionnaire.\textsuperscript{96} The results of the Heart Outcome Prevention Evaluation trial regarding the effect of vitamin E use on cardiovascular events in a high risk group of participants, many with established PAD, were disappointing.\textsuperscript{97}

**Ketanserin**

Ketanserin is a selective S\textsubscript{2}-serotonin receptor antagonist with actions including vasodilation, decreased blood viscosity, and perhaps dilation of collateral vessels. Clinical trials evaluating the effect of ketanserin in the treatment of IC have been controversial. Although a small placebo-controlled study found an improvement in walking distance, ketanserin failed to improve treadmill walking distance compared to the placebo in a multicenter trial involving 179 participants with IC.\textsuperscript{98,99} In this study, a serendipitous discovery of a higher incidence of cardiovascular complications in the placebo group was made, which was subsequently confirmed in a pooled analysis, suggesting that ketanserin may possess a protective effect against thrombovascular complications.\textsuperscript{100} This led to the PACK trial (Prevention of Atherosclerotic Complications with Ketanserin), which was designed to determine the effect of ketanserin on cardiovascular events during 1 year of treatment.\textsuperscript{101}

In the PACK trial, 3,899 participants with IC were randomized to receive ketanserin or the placebo; however, many participants were withdrawn prematurely due to excessive mortality in the ketanserin group. This has since been attributed to QT-interval prolongation in association with hypokalemia caused by potassium-wasting diuretic agents. Ketanserin is not available in the United States, and its role in the treatment of IC remains undefined.

**Naftidrofuryl**

Naftidrofuryl is a serotonin-receptor antagonist that inhibits platelet aggregation and enhances oxidative metabolism in ischemic tissue. A moderate beneficial effect of naftidrofuryl in the treatment of IC has been suggested in a number of randomized trials. A recent meta-analysis of 4 randomized trials found that naftidrofuryl increased ICD by 59 m and ACD by 71 m compared to the placebo.\textsuperscript{5} Another randomized trial involving 188 participants with severe IC found an improvement in ICD but no effect on ACD or ABI.\textsuperscript{102} Subjectively, there was a delay in the deterioration of symptoms with naftidrofuryl. The recommended dose of naftidrofuryl is 400 to 800 mg daily. The most common adverse effects are mild, tolerable GI symptoms. This agent is not available in the United States, but has been used in Europe for the symptomatic treatment of IC for over 20 years.

**Defibrotide**

Defibrotide is a polydeoxyribonucleotide that modulates endothelial function, enhancing the release of t-PA, de-
creasing the release of t-P inhibitor, stimulating the release of prostacyclin and other prostanoids, and, perhaps, inhibiting platelet aggregation. In a double-blind, placebo-controlled trial involving 227 participants with IC, defibrotide increased ACD by about 50% compared to 17% in the placebo group. A trend towards improvement in ABI was reported, although this may be explained by a reduction in systolic blood pressure. In another small open study, defibrotide improved walking distance and rest pain. Defibrotide is dosed 200 to 400 mg twice daily. This agent deserves further investigation but is presently unavailable for use.

Buflomedil

Buflomedil acts through several mechanisms to promote vasodilation and improve rheology, promoting platelet disaggregation and improving erythrocyte deformability. The results of clinical investigations evaluating its efficacy in the treatment of IC have been conflicting. In a randomized trial involving 93 participants with IC, treatment with buflomedil for 12 weeks improved both ICD and ACD by 100% and 97%, respectively compared with the placebo 38% and 42% respectively. Another small study comparing buflomedil to pentoxifylline or nifedipine found that the improvement in ICD with buflomedil was less than that noted with pentoxifylline. Perhaps most intriguing was a study involving 2,078 participant in a randomized, double-blind, placebo-controlled trial involving 153 participants with IC found that chelation therapy did not improve walking distance, angiographic findings, tissue oxygen tension, ABI, or subjective assessments of symptoms. Despite its supporters, this type of treatment is of dubious benefit and has significant potential adverse effects, such as hypocalcemia and renal failure.

Ginkgo Biloba

Ginkgo biloba extract has long been suspected to have potential benefit in PAD (see Chapter 30). In a recent meta-analysis involving 11 trials with a total of 477 participants, there was a modest effect on walking distance as ACD increased with an overall effect size of 3.57 kilocalories. It was felt that publication bias with missing data and “negative” trials likely inflated the effect size. Thus it was concluded that there is no evidence that Ginkgo biloba has a clinically significant benefit for patients with PAD.

Raynaud’s Syndrome

Raynaud’s phenomenon, described by Maurice Raynaud in 1888, is characterized by paroxysmal episodes of digital ischemia resulting from vasospasm of the digital arteries, with subsequent dilation and reperfusion. Clinically it is manifested by episodes of sharply demarcated “color changes” of the skin of the digits, often precipitated by cold exposure or emotional stress. Raynaud’s syndrome (RS) is considered primary (or idiopathic) if the symptoms occur in the absence of an associated systemic disorder and secondary if they occur in association with a disorder such as systemic lupus erythematosus or scleroderma.

Management of RS includes nonpharmacologic measures, pharmacologic treatment and/or surgical intervention. The exact mechanism of RS is unknown but is believed to be due to derangement of several different factors, acting by local, humoral, and nervous system mechanisms, which affect the normal regulation of blood flow to the fingers. The available pharmacologic agents
could specifically target one of these abnormalities responsible for the disease.

The approach to treating patients with RS should be individualized, depending upon the severity and frequency of the vasospastic attacks, presence or absence of the underlying connective disease, and the risk of developing ischemic ulceration, gangrene, or loss of digits.

Primary RS usually does not require drug therapy; typically, it responds well to conservative measures such as education, reassurance, and behavior modification. The patient should be educated about the nature and prognosis of the disease and reassured that the disorder is benign with little risk of progression, finger ulcers, or digit loss. They should be advised on minimizing cold exposure through the use of mittens (rather than gloves), the use of hand and foot warmers, and, importantly, keeping the entire body warm (to avoid reflex sympathetic vasoconstriction). Drug therapy becomes necessary if the frequency and severity of vasospastic episodes interfere with daily functioning or quality of life.

On the contrary, drug therapy is often required in patients with secondary RS, in addition to behavioral modification therapy.

A variety of agents have been evaluated for the treatment of RS (Table 34-3). Most of these medications, which have potent direct or indirect vasodilator properties, may help to decrease the intensity and frequency of vasospastic episodes, but they do not cure the underlying cause of vasospasm.

Choosing the best medication has been difficult because of the lack of large prospective, randomized, double-blind studies comparing the efficacy of different medications in RS. Most clinical trials rely on the participant’s self-assessment of the response to the medications. Moreover, it is not feasible to quantitatively reproduce vasospastic attacks in the vascular laboratory, making it quite difficult to confirm the clinical response to a medication. Currently, none of the available drugs are approved by the FDA for the treatment of RS.

**Calcium-Channel Blockers**

Calcium-channel blockers are the pharmacologic agents most commonly used for the treatment of RS. They inhibit the influx of the extracellular calcium ions into smooth muscle cells, which causes relaxation of vascular smooth muscle and resultant vasodilatation. As a group, these agents have been shown to reduce the frequency, duration, and severity of attacks. However, calcium-channel blockers differ in their vasodilator potency, with the dihydropyridine class seeming to be the most potent and effective agents.

Nifedipine has been the most intensively investigated of the calcium-channel blockers and is considered by many as the gold standard for the pharmacologic treatment of RS. Several double-blind, placebo-controlled trials have shown it to decrease the frequency and severity of attacks. One such study used a crossover design and found that 60% of participants with RS reported moderate to marked improvement in clinical symptoms, with a decreased attack rate while receiving nifedipine, compared with 13% of participants receiving the placebo.114 The largest trial, involving 313 participants with primary RS, found a 66% reduction in vasospastic attacks in the nifedipine-treated participants compared with the placebo-treated participants.115 A meta-analysis of 18 double-blind randomized controlled trials that evaluated the efficacy of calcium-channel blockers in participants with primary RS found an average reduction of 2.8 to 5.0 attacks per week and a 33% reduction in the severity of attacks.116 Another meta-analysis of studies evaluating the effect of calcium-channel blockers in participants with scleroderma-associated RS found similar results with an average reduction of 4.0 attacks per week and a 35% reduction in the severity of attacks.117 Despite convincing subjective benefits, confirmation of objective improvement in digital blood flow with nifedipine and other calcium-channel blockers has been difficult to substantiate. Early studies reported that nifedipine had variable effects on the peripheral circulation in participants with RS. The drug failed to attenuate cold-induced reduction in digital artery pressure in one study of participants with RS.118 In contrast, although nifedipine did not significantly increase finger blood flow following acute sublingual administration, it did decrease vascular resistance, indicating that vasodilation of digital vessels has occurred.119 A large trial involving 158 participants with primary RS demonstrated higher digital pressure during cooling in nifedipine-treated participants.120

The recommended dose of nifedipine is 10 to 30 mg 3 times daily for the short-acting preparation or 30 to 90 mg once daily for the long-acting preparations. The long-acting, sustained-release preparations appear to be better tolerated and are probably as effective as the short-acting, immediate-release form.114,115 Only 15% of participants discontinued therapy due to adverse effects. Nifedipine may be used intermittently for cold exposure if it is tolerated. The treatment should be started with low dose, followed by an upward titration according to the therapeutic effect, blood pressure, and toleration. The most common adverse effects are headache, dizziness, nausea, heartburn, pruritus, palpitations, and peripheral edema. The headache is often mild and transient, lasting for the first several days of use.

Other dihydropyridine calcium-channel blockers, including amlodipine, felodipine, isradipine, nicardipine, and nisoldipine, have also been shown to have favorable effects in patients with RS.120–125 Other types of calcium-channel blockers have played a limited role in the treatment of this condition.
### Table 34-3. Drug Therapy for Raynaud’s Phenomenon

<table>
<thead>
<tr>
<th>Agent</th>
<th>Daily Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-channel blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>30–90 mg</td>
<td>Headache, leg edema, flushing, palpitations</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5–10 mg</td>
<td>Same as above</td>
</tr>
<tr>
<td>Isradipine</td>
<td>5–20 mg</td>
<td>Same as above</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>120–360 mg</td>
<td>Constipation, nausea, headache, flushing</td>
</tr>
<tr>
<td>Sympathetic blocking agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>2–8 mg</td>
<td>Nausea, headache, dizziness, dyspnea, edema, diarrhea</td>
</tr>
<tr>
<td>Reserpine</td>
<td>0.25–1 mg</td>
<td>Postural hypotension, bradycardia, lethargy, depression</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGI₂ (IV)</td>
<td>7.5 to 10 ng/kg/min for 5-7 days</td>
<td>Hypotension, flushing, nausea, diarrhea, abdominal pain, and vomiting</td>
</tr>
<tr>
<td>Iloprost (IV)</td>
<td>0.5 to 2.0 ng/kg/min for 5-7 days</td>
<td>Same as above</td>
</tr>
<tr>
<td>Epoprostenol (IV)</td>
<td>1-2 ng/kg/min then titrate up to 20-40 ng/kg/min</td>
<td>Same as above</td>
</tr>
<tr>
<td>Iloprost (oral)</td>
<td>100 to 200 microgram</td>
<td>Same as above</td>
</tr>
<tr>
<td>Serotonin blocking agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketanserin</td>
<td>20-80 mg</td>
<td>Dizziness, tiredness, edema, dry mouth, weight gain, prolonged QTc</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg</td>
<td>Dizziness, nausea, vomiting, diarrhea, insomnia, seizures, agitation</td>
</tr>
<tr>
<td>Angiotensin system blocking agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril *</td>
<td>75 to 150 mg</td>
<td>Cough, rash, renal, insufficiency, hyperkalemia, angioedema</td>
</tr>
<tr>
<td>Losartan †</td>
<td>50 to 100 mg</td>
<td>Same as above (except cough)</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosentan</td>
<td>125 to 250 mg</td>
<td>Headache, flushing, edema, hepatic dysfunction; contraindicated in pregnancy</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cilostazol</td>
<td>100 to 200 mg</td>
<td>GI symptoms, headaches, and palpitations. May exacerbate heart failure.</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>100 mg</td>
<td>Headache, flushing, dizziness, diarrhea, heartburn, blurred vision</td>
</tr>
<tr>
<td>Nitric oxide (NO) donors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-arginine</td>
<td>8 g</td>
<td>Hypotension, GI symptoms, headache, leg edema</td>
</tr>
</tbody>
</table>

*Comparable dose ranges of any of the available ACE inhibitors can be considered for use.
†Comparable dose ranges of any of the available angiotensin-receptor blockers can be considered for use.
GI = gastrointestinal
There is controversy regarding the effect of diltiazem. A reduction in the frequency and severity of attacks was shown with diltiazem, with the most benefit seen among participants with primary RS.\textsuperscript{126} Another study found that diltiazem was ineffective in the treatment of RS associated with connective tissue disease.\textsuperscript{127} One trial reported that verapamil was ineffective in a group of participants with severe RS.\textsuperscript{128}

### Sympathetic Blocking Agents

Sympathetic adrenergic stimulation of digital arteries, especially involving $\alpha_1$ and $\alpha_2$ adrenergic receptors, plays an important role in the regulation of digital blood flow. A variety of sympatholytic drugs have been used in the treatment of RS, but few controlled trials have been conducted to evaluate their efficacy.

Prazosin is the $\alpha_1$-adrenoceptor antagonist that has been the best studied of this class of agents for the treatment of patients with RS, particularly Raynaud's phenomenon in progressive systemic sclerosis.\textsuperscript{129} Several placebo-controlled studies have found a decrease in the frequency, duration, and severity of vasospastic attacks in approximately two-thirds of participants with RS after 2 weeks of treatment with prazosin.\textsuperscript{130-132} Its effectiveness, however, appears to decrease with prolonged use, despite titration to the maximally tolerated dose.\textsuperscript{125} In a Cochrane review, two studies showed modest results with prazosin in the treatment of RS.\textsuperscript{129} The recommended dose range is from 2 to 8 mg daily. Adverse effects, including postural hypotension, palpitations, dizziness, fatigue, headache, dyspnea, edema, rash, and diarrhea, may limit its use.

Thymoxamine, another $\alpha_1$-adrenoceptor antagonist, has also been evaluated in the treatment of RS. In an uncontrolled study, thymoxamine at a dose of 40 mg 4 times daily resulted in clinical improvement, with a decrease in the frequency of attacks and an improvement in digital perfusion during cold challenge.\textsuperscript{133} Adverse effects are reported to be less frequent than with prazosin; however, experience with this agent is limited and it is not available in the United States.

There are limited controlled data to support the routine use of $\alpha_2$-adrenoceptor antagonists in the treatment of RS, although many vascular specialists find these agents useful. However, these agents have not been shown to be more effective than calcium-channel blockers. They may be considered for patients who do not tolerate calcium-channel blockers or for those with refractory symptoms that do not respond to other measures.

It was found that the predominant types of receptors in the vascular smooth muscle of distal micro-vasculature are $\alpha_1$-adrenergic receptors.\textsuperscript{134} A study compared the effect of an oral selective $\alpha_2$-adrenergic receptor blocker OPC-28326 at a dose of 40 mg per day to the placebo in 13 participants with scleroderma-associated RS. There was a significant improvement in digital perfusion and a shorter time for skin temperature recovery after cold provocation test.\textsuperscript{135}

The experience with several other sympatholytic agents, including reserpine, guanethidine, methyldopa, phenoxybenzamine, and tolazoline, is limited.

### Prostaglandins

Prostaglandins are potent vasodilating agents that also inhibit platelet aggregation, inhibit smooth muscle cell proliferation, and increase vascular permeability. The potent vasoactive properties have led to interest in their potential use for the treatment of patients with refractory RS. Intravenous infusion with prostacyclin is an accepted treatment in patients with severe Raynaud's phenomenon with ischemic digital ulcers.

Studies evaluating prostacyclin and its analogues (iloprost, epoprostenol, treprostinil, and beraprost) have shown a clinical benefit of these agents in participants with intractable RS. Infusion of prostacyclin 7.5 to 10 ng/kg/minute decreased the frequency and severity of vasospastic attacks compared to the placebo.\textsuperscript{136,137} It is unclear whether this subjective improvement is associated with objective improvement in digital flow or finger temperature.

Iloprost is a chemically stable prostacyclin analogue with a longer half-life of 20 to 25 minutes. In a placebo-controlled, double-blind study involving 131 participants with RS associated with scleroderma, iloprost decreased the frequency and severity of Raynaud's attacks.\textsuperscript{138} Another study found that infusion of 0.5 to 2.0 ng/kg/min of iloprost for 8 hours on 3 days was equivalent to nifedipine at decreasing the frequency, duration, and severity of vasospastic attacks and in promoting the healing of digital lesions.\textsuperscript{139} A review of 4 trials found that intravenous iloprost was effective in the treatment of secondary RS associated with scleroderma as it decreased the frequency and severity of attacks and prevented digital ulceration or promoted healing in these participants.\textsuperscript{140}

Iloprost has even been suggested to have some disease-modifying effects in scleroderma-associated vasculopathy. A study found significant skin softening in scleroderma participants treated with iloprost.\textsuperscript{141} Another study found that after a 5- to 7-day infusion of iloprost, scleroderma participants with secondary RS experienced reduced serum levels of s-intracellular adhesion molecule-1, s-vascular cell adhesion molecule-1, sE-selectin, and VEGF.\textsuperscript{142} These findings suggest inflammation-modulating properties of iloprost, in addition to vasodilatory properties. Adverse effects of iloprost occur primarily during the infusion and include hypotension, flushing, nausea, vomiting, myalgia, and pain at the infusion site.
Epoprostenol, another intravenous prostacyclin analogue with a very short half-life (~6 minutes), has been shown to be beneficial. It is administered as an infusion at 1-2 ng/kg/min initially, then titrated up to 20-40 ng/kg/min. The therapeutic effect of epoprostenol was demonstrated by a decrease in the severity of vaso spasms and frequency of digital ulcers in a large randomized controlled trial involving 111 scleroderma participants with secondary RS.143

Oral prostaglandins have been under intensive investigation over the past several years; however, the results have been mixed and often disappointing.144,145 A multicenter, placebo-controlled, dose-comparative study with 103 scleroderma participants with secondary RS treated with oral iloprost 50 to 100 µg twice a day resulted in reduced duration and severity of attacks.146 However, in another double-blind, multicenter, placebo-controlled study, the improvement of oral iloprost in RS did not reach statistical significance.147 An oral prostacyclin analogue beraprost was shown to improve digital perfusion and increase skin temperature in scleroderma participants with PAH and RS.148

The exact role that prostaglandins play in the management of RS awaits further clarification, but these agents seem to be effective in providing short-term palliation in patients with ischemic acute digital ulcerations.

**Serotonin Blocking Agents**

Both the serotonin receptor antagonists and serotonin reuptake inhibitors have been evaluated in the treatment of RS. Ketanserin is a serotonin receptor antagonist that has been used for the treatment of RS for a long time. It has several actions on vascular reactivity that may be useful in the treatment of RS. In addition to preventing vasoconstriction and inhibiting platelet aggregation caused by serotonin, it also increases finger blood flow during reflex sympathetic vasoconstriction. In a double-blind, placebo-controlled trial involving 222 participants with RS, ketanserin at a dose of 40 mg 3 times daily significantly reduced the frequency of vasospastic episodes (34% with ketanserin compared with 18% in the placebo group).149 A subjective global evaluation of symptoms completed by both participants and physicians favored ketanserin; however, the severity and duration of attacks was not affected. There was no change in finger blood flow at rest or in response to cold challenge. However, a review of 3 trials found that ketanserin is not significantly different from the placebo for the treatment of secondary RS in progressive systemic sclerosis except for some decrease in the duration of attacks.150 Ketanserin is available in several countries but not in the United States.

Another serotonin receptor antagonist has been evaluated in RS. Sarpogrelate hydrochloride, a 5-HT₁-receptor antagonist, was given for one year to 72 participants with secondary RS.151 There was a subjective improvement of symptoms in 59.3% of participants, with a significant increase in the acceleration plethysmograms compared with baseline, suggesting an improvement in peripheral hemodynamics. These studies have been inadequately controlled, and further investigation is required.

The antiplatelet and endothelium-protective properties of fluoxetine, a selective serotonin reuptake inhibitor, may represent an attractive additional advantage in patients with scleroderma and depression. Patients with scleroderma should be screened for depression, and selective serotonin reuptake inhibitors might be considered. One study found a reduction in severity and frequency of vasospastic attacks with fluoxetine (20 mg daily) compared to nifedipine (40 mg daily) in both primary and secondary RS.152

**Angiotensin Blocking Agents**

Both ACE inhibitors and angiotensin receptor antagonists may have a role in the treatment of RS. These agents may improve local blood flow by blocking the vasoconstrictive action of angiotensin II and, in the case of ACE inhibitors, potentiate the action of bradykinin.

Interest in the use of these agents developed following the report of remarkable improvement in the vasospastic-induced ischemic digital ulceration in a small number of patients being treated with captopril for scleroderma-associated hypertensive renal crisis.153 In uncontrolled studies, captopril at a dose of 25 mg 3 times daily has been reported to decrease the frequency and severity of attacks in patients with primary RS but not in those with RS associated with scleroderma.154 These subjective benefits were supported by attenuation in the cold-induced vasoconstriction. Similar findings were observed with the angiotensin receptor antagonist losartan, which decreased the frequency and severity of attacks in primary RS.155 A pilot study indicated that losartan 50 mg daily was more effective than nifedipine 40 mg daily in decreasing the frequency of vasospastic episodes in both primary and secondary RS.156 Despite this finding, most vascular clinicians have not found ACE inhibitors to be useful clinically in the prevention or treatment of vasospastic attacks. In fact, a recent meta-analysis concluded that there is no definite evidence to suggest angiotensin receptor blockers or ACE inhibitors are superior to the traditionally used treatments such as calcium-channel blockers.157

**Endothelin Blocking Agents**

Endothelin-1, a potent substance derived from vascular endothelium, plays a key role in the pathogenesis of Raynaud’s phenomenon and PAH secondary to connec-
tive tissue diseases (see Chapter 25, Prostacyclins, Endothelin Inhibitors, and Phosphodiesterase-5 Inhibitors in Pulmonary Hypertension). It causes a number of deleterious effects including vasoconstriction, fibrosis, inflammation, and vascular hypertrophy. Several endothelin receptor antagonists have shown beneficial effects in participants with RS associated with scleroderma.

Bosentan, a non-selective endothelin receptor antagonist, is the first drug from this group approved by the FDA, but it was approved for the treatment of PAH associated with connective tissue diseases. As a potent vasodilator, it has also been shown to be effective in other vasospastic diseases including RS associated with scleroderma. Two large multicenter, double-blind, placebo-controlled trials were performed to evaluate the effectiveness of bosentan in the treatment and prevention of acute ischemic ulcers in participants with scleroderma-associated RS. These studies showed that bosentan was effective in the prevention of new digital ulcers (an average of 48% less than the placebo). It is administered orally at a dose of 62.5 mg twice a day (up to 250 mg a day). Adverse effects include headache, flushing, edema, and elevation of liver transaminases. It is also contraindicated in pregnancy.

Newer, highly selective endothelin receptor antagonists, sitaxsentan and ambrisentan, are highly specific for ETA receptors and could potentially be beneficial in patients with scleroderma-associated RS. These agents have been proven to have significant vasodilatory effects in PAH in multicenter randomized controlled trials.

Phosphodiesterase Inhibitors

Nitric oxide, a potent vasodilator, produces its effects via cyclic guanosine monophosphate (cGMP). The intracellular concentration of cGMP is regulated by PDEs, which rapidly degrade cGMP in vivo. Pentoxifylline is from this group of agents but has not proven to be effective in the treatment of severe forms of RS. One study reported some beneficial effects on the peripheral circulation, resulting in an increase in resting digital blood flow and an attenuation of cold-induced vasoconstriction in participants with RS. Despite a suggestion of clinical improvement, double-blind, placebo-controlled studies have not demonstrated convincing beneficial effects of pentoxifylline compared with the placebo.

Sildenafil, a specific inhibitor of PDE-5 isoform, has been shown to cause digital artery vasodilation. In a double-blind, placebo-controlled study, sildenafil at 100 mg daily improved symptoms and increased digital perfusion in participants with secondary RS after 4 weeks of treatment.

Cilostazol, a specific inhibitor of PDE-3 isoform, did not improve symptoms of RS or microcirculatory blood flow after 6 weeks of treatment. Further studies with a larger number of participants are necessary to confirm the ultimate effectiveness of this group of drugs.

Nitric Oxide Donors

Nitric oxide is a potent vasodilator produced by endothelial cells from its precursor amino acid L-arginine. Nitrates are nitric oxide donors and have been used in the treatment of RS as topical, oral, and intravenous preparations. Poor dose-response characteristics and the occurrence of nitrate-induced headaches generally limit the use of oral nitrates. Intravenous nitroglycerin causes systemic vasodilation, rather than selectively increasing digital microcirculation. Topical nitroglycerin seems to be effective and has been shown to reduce the severity and frequency of vasospastic episodes in patients with primary and secondary RS. Nevertheless, due to potent vasodilation, even the topical nitrates can cause adverse effects such as headache and cutaneous rash. In general, nitrates are not considered first-line therapy for RS but may be considered to assist in the healing of ulcers.

L-arginine supplementation, which enhances the endogenous production of nitric oxide, is an intriguing potential agent in the treatment of RS. In patients with primary RS, L-arginine at a dose of 8 g/day for 28 days had no significant effect on the cutaneous vascular response to acetylcholine or sodium nitroprusside. However, there was no description of the effect on the frequency or severity of vasospastic episodes. In contrast, topical application of a nitric oxide–generating gel in patients with primary RS increased microcirculatory volume and flux. Intra-arterial infusion of L-arginine at 8.5 mg/minute reduced cold-induced vasoconstrictive response in participants with RS. This line of therapy requires further investigation prior to suggesting this as a treatment for RS.

Other Agents

A large number of alternative vasodilators have been used in the treatment of severe RS, including minoxidil, hydralazine, and sodium nitroprusside. The use of these agents is not recommended, however, because controlled trials have not been performed and alternative agents are readily available.

Thyroid preparations had been recommended for the treatment of Raynaud’s phenomenon since the 1960s. In a double-blind, placebo-controlled, crossover trial of 18 participants with RS, a daily dose of 80 μg of triiodothyronine significantly reduced the frequency, duration, and severity of attacks. However, there was an increase in heart rate, and one-third of participants reported episodic palpitations. The authors suggested that lower (“physiologic”) doses of triiodothyronine should be evaluated.
Selective thromboxane synthetase inhibitors have also been evaluated in the treatment of RS. This class of agents may have useful effects by inhibiting production of thromboxane A₂ and preserving production of endogenous prostacyclin, thus promoting vasodilation and inhibiting platelet aggregation. In a double-blind, placebo-controlled trial, administration of dazoxiben 400 mg daily for 6 weeks improved the clinical manifestations of primary RS. These results are controversial, however, as other studies have found dazoxiben to be ineffective in the treatment of RS.

Calcitonin gene-related peptide, a potent vasodilator, is a neuropeptide produced by peripheral sensory nerves. It has been observed that patients with RS appear to be deficient in this peptide. In addition, patients who received calcitonin gene-related peptide infusion demonstrated a significant increase of skin temperature and an improvement in blood flow compared to saline infusion. There was also healing of digital ulcers in 4 patients. Adverse effects included flushing, diarrhea, headache, and hypotension.

Since patients with RS have enhanced platelet aggregation, low doses of aspirin are recommended, especially for those with digital ischemia and recurrent ulcers. Low-molecular-weight heparin (LMWH) has also been shown to be beneficial in patients with severe RS. A study found improved finger blood flow in 16 participants with severe RS receiving LMWH. Further studies are needed to confirm the potential beneficial effects of anticoagulants in RS.

**Deep Vein Thrombosis**

DVT and pulmonary embolus are expressions of venous thromboembolism (VTE), which is a major cause of hospital morbidity and mortality. The goal of therapy for established VTE is to prevent thrombus propagation, recurrent thrombosis, pulmonary embolization, and mortality, as well as the development of late complications. The benefit of anticoagulation in the management of thromboembolic disease is undisputed. Furthermore, prophylactic anticoagulant strategies are an effective means to prevent the development and complications of DVT, particularly in higher-risk patients.

Currently available anticoagulants include both parenteral and oral agents. Rapidly acting parenteral anticoagulants are usually used for the initial treatment of VTE, whereas oral agents are employed for long-term therapy. For long-term anticoagulation, oral agents are preferred over parenteral drugs. Limitations of existing antithrombotic drugs have prompted a search for novel agents with more predictable pharmacokinetics, a wide therapeutic window, fewer drug or dietary interactions, longer half lives, and importantly, no need for routine monitoring.

The American College of Chest Physicians has specific recommendations (Table 34-4) regarding the management of VTE and prevention of thromboembolic complications in various medical and surgical situations. This section will review various drug options available for the management of VTE with the limitations of the existing agents followed by a discussion of newer agents, which have shown encouraging results in the prevention and management of VTE.

**Heparins**

**Unfractionated Heparin**

Unfractionated heparin (UH) has been the mainstay of treatment and prevention of DVT. Heparin forms complexes with antithrombin, leading to the inactivation of factors IIa, Xa, and IXa, and the inhibition of factor V and VIII activation by thrombin. UH is generally administered by either continuous IV infusion or intermittent subcutaneous injections. Initial dosing of IV heparin for VTE is either weight-based (80 U/kg bolus and 18 U/kg/h infusion) or administered as a bolus of 5,000 U followed by an infusion of at least 32,000 U/day. If heparin is given subcutaneously for treatment of VTE, there are at least two options: (1) an initial IV bolus of approximately 5,000 U followed by 250 U/kg twice daily; or (2) an initial subcutaneous dose of 333 U/kg followed by 250 U/kg twice daily. Because the anticoagulant response to heparin is unpredictable and varies among patients, it is standard practice to monitor heparin and to adjust the dose based on the results of coagulation tests, commonly monitored using the activated partial thromboplastin time (aPTT). It has been suggested that an aPTT ratio between 1.5 and 2.5 is associated with a significantly reduced risk of recurrent VTE. This is widely accepted and has been shown to correspond to a heparin blood level of 0.2 to 0.4 IU/mL by protamine sulfate titration assay and a heparin level of 0.3 to 0.7 U measured by an anti-Xa assay.

The beneficial effects of heparin in the treatment of VTE have been known since 1960. In a randomized trial, participants with proximal DVT treated with continuous IV heparin had a lower rate of recurrent thromboembolism compared with those treated with subcutaneous heparin (5.2% versus 19.3% over 6 weeks). The efficacy of heparin was found to be highly dependent upon achieving a therapeutic level within the first 24 hours of therapy. The use of weight-based nomograms has facilitated the time required to achieve a therapeutic aPTT.

Complications of heparin therapy include bleeding, thrombocytopenia (often with paradoxical thrombosis),
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One of the common problems of heparin treatment is heparin resistance, which affects 25% of patients with VTE. It is defined as a heparin requirement of more than 35,000 units per day. Some causes implicated include anti-thrombin deficiency, elevated circulating factor VIII and fibrinogen levels, increased heparin clearance, or use of concomitant medications such as aprotinin or nitroglycerin. The options in such a situation are to either increase the heparin dose further or switch to an LMWH or a direct thrombin inhibitor.

Another challenge with heparin therapy is (type 2) heparin-induced thrombocytopenia (HIT), which is caused by heparin-dependent IgG antibodies with ability to induce immune mediated platelet activation and destruction. HIT affects 5% to 7% of patients receiving heparin therapy and typically occurs 5 to 10 days after the initiation of therapy. The diagnosis is suspected if the platelet count decreases by 50% or more from baseline or the absolute platelet count decreases to less than 100 x 10⁶ per liter. HIT is dangerously associated with a paradoxic risk of thrombotic events, which can occur in up to 50% of affected patients, and the risk can last for up to 30 days or more after heparin withdrawal. Hence, an alternative anti-thrombotic agent is initiated in these patients after withdrawing heparin. ACCP guidelines suggest monitoring platelet counts every other day in patients initiated on heparin therapy.

UH has also been shown to be effective in the prevention of DVT formation in many higher-risk patient populations. Fixed-dose subcutaneous heparin (5000 U given 2 hours before and every 8 to 12 hours after surgery) reduced the incidence of VTE by 70% and fatal pulmonary embolus by 50% following general surgical procedures. Benefits have also been reported in neurosurgical, general medical, ischemic stroke, and trauma patients as well as those with acute spinal cord injuries and possibly also orthopedic patients. However, the effect in orthopedic patients undergoing knee or hip surgery was relatively slight and less than that of alternative strategies. Use of dose-adjusted subcutaneous heparin to keep the aPTT in the high normal range may be more effective but has not been widely tried. One study found that following hip arthroplasty, only 5 of 38 participants on adjusted-dose heparin developed DVT, compared to 16 of 41 participants on fixed-dose heparin. The use of heparin prophylaxis appears to be safe, as the incidence of major bleeding is not increased, although minor wound hematomas may ensue.

Low-Molecular-Weight Heparins

LMWHs are largely replacing UH for the prevention and treatment of DVT (see Chapter 18, Antiplatelet and Other Antithrombotic Drugs). The constituents of UH have a molecular weight ranging from 3,000 to 30,000 Da, while LMWHs have fragments of UH with a mean molecular weight of about 5,000 Da. Their mechanism of action is similar to that of UH, although they possess greater relative inhibitory activity against factor Xa than against factor IIa. LMWH is used in both fixed and weight-adjusted dosing regimens and is administered subcutaneously once or twice daily. Compared to UH, LMWH

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Clinical Feature</th>
<th>Prophylaxis Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Medical–Fully mobile Surgical–Brief procedure with no risk factors</td>
<td>No specific prophylaxis Early ambulation</td>
</tr>
<tr>
<td>Moderate</td>
<td>Medical–Bed bound Surgical–Major general, urologic, and gynecologic</td>
<td>LMWH UH-SQ Fondaparinux Compression therapy for high bleeding risk</td>
</tr>
<tr>
<td>High</td>
<td>Medical–Trauma Surgical–Orthopedic</td>
<td>LMWH Fondaparinux UH-SQ Vitamin K antagonist (INR 2-3)</td>
</tr>
</tbody>
</table>

LMWH = low-molecular weight heparin; UH-SQ = subcutaneous unfractionated heparin; INR = International Normalized Ratio

has a more predictable anticoagulant response (with no need for routine monitoring), reflecting its better bioavailability, longer half-life, and non-dose-dependent clearance. Additional potential advantages of LMWH include fewer bleeding complications and a lower risk of thrombocytopenia. LMWH may be used in HIT; however, there is a significant risk of cross-reactivity.

LMWHs typically are administered in fixed or weight-adjusted doses for thromboprophylaxis and in weight-adjusted doses for therapeutic purposes. Routine laboratory monitoring is not generally necessary; however, monitoring should be considered in patients with severe renal insufficiency (creatinine clearance < 30 ml/min), pregnant patients, and morbidly obese patients. If monitoring is required, the anti-Xa level is the recommended test. This should be measured 4 hours after the last dose. The therapeutic level for most of the available LMWH preparations should generally be 0.5 to 1.0 IU/ml for a twice daily dosing regimen and 1.0 to 2.0 IU/ml for once daily dosing regimen.

The ACCP recommends the use of UFH instead of LMWH in patients with severe renal insufficiency (CrCl < 30 mL/min) who require therapeutic anticoagulation. If LMWH is chosen, anti-Xa monitoring and/or dose reduction should be done to assure that there is no accumulation. In the case of enoxaparin, dose reduction to 50% of the usual dose may be used in patients with CrCl < 30 mL/min.

The use of LMWH in both the prophylaxis and treatment of DVT was evaluated in numerous randomized, controlled trials and has been the subject of meta-analyses. LMWH was more effective than fixed-dose UFH and equivalent (or superior) to adjusted-dose UFH in preventing DVT. It has been shown to be effective in many patient populations, including acutely ill medical, general surgical, neurosurgical, and orthopedic surgical patients. Similarly, LMWH appears to be at least as effective and safe as UFH for the treatment of DVT, even DVT involving the proximal veins. Several recent meta-analyses found that LMWH was more effective than UFH in preventing thrombus propagation, reducing recurrent thromboembolism, and reducing mortality, with a similar or lower rate of major bleeding.

An open-label study found that a LMWH was more effective than UFH in promoting thrombus regression as assessed by venography. Furthermore, recent studies have supported the feasibility and safety of outpatient treatment of DVT with LWMH in 50% to 75% of patients, which would significantly lower the cost of therapy. This has led to suggestions regarding the need for vigilance with the use of home therapy, including the need for appropriate patient selection, adequate resources for clinical services, and documentation of effectiveness of individual centers. In the United States, several agents in this class are currently approved for the prevention and treatment of DVT as well as for unstable coronary syndromes (Table 34-5).

**Danaparoid**

Danaparoid, a derivative of the intestinal mucosa of the pig after removal of heparin, is a mixture of heparan, dermatan, and chondroitin sulfates. It is an even more selective inhibitor of factor Xa than LMWH. The anti-Xa-to-anti-thrombin activity ratio of heparin is about one, whereas that of LMWH is about 2 to 4 and that of danaparoid is ≥ 20. It is reported to be safe and effective in the prophylaxis of DVT in patients after cancer surgery, hip fracture surgery, or hip replacements, and in patients with nonhemorrhagic stroke. In an open-label, randomized, multicenter study, subcutaneous danaparoid was compared with continuous IV infusion of UFH for the treatment of VTE. Danaparoid was more effective in the prevention of thrombus extension or recurrent thromboembolism, with a similar risk of bleeding. In another study, danaparoid resulted in the lowest DVT rate compared to enoxaparin and dalteparin with respective rates of 5.7%, 15.4%, and 8.8%. Danaparoid has all the advantages of LMWH and has minimal cross-reactivity with antibodies generated in HIT. Danaparoid is approved for the prevention of DVT in patients undergoing elective hip replacement surgery. The dose of danaparoid is 750 anti–factor Xa units twice per day; adverse effects include hemorrhage and fever.

**Vitamin K Antagonists**

The coumarins or vitamin K antagonists have been the mainstay of oral anticoagulant therapy for more than 60 years. Warfarin is the most common among the vitamin K antagonists used in clinical practice. It produces its anticoagulant effect by interfering with the action of vitamin K by inhibiting vitamin K epoxide reductase, which in turn leads to impaired function of prothrombin (factor II), factor VII, factor IX, and factor X. The relationship between the dose of warfarin and the individual patient's response to the dose is important clinically. This relationship is modified by genetic factors and environmental factors, which can influence its pharmacokinetics and pharmacodynamics. Important genetic factors identified include the mutations in genes coding for 2CYP9 hepatic enzymes, which are responsible for differences in the metabolism of warfarin, and the mutations in genes coding for VKORC enzymes, which are responsible for differences in the response to warfarin and therefore account for the differences in warfarin doses required to maintain a therapeutic international normalized ratio (INR).
Table 34-5. Drug Therapy for Deep Venous Thrombosis (Including Investigational Agents)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Typical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Prophylaxis</td>
<td>5000 U bid or tid</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>Adjusted for aPTT per weight-based nomogram</td>
</tr>
<tr>
<td>Low Molecular Weight Heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Prophylaxis</td>
<td>30 to 40 mg once or twice daily*</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>1 mg/kg twice daily or 1.5 mg/kg once daily</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Prophylaxis</td>
<td>2500 to 5000 U once or twice daily*</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>100 U/kg twice daily</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>Prophylaxis</td>
<td>3100 U or 40 U/kg daily</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>90 U/kg twice daily</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Prophylaxis</td>
<td>3500 U or 50 U/kg daily</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>175 U/kg daily</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Prophylaxis</td>
<td>10 to 20 mg twice daily</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Prophylaxis</td>
<td>Start on day of surgery; adjust dose for INR</td>
</tr>
<tr>
<td></td>
<td>“Treatment”</td>
<td>Adjust for INR 2.0 to 3.0</td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Prophylaxis</td>
<td>2.5 mg SC daily</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>Weight-based dose</td>
</tr>
<tr>
<td>Idraparinux</td>
<td>DVT Treatment</td>
<td>2.5 mg SC once weekly</td>
</tr>
<tr>
<td>Direct Factor Xa Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Prophylaxis</td>
<td>Oral 2.5 mg twice daily</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Prophylaxis</td>
<td>Oral 10 mg daily</td>
</tr>
<tr>
<td>Inhibitors of Fibrin Generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirudin</td>
<td>Prophylaxis</td>
<td>12502500 U twice daily</td>
</tr>
<tr>
<td>Argatroban</td>
<td>HIT</td>
<td>Adjusted for aPTT</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>HIT</td>
<td>Adjusted for aPTT</td>
</tr>
<tr>
<td>Dabigatran Etexilate</td>
<td>Prophylaxis</td>
<td>Oral 150 or 220 mg once daily</td>
</tr>
<tr>
<td>Thrombolytic Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Treatment</td>
<td>250,000 IU load; 100,000 IU/h for 48 to 72 h</td>
</tr>
<tr>
<td>Urokinase</td>
<td>Treatment</td>
<td>4400 IU/kg load; 2200 IU/kg/h for 48 to 72 h</td>
</tr>
<tr>
<td>t-PA</td>
<td>Treatment</td>
<td>0.05 mg/kg/h for 8 to 24 h</td>
</tr>
<tr>
<td>rtPA</td>
<td>Treatment</td>
<td>100 mg over 2 hours</td>
</tr>
</tbody>
</table>

SC = subcutaneous; t-PA = tissue plasminogen activator; rtPA = recombinant tissue plasminogen activator; aPTT = activated partial thromboplastin time; PT = prothrombin time; INR = international normalized ratio.

*Dose varies according to the risk
Environmental factors such as drugs and diet as well as various disease states can alter the pharmacokinetics of warfarin. Consequently, the INR should be measured more frequently than the usual 4-week interval when virtually any new drug, dietary supplement, or herbal medicine is added or withdrawn from the regimen of a patient treated with warfarin. Hepatic dysfunction potentiates the response to warfarin through the impaired synthesis of coagulation factors. Hypermetabolic states, such as fever or hyperthyroidism, increase warfarin responsiveness by increasing the catabolism of vitamin K-dependent coagulation factors.

Except for bleeding, adverse effects with warfarin are generally infrequent. A rare complication of warfarin therapy is skin necrosis seen in patients with protein C deficiency started on warfarin therapy alone.

It is recommended that anticoagulation therapy in patients with VTE should not be started with warfarin alone because of the theoretical risk of enhanced thrombosis with an early inhibition by warfarin of the vitamin K dependent antithrombotic factors with shorter half lives (protein C and S) before the inhibition of some of the vitamin K dependent thrombotic factors with longer half lives (factors II, VII, IX, and X). Treatment with heparin preparation should be concomitantly used during the initiation of warfarin therapy until a stable therapeutic INR is achieved on two occasions 24 hours apart. Warfarin should be avoided in pregnancy due to the risk for embryopathy and fetal bleeding.

Warfarin therapy is best monitored by measuring the INR, which standardizes the prothrombin time to an international reference thromboplastin to allow for comparison between different laboratories. The effectiveness and safety of warfarin therapy critically depends on maintaining the INR in the therapeutic range. The dose of warfarin is typically adjusted to maintain a therapeutic value in the moderate intensity range (INR 2.0 to 3.0) for the treatment of VTE. It has been found that maintaining a moderate INR intensity of 2.0 to 3.0 was more effective than a lower intensity of 1.5 to 2.0 and was not associated with a greater risk of bleeding. Another clinical trial showed that VTE participants who were assigned to an INR intensity of 2.0 to 3.0 experienced less bleeding without apparent loss of efficacy than those who were assigned to an INR of 3.0 to 4.5. The results of these trials influenced the decision to keep the target INR range to 2.0 to 3.0 for patients with VTE.

The effectiveness of warfarin has been established by well-designed clinical trials for the primary and secondary prevention of VTE. After the acute phase of DVT treatment with heparin or LMWH, anticoagulation with warfarin is usually continued to prevent recurrent disease and late complications. In patients with proximal DVT, long-term administration of warfarin reduced the recurrence of VTE from about 47% to about 2%. Recommendations regarding the duration of treatment with warfarin have been the subject of debate. One study found a marked reduction in the recurrence rate with prolonged therapy for idiopathic DVT compared to a standard 6 months of therapy (1.3% versus 27%). Another study found that after a second DVT, 4 years of therapy with warfarin reduced the recurrence of VTE (2.6% versus 20.7%), although the risk of bleeding significantly increased (8.6% versus 2.7%). Therefore, in general, unprovoked thrombosis should be treated for at least 6 months, while a provoked thrombosis with transient risk factors can be treated for 3 months. Furthermore, it has been shown that prolonged treatment for idiopathic DVT with warfarin in the therapeutic range (INR of 2.0 to 3.0) for over 2 years was effective in reducing the recurrence rate of VTE by 3 fold, but low-intensity therapy (INR of 1.5 to 2.0) does not appear to be beneficial.

In patients with idiopathic VTE, the hypothesis that low-intensity warfarin is effective in decreasing recurrent thrombotic events has been tested in two major trials. In one trial, a comparison was made of low-dose warfarin (INR, 1.5 to 2.0) with the placebo or conventional moderate-dose warfarin (INR, 2.0 to 3.0) in participants with idiopathic DVT after completing 6 months of conventional therapy. The combined data suggested that continuing warfarin in idiopathic VTE reduces the recurrence of thrombotic events by 3- to 10-fold compared with the placebo, and the bleeding rates with conventional therapy were similar to those with low-intensity treatment.

- ACCP guidelines suggest that patients with VTE caused by transient (reversible) risk factors should be treated for 3 months, and all patients with unprovoked VTE should be treated for at least 3 months and then evaluated for long-term therapy. For patients with a first unprovoked VTE that is a proximal DVT and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, long-term treatment is recommended. Similarly, long-term treatment is recommended for those with a second unprovoked DVT.
- Patients with a first unprovoked isolated calf vein thrombosis should be treated for 3 months rather than undergo indefinite therapy.
- In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals.

For health-care providers who manage oral anticoagulation therapy, the ACCP recommends that they do so in a systematic and coordinated fashion, incorporating patient education, regular INR testing, tracking, follow-up, and good patient communication of results and dosing.
decisions as occurs in a specialized anticoagulation clinic. In general, the rate of adverse events, recurrent thromboses, or bleeding are highest when the anticoagulation is managed by the primary care physicians. In the primary care environment, the major hemorrhagic rates ranged from 2.8% to 8.1% per patient year of therapy, and the recurrent thromboembolic event rates ranged from 6.2% and 8.1% per patient year. In contrast, studies of care provided by a specialized anticoagulation clinic reported rates of major hemorrhage or thrombosis ranging from 1.4% to 3.3% and 0.7% to 6.3% per patient year of therapy, respectively. Finally, the results of a recent systematic analysis consistently indicated that care provided by a specialized anti-coagulation clinic had better outcomes or more stable therapy than usual care by a primary physician.

Despite its delayed onset of action, warfarin was also found to be effective in the prevention of DVT following orthopedic surgery, but it has largely been replaced by LMWH for reasons of efficacy and convenience. However, it remains on the list of acceptable agents for DVT prophylaxis including following orthopedic surgery according to the American College of Chest Physician’s Guidelines. It should be dosed following the INR for a target of 2.0 to 3.0.

Newer Anticoagulants

Despite their widespread use, it has been quite challenging to use vitamin K antagonists in clinical practice for the following reasons: (1) they have a narrow therapeutic window; (2) they exhibit considerable inter- and intrapatient variability in dose response due to genetic and other factors; (3) they are subject to interactions with drugs and diet; (4) their laboratory control is difficult to standardize. A fifth reason that vitamin K antagonists are challenging is that maintenance of a therapeutic level of anticoagulation requires a good understanding of the pharmacokinetics and pharmacodynamics of warfarin and good patient communication. These factors render the effects of warfarin very unpredictable and require the patients to be regularly monitored to assure that the levels are consistently in the safe and efficacious range.

The greatest unmet need in anticoagulation therapy has been the replacement of warfarin with an orally active agent that can be given in fixed doses without need for routine coagulation monitoring. Consequently, most of the current attention is focused on development of newer anticoagulants that could potentially have a predictable anticoagulant response and few food or drug interactions, thus avoiding routine frequent coagulation monitoring and simplifying the long-term anticoagulant therapy.

Most of the newer anticoagulants under evaluation either inhibit the initiation or propagation of coagulation or attenuate fibrin formation. Drugs may block the initiation of coagulation by targeting the tissue factor/factor VIIa complex; block the propagation of coagulation by inhibiting factor IXa or Xa (or their cofactors, factor VIIa and Va); or attenuate fibrin generation by targeting thrombin. Among these newer drugs, the oral direct thrombin inhibitors (eg, dabigatran) and the factor Xa inhibitors (eg, rivaroxaban) have shown the most promise and potential to replace existing anticoagulants.

Inhibitors of Coagulation Initiation

Drugs that target the factor VIIa/tissue factor complex inhibit the initiation of coagulation. Several parenteral agents in this category (including tifacogin, recombinant nematode anticoagulant peptide (NAPc2), and factor VIIa inhibitor-factor VIIai) have been evaluated in phase 2 or 3 clinical investigations, but only NAPc2 has been studied for VTE.

NAPc2 is an 85-amino acid polypeptide that binds to a noncatalytic site on factor X or factor Xa. Once bound to factor Xa, the NAPc2/factor Xa complex inhibits tissue factor-bound factor VIIa. Because it binds factor X with high affinity, NAPc2 has a half-life of approximately 50 hours after subcutaneous injection. In 293 participants undergoing elective knee arthroplasty, the effect of various doses of NAPc2 on VTE prophylaxis was evaluated. The best results were observed with a NAPc2 dose of 3.0 μg/kg administered one hour after surgery. The rate of venographically detected DVT in the operated leg was 12%, but only 1% had a proximal DVT. Major bleeding occurred in 2% of participants. Thus, NAPc2 appears to be safe and effective in VTE prophylaxis, but prospective randomized trials are needed to confirm these findings.

Inhibitors of Coagulation Propagation

Propagation of coagulation can be inhibited by drugs that target factor IXa or factor Xa or by agents that inactivate their respective cofactors, factor VIIIa and factor Va. Among this class, several factor Xa inhibitors have shown promise in the management of VTE. New factor Xa inhibitors include agents that block factor Xa both directly and indirectly. Indirect inhibitors act by catalyzing factor Xa inhibition by antithrombin. In contrast, direct factor Xa inhibitors bind directly to the active site of factor Xa, thereby blocking its interaction with its substrates.

Indirect Factor Xa Inhibitors

Fondaparinux

The prototype of the new indirect factor Xa inhibitors is fondaparinux, a first-generation synthetic analog of the antithrombin-binding pentasaccharide. It has increased affinity for AT and a specific anti-Xa activity, which is
higher than that of LMWH (about 700 U/mg and 100 U/mg, respectively). It is eliminated primarily by the kidneys and has a longer half-life of 17 to 21 hours compared to 4 to 6 hours for LMWH. It also has a very LMW (1,728 Da) with essentially a neutral net charge; thus it does not bind significantly to other plasma proteins. Specifically, it does not bind platelet factor 4, resulting in a negligible risk of HIT. On the other hand, because of the neutral net charge, it is not inhibited by protamine and has no available antidotes for bleeding. Fondaparinux, like LWMH, does not require routine monitoring, but when necessary, anti-factor Xa activity can be measured. The drug has been shown to prevent DVT as effectively or more effectively than enoxaparin after hip or knee surgery, as well after general surgery.223-226 It is also shown to be as effective and safe as heparin or LMWH for initial VTE treatment.

In a randomized open-label trial involving 2,213 participants with acute pulmonary embolism, the efficacy and safety of fondaparinux was compared with UH.227 The rate of recurrent VTE was 3.8% in those assigned to receive fondaparinux compared to 5% in those assigned to receive UH. Major bleeding occurred in 1.3% of participants treated with fondaparinux and 1.1% of participants treated with UH.227 In the DVT arm of the study, 2,205 participants with acute DVT were randomized in a double-blind fashion to receive either fondaparinux or enoxaparin for at least 5 days, followed by a minimum of a 3-month course of treatment with a vitamin K antagonist. At 3 months, rates of recurrent symptomatic VTE with fondaparinux or enoxaparin were 3.9% and 4.1%, respectively, whereas rates of major bleeding were 1.1% and 1.2%, respectively. It was concluded that fondaparinux was at least as effective and as safe as UH in the initial treatment of participants with DVT and hemodynamically stable participants with pulmonary embolism (PE).

This drug is approved in the prophylaxis of DVT in patients undergoing hip fracture surgery, hip replacement surgery, and knee replacement surgery. The dose for VTE prophylaxis is 2.5 mg subcutaneously daily for 5 to 9 days. It is also approved as a substitute for heparin or LMWH for initial treatment of VTE. The recommended dose for VTE treatment is weight-based as follows: < 50 kg receive 5 mg, 50 to 100 kg receive 7.5 mg, and > 100 kg receive 10 mg once daily. The drug is also useful for superficial phlebitis.228a

Idraparinux

Idraparinux is a new synthetic pentasaccharide with a longer half-life and can be given subcutaneously on a once-weekly basis. In a large phase 3 randomized, controlled trial, idraparinux given as subcutaneous injection at a dose of 2.5 mg once weekly was shown to be as effective as conventional treatment (LWMH/warfarin) in DVT but was less effective than conventional therapy in PE at 3 months.230 It was concluded that PE requires higher initial doses of idraparinux than DVT; however, further studies with higher doses showed excessive bleeding.

Direct Factor Xa Inhibitors

All of the direct factor Xa inhibitors are small molecules that reversibly block the active site of factor Xa. A large number of oral factor Xa inhibitors are being evaluated in the management of VTE, which highlights the continued focus on development of new oral anticoagulants that can replace traditional vitamin K antagonists.

Razaxaban

Razaxaban, a nonpeptidic oral factor Xa inhibitor, underwent phase II evaluation for thromboprophylaxis after knee arthroplasty.230 The primary endpoint, a composite of venographically detected DVT and symptomatic VTE, occurred in 8.6% of those randomized to the lowest dose of razaxaban and in 15.9% of those given enoxaparin. Major bleeding occurred in 0.7% of participants given the lowest dose of razaxaban and in none of those treated with enoxaparin; however, the 3 higher-dose razaxaban arms were stopped prematurely because of increased rates of major bleeding. Because of the narrow therapeutic index and pharmacological limitations, further development of razaxaban was halted in favor of newer drugs such as apixaban.

Apixaban

Apixaban is a variant of razaxaban with superior pharmacologic properties such as high oral bioavailability and a prolonged half-life of about 12 hours. Food has no effect on its absorption, and the drug produces a predictable anticoagulant effect. Apixaban is cleared through both fecal and renal routes with renal elimination accounting for about 25% of drug clearance. Since the clearance of apixaban is mainly via the biliary/fecal route, apixaban is less likely to accumulate in patients with renal insufficiency.231

Apixaban (at a dose of 2.5 mg twice daily) was compared with enoxaparin (30 mg subcutaneously every 12 hours) in 3,195 participants undergoing total knee replacement.232 The rate of VTE was 9.0% with apixaban as compared with 8.8% with enoxaparin (relative risk, 1.02, 95% confidence interval, 0.78 to 1.32). The composite incidence of major bleeding and clinically relevant nonmajor bleeding was 2.9% with apixaban and 4.3% with enoxaparin (P = .03). Apixaban appears to have similar efficacy as enoxaparin for thromboprophylaxis after knee replacement, and its use was associated with lower rates of clinically relevant bleeding. Apixaban is also being evaluated for thromboprophylaxis in medical patients and for the treatment of VTE.
Rivaroxaban

Rivaroxaban, an oxazolidone derivative, is a novel direct factor Xa inhibitor that has received approval in the European Union and Canada for the prevention of VTE in patients undergoing elective total hip or knee replacement surgery. It exhibits predictable, dose-proportional pharmacokinetics, with high oral bioavailability; it has a half-life of 9 hours and a rapid onset of action (maximum plasma concentrations are reached after 1.5–2.0 hours). The drug has a dual mode of elimination: two-thirds are metabolized by the liver (mostly via CYP3A4 and CYP2J2), with no major or active circulating metabolites identified, and one-third is excreted unchanged by the kidneys.

The efficacy of rivaroxaban at preventing VTE was investigated in 4 large studies involving more than 12,500 participants undergoing elective hip or knee replacement. Rivaroxaban at a dose of 10 mg daily was shown to be significantly superior to enoxaparin in reducing the primary endpoint—a composite of DVT, non-fatal pulmonary embolism, and all-cause mortality. Rivaroxaban was shown to have a good safety profile with rates of major bleeding similar to that observed with enoxaparin and no evidence of drug-induced liver injury.

Studies have also shown superiority of rivaroxaban over enoxaparin in the treatment of VTE. One trial randomized 613 participants to a 3-month course of rivaroxaban (at doses of 10, 20, or 30 mg twice daily or 40 mg once daily), or to LMWH followed by a vitamin K antagonist. The primary efficacy outcome of recurrent thrombotic events was similar to those treated with conventional treatment. Another study randomized 543 participants with proximal DVT to a 3-month course of once-daily rivaroxaban (at doses of 20, 30, or 40 mg) or to heparin or LMWH followed by a vitamin K antagonist. The primary endpoint, a composite of symptomatic events (VTE-related death, DVT, or pulmonary embolism), plus an increase in thrombus burden as detected by repeated ultrasound and ventilation-perfusion lung scanning, occurred in 6% of those given rivaroxaban compared with 9.9% of those receiving conventional therapy. There was no apparent dose-response with rivaroxaban in these trials, but the rates of bleeding were higher with increasing doses of rivaroxaban. On the basis of these trials, a 20 mg once-daily dose of rivaroxaban is being evaluated for the treatment of VTE in several large phase 3 trials.

Inhibitors of Fibrin Generation

Several newer inhibitors of thrombin, the enzyme that converts fibrinogen to fibrin, have been developed. Among these, the direct thrombin inhibitors are promising as they produce a more predictable anticoagulant response. Secondly, unlike heparin, direct thrombin inhibitors do not bind to platelet factor 4 and thus will not cause HIT. Finally, direct thrombin inhibitors inactivate fibrin-bound thrombin, as well as fluid-phase thrombin. Three parenteral direct thrombin inhibitors (hirudin, argatroban, and bivalirudin) have been licensed in North America for limited indications, and two oral direct thrombin inhibitors have shown encouraging results in VTE.

Hirudin

Hirudin is a direct thrombin inhibitor that directly binds to the fibrinogen recognition and catalytic site of thrombin. Two recombinant forms of hirudin, known as lepirudin and desirudin, are currently approved for clinical use in North America and in Europe, respectively. Lepirudin is licensed for treatment of thrombosis-complicating HIT, whereas desirudin is approved for postoperative thromboprophylaxis in patients undergoing elective hip arthroplasty.

In addition to the management of acute coronary syndrome, this agent has been evaluated in the prevention of DVT following surgery. In a multicenter, randomized, controlled trial involving 1,119 participants undergoing hip surgery, recombinant hirudin (lepirudin) was found to be more effective than fixed-dose subcutaneous heparin at preventing DVT formation. In another study involving 2,070 participants, subcutaneous recombinant hirudin (desirudin) was compared with enoxaparin in the prevention of DVT following total hip replacement. The rate of all DVT (18.4% versus 25.5%) and proximal DVT (4.5% versus 7.5%) was significantly lower among those receiving hirudin than among those receiving enoxaparin, as assessed by follow-up venography.

The recommended dose of IV lepirudin for HIT is 0.15 mg/kg/hour, with or without an initial bolus of 0.4 mg/kg. The anticoagulant effect of lepirudin is monitored by using the aPTT, and the dose is adjusted to achieve a target aPTT ratio of 1.5 to 2.5. When given for thromboprophylaxis after elective hip replacement surgery, desirudin is given subcutaneously at a dose of 15 mg twice daily. Routine aPTT monitoring is unnecessary with this dose of desirudin. Antibodies against hirudin develop in up to 40% of patients treated with lepirudin, resulting in significant risk of serious reactions including anaphylaxis if patients with antibodies are reexposed to hirudin. Consequently, an alternative anticoagulant should be used in HIT patients who have previously been treated with hirudin.

Argatroban

A competitive inhibitor of thrombin, argatroban binds noncovalently to the active site of thrombin to form a reversible complex. The plasma half-life of argatroban is 45 minutes. It is metabolized in the liver and must be used with caution in patients with hepatic dysfunction.
Since it is not renally excreted, argatroban is useful in HIT patients with severe renal impairment. Argatroban is licensed for the treatment and prevention of HIT-associated thrombosis and for anticoagulation during percutaneous coronary interventions when heparin is contraindicated because of a recent history of HIT. Argatroban is given as a continuous IV infusion at a dose of 2 μg/kg/min, and the dose is adjusted to maintain the aPTT ratio in the 1.5 to 3.0 range.

**Bivalirudin**

Bivalirudin, a synthetic analog of hirudin, is licensed as an alternative to heparin in HIT. The currently recommended dose is a bolus of 0.7 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure.

**Ximelagatran**

Ximelagatran is an oral direct thrombin inhibitor. It does not interact with food, has a low potential for drug interactions, and produces a predictable anticoagulant response. Ximelagatran underwent extensive evaluation for prevention and treatment of VTE and other conditions warranting anticoagulation. Initial studies led to its temporary licensing in Europe for thromboprophylaxis in patients undergoing major orthopedic surgery. However, the drug was not approved in North America and was eventually withdrawn from the world market because of potential hepatic toxicity.

**Dabigatran etexilate**

Dabigatran etexilate, a double prodrug, is a promising direct oral thrombin inhibitor. Once absorbed, it is converted by esterases into its active metabolite, dabigatran. At least 80% of the drug is excreted unchanged via the kidneys; therefore, the drug is contraindicated in patients with renal failure.

Dabigatran etexilate has been evaluated for thromboprophylaxis in patients undergoing hip or knee arthroplasty. In two large trials involving 2,076 participants undergoing knee arthroplasty and 3,494 participants undergoing hip replacement surgery, dabigatran was shown to have a similar efficacy and safety profile as enoxaparin. Recently, dabigatran etexilate was compared with warfarin for the treatment of VTE in a large multicenter, double-blind, randomized trial involving 1,274 participants. Dabigatran administered at a dose of 150 mg twice daily was as effective as warfarin, with recurrent VTE occurring in 2.4% of those receiving dabigatran compared with 2.1% of those receiving warfarin. Dabigatran had a similar safety profile as that of warfarin with a comparable rate of bleeding as well as hepatic dysfunction.

**Thrombolytic Agents**

Thrombolytic agents, including streptokinase, urokinase, and t-PA, have been studied in the treatment of DVT. Thrombolytics have been shown to enhance the rate of lysis in peripheral veins, with a greater likelihood of having complete or near complete resolution of the thrombus. In contrast, standard treatment with heparin reduces the extension and embolization of a thrombus but does not appear to affect the rate of lysis.

There remains controversy regarding the benefit of thrombolysis in the treatment of proximal DVT. These agents have not been shown to reduce the subsequent development of pulmonary embolus or to reduce mortality. It appears that their early use may decrease subsequent pain, limb swelling, and loss of venous valves; however, the benefit in reducing the late complications, such as postphlebitic syndrome, remains poorly defined. Furthermore, delayed use of thrombolytics has been less successful, especially if thrombus has been present for more than 7 days. A review of randomized trials using rt-PA in the treatment of lower extremity DVT did not support the routine use of rt-PA. Thrombosis within other venous systems, primarily the subclavian veins, has been treated by direct infusion of thrombolytic agent into the distal vein, which has been successful in preventing surgical thrombectomy. However, this often discloses an anatomic abnormality that led to the development of the thrombus, such a thoracic outlet syndrome, which may require surgical correction.

The present recommendations are to consider local catheter-directed thrombolysis for massive iliofemoral DVT, typically with marked limb swelling and threatened foot ischemia, if there is a low risk of bleeding. Many have also considered thrombolysis for subclavian vein thrombosis with occlusion.

The commonly used dosing regimen of streptokinase is a 250,000 IU load followed by an infusion of 100,000 IU/hour for 48 hours and t-PA 0.05 mg/kg/hour for 8 to 24 hours. Successful thrombolytic administration must be followed by systemic antithrombotic therapy and long-term anticoagulation. Systemic fibrinolytic therapy is being used for the treatment of massive pulmonary embolism and for management of selected patients with submassive pulmonary embolism.

**Large Vessel Vasculitis**

The vasculitides are a heterogeneous group of disorders characterized by leukocyte infiltration into the vessel wall with reactive damage, leading to tissue ischemia and necrosis. The pattern of vessel involvement, in terms of size and location, varies with the specific disorders. Those...
involving the large vessels, such as Takayasu arteritis and giant-cell arteritis, are frequently encountered by the vascular clinician. Takayasu arteritis primarily affects the aorta and its major branches. The presenting symptoms early in the course of the disease are those of systemic inflammation, whereas the later clinical syndrome is typified by vascular insufficiency. Giant-cell or temporal arteritis most prominently involves the cranial branches of the arteries originating from the aortic arch. The most common presenting symptom is headache, but visual problems, scalp tenderness, malaise, fever, and weight loss are common.

Corticosteroids and immunosuppressive agents are useful in the treatment of most forms of vasculitis, particularly in the acute phase. Systemic vasculitides usually require at least corticosteroid therapy to induce a remission. Rapidly progressive and steroid-refractory vasculitides require combination therapy with corticosteroids and cytotoxic drugs such as cyclophosphamide, azathioprine, or methotrexate. More recently, tremendous growth has been in the arena of immunomodulation. A major class of agents includes antagonists of tumor necrosis factor-α (TNFα).

Glucocorticoids

Glucocorticoids are the mainstay of therapy for many vasculitides including both giant-cell arteritis and Takayasu arteritis. These agents decrease inflammation by suppressing the migration of polymorphonuclear leukocytes and decreasing capillary permeability. There is suppression of the immune system by reducing the activity and volume of the lymphatic system.

Blindness occurred in up to 80% of patients with giant-cell arteritis prior to the use of steroids. However, remission is induced in nearly all cases with an initial dose of 40 to 60 mg of prednisone in a single or divided daily dose.

Therapy with intravenous pulse methylprednisolone should be initiated in those with recent visual loss. Once a clinical remission has been induced, the dose of steroids is gradually reduced to a minimally suppressive dose. Laboratory evaluations, such as the sedimentation rate or C-reactive protein, are usually monitored to confirm the persistence of the remission. Steroids are often discontinued within a few years as giant-cell arteritis usually runs a self-limited course. However, approximately half of all patients will experience a relapse during corticosteroid tapering and the need for long-term corticosteroid therapy leads to adverse events from the steroids in a majority of patients.

Glucocorticoids are effective agents to suppress systemic symptoms and arrest progression of arterial lesions in Takayasu arteritis. Early in the course of the disease, treatment with corticosteroids may reverse arterial stenoses, even with a restoration of pulses, and can improve ischemic symptoms. The response is diminished once fibrosis or thrombosis has developed within the affected vessels. A commonly accepted initial dose of prednisone for Takayasu arteritis is 40 to 60 mg per day to induce a remission but then gradually tapered to sustain remission. Laboratory markers of systemic inflammation are monitored to confirm the persistence of a remission. As with giant-cell arteritis, many patients with Takayasu arteritis will experience a relapse during corticosteroid tapering, and complications of long-term corticosteroid therapy are common.

Cytotoxic Drugs

Various cytotoxic agents are used for steroid-resistant disease that has failed to enter remission with corticosteroids. Cytotoxic agents have also been used for their steroid-sparing effects in an attempt to reduce the corticosteroid requirement to keep the disease quiescent. These agents, including cyclophosphamide, azathioprine, and methotrexate, should only be handled by physicians well versed in their use. With the large- vessel vasculitides, the use of methotrexate has been evaluated. The experience with the other agents is very limited.

There is controversy regarding the steroid-sparing effect of methotrexate in giant-cell arteritis. In a double-blind, placebo-controlled trial, 42 participants with new-onset giant-cell arteritis were randomized to weekly methotrexate at a dose of 10 mg for 24 months plus prednisone, or the placebo plus prednisone. Treatment with methotrexate significantly reduced the proportion of patients who experienced a relapse (45% versus 84%, \( P = .02 \)), reduced the duration of use of prednisone (median time of 29 and 94 weeks, \( P < .01 \)), and reduced the mean cumulative dose of prednisone (4.2 versus 5.5, \( P < .001 \)). The rate and severity of adverse effects was similar in the two groups. In contrast, a preliminary report in another placebo-controlled trial found that weekly methotrexate failed to lower the dose of corticosteroids.

The use of methotrexate has been evaluated in the treatment of persistent or recurrent Takayasu arteritis that is refractory to glucocorticoids. An open-label study evaluated the effect of low-dose methotrexate with glucocorticoids in 18 participants with refractory Takayasu arteritis; 16 were followed for a mean period of 2.8 years. Weekly administration of methotrexate (mean dose of 17.1 mg) and glucocorticoids induced remission in 81% of participants (13 of 16). However, when the dose of glucocorticoid was tapered, relapse occurred in 44% of participants (7 of 13) requiring retreatment leading to a remission. There was a sustained remission (with a mean
of 18 months) in half of the participants treated with low-dose weekly methotrexate.

**Immunomodulatory Agents**

Corticosteroids and cytotoxic drugs have reduced the mortality in patients with vasculitis, but their use carries a substantial risk of toxicity. Efforts to reduce toxic maintenance regimens, have led to newer immunomodulatory agents for the treatment of large vessel vasculitis.

**Mycophenolate mofetil**

Mycophenolate mofetil is a novel agent, approved primarily for the prophylaxis and treatment of acute solid organ allograft rejection. Recently, it is increasingly used for indications outside solid organ allograft rejection, including patients with large vessel vasculitis. It is a potent immunosuppressant, which causes inhibition of de novo synthesis of purines required for the proliferation of T and B lymphocytes. In a study involving participants with systemic vasculitis and renal involvement, mycophenolate mofetil was shown to be an effective and well-tolerated option in sustaining short- and medium-term remission. It was also shown to be effective in the induction and maintenance therapy of Takayasu’s arteritis.

**TNF Inhibitors**

TNF inhibitors, including infliximab and etanercept, have also shown some promise in the treatment of large vessel vasculitis. The rationale for this approach is that the vasculitic lesions in the large vessel vasculitis, such as giant cell arteritis and Takayasu arteritis, have prominent macrophage infiltration with excessive TNFα production demonstrated by immunohistochemistry.

**Infliximab**

Infliximab, a chimeric monoclonal antibody directed against TNFα that binds both circulating and membrane-bound TNF, has been used in the treatment of giant cell arteritis and Takayasu arteritis. It has been reported that Takayasu arteritis patients who did not respond well to conventional therapy with glucocorticoid and methotrexate were successfully treated with infliximab. Infliximab therapy was also shown to lead to a durable remission and reduction in glucocorticoid requirements in patients with Takayasu arteritis.

**Etanercept**

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding protein of TNF receptor linked to the Fc portion of a human IgG1. It competitively inhibits the interaction of TNF with cell-surface receptors, preventing TNF-mediated cellular responses and modulating the activity of other proinflammatory cytokines that are regulated by TNF. In a multicenter, double-blind, placebo-controlled study involving participants with biopsy-proven giant cell arteritis and adverse effects secondary to corticosteroids, 50% of the participants in the etanercept group were able to control the disease without corticosteroid therapy after 12 months compared with 22.2% in the placebo group. Participants in the etanercept group had a significantly lower dose of steroid requirement during the first year of treatment ($P = .03$). Etanercept was also well tolerated.

**Thromboangiitis Obliterans**

Thromboangiitis obliterans is a vasculitis that is characterized by a cellular inflammation thrombus with relative sparing of the blood vessel walls. The combination of arterial occlusive disease and superficial phlebitis in a young adult smoker is most consistent with the diagnosis.

**Therapy**

Smoking cessation is the most definitive therapy for this condition. Bupropion and varenicline are the preferred smoking cessation agents. Other drug therapies for thromboangiitis obliterans include the use of vasodilators for symptom relief, such as alpha-adrenergic blockers, calcium channel blockers and sildenafil. Therapeutic angiogenesis has also been utilized with short-term benefit, but more definitive studies need to be done.

**Conclusions**

Despite years of intense investigation, effective drug therapy for the symptomatic treatment of manifestations of PAD remains elusive. The current focus still relies on the treatment of modifiable risk factors for atherosclerosis (including smoking cessation and lipid-lowering therapy) and an exercise regimen. Statin therapy, commonly used for cholesterol lowering, reduces cardiovascular events and may even improve symptoms in PAD. Antiplalet agents hold promise in reducing cardiovascular morbidity and mortality among individuals with PAD.

Only two agents, pentoxifylline and cilostazol, are available in the United States for the symptomatic treatment of IC. Investigational agents involving nitric oxide and carnitine metabolism remain possible therapeutic targets in the management of IC. The drug treatment of CLI is focused on increasing blood flow to the affected extremity to relieve pain, heal ischemic ulcerations, and avoid limb loss. There was minimal long-term benefit to the use of prostaglandins in the treatment of CLI, and angiogenesis therapies are still in the early stages of development. There
is a role for catheter-guided thrombolytic therapy in the treatment of acute arterial occlusion of the extremities.

While the medications may help to decrease the intensity and frequency of vasospastic episodes in RS, they do not cure the underlying cause of vasospasm. The dihydropyridine-type calcium-channel blockers are still the most commonly used drugs at present. Alternative vasodilators, such as prazosin, may be tried if calcium-channel blockers are ineffective or intolerable. Other agents, including prostaglandins, continue to be evaluated in the treatment of refractory RS to allow wound healing.

Heparin has been the standard agent in the prevention and short-term management of DVT, followed by administration of warfarin for long-term management. The use of weight-based nomograms has facilitated achieving therapeutic anticoagulation with heparin more safely than with the prior regimens. LMWHs are largely replacing UH for the prevention and treatment of DVT. The ease of administration and fewer adverse effects with equivalent (or better) efficacy are keys to the flourishing use of LMWH. Newer agents including heparinoids, factor Xa inhibitors and direct thrombin inhibitors, are emerging as alternative agents in the prevention and management of DVT. While the vitamin K antagonists have been the mainstay of oral anticoagulant therapy, some of these newer oral anticoagulants seem to have the potential to replace warfarin in the near future.

Currently, warfarin should be continued for at least 3 to 6 months to maintain an INR of 2.0 to 3.0 for treatment of DVT, although more prolonged therapy should be considered for idiopathic and recurrent DVT. Thrombolysis may be used selectively for the treatment of proximal DVT, particularly if evidence for limb ischemia is present. Although great strides have been made in the prevention of DVT in high-risk patients, there is still a higher-than-acceptable incidence.

Glucocorticoids and cytotoxic agents remain common treatments for managing patients with large vessel vasculitis; however, newer immunomodulatory agents, including TNFα inhibitors, are beginning to be used.

Note: References for this chapter can be found here: www.cvpc13.com
In this chapter, the authors discuss the current recommendations for the treatment and prevention of infective endocarditis (IE) and acute rheumatic fever.

Infective Endocarditis

IE is a disease with protean manifestations resulting from an endovascular infection within the heart. The location of infection is usually the heart valves; however, in addition, the chordae tendinae, mural endocardium, and septal defects may be involved. The initial event in the pathogenesis of IE is endothelial damage at a site of turbulent blood flow. Fibrin, leukocytes, and platelets are deposited on the abnormal endothelial surface forming a sterile vegetation referred to as nonbacterial thrombotic endocarditis. Pathogenic organisms gaining access to the bloodstream may become incorporated in the fibrin-platelet network resulting in an infected vegetation, the pathologic hallmark of IE. Continued deposition of fibrin and platelets protects microorganisms from cellular defense mechanisms and, perhaps, from contact with antimicrobials and allows the density of organisms to reach high levels. Virulent bacteria such as *Staphylococcus aureus* or *Streptococcus pneumoniae* with the capacity to adhere to less severely damaged endothelium may cause infection on apparently normal heart valves.

Embolization, one of the dreaded complications of the disease, occurs when portions of friable vegetation are lost in the circulation. Vegetations on the left side of the heart give rise to systemic emboli leading to organ and limb infarction, including stroke or coronary artery occlusion. Right heart vegetations embolize to the lungs. Rarely, in the setting of a septal defect or elevated right atrial pressures with a patent foramen ovale, paradoxical emboli to the systemic circulation occur with right-sided valvular lesions. Emboli from either side of the heart may be septic or bland.

From the vegetation, infection may spread locally to damage the valve itself or its supporting structures. The valvular incompetence that ensues can result in hemodynamic compromise and congestive heart failure. Invasion of the myocardium, through direct spread or embolization, may cause abscesses that can lead to myocardial dysfunction, continued sepsis, and conduction abnormalities, including complete heart block. In the absence of effective therapy, the vegetation is a source of continuous bacteremia, leading to peripheral foci of infection and eventually death. Some of the more subtle manifestations of the disorder are caused by the immunologic response to the persistent bacteremia, including glomerulonephritis, arthritis, Osler nodes, Janeway lesions, and Roth spots.

Therapy

In the absence of antibacterial chemotherapy, bacterial endocarditis is a uniformly fatal disease; host defense mechanisms alone are inadequate. Furthermore, therapy of bacterial endocarditis requires the use of bactericidal agents. The goals of therapy are the eradication of all organisms within the vegetation and the prevention of embolic and immunologic phenomena and valve destruction.

Several factors make this vegetation particularly difficult to treat. Because it is endovascular, white blood cells alone are ineffective in eliminating the infection. Antibiotic therapy is problematic because: (1) the inner layers of the vegetation may be exposed to very low concentrations of antibiotic due to poor penetrability; (2) those antibacterial agents that require active growth for killing (most cell wall active agents) are relatively ineffective against the slow-growing organisms found deep
within the vegetation; and (3) high density of bacteria in vegetation may produce exceedingly high local levels of antibiotic modifying enzymes.

For these reasons, the therapy of IE customarily has required high doses of bactericidal agents for prolonged periods of time. A controversial issue has been the usefulness of serum inhibitory and bactericidal levels in monitoring therapy of endocarditis. As initially reported by Schlichter et al., the trough serum inhibitory concentration (SIC) is determined by serially diluting the patient's serum obtained just prior to the next dose of antibiotic and testing the ability of these dilutions to inhibit the growth of a standard inoculum of the patient's bacterial isolate. The highest serum dilution to inhibit growth is the SIC. The serum bactericidal concentration (SBC) is determined by subculturing those tubes with inhibited growth onto fresh agar and demonstrating killing of the initial inoculum. The highest serum dilution to accomplish this degree of killing is the SBC. The same determinations can be made for peak inhibitory and bactericidal levels by drawing serum shortly after administration of an antibiotic dose.

Although previously the American Heart Association (AHA) recommended that the peak SBC be maintained at 1:8 or higher in the treatment of Viridans streptococcus endocarditis, clinical experience has not supported an association between these levels and clinical outcome. Current AHA guidelines do not recommend the use of serum bactericidal titers in most cases of IE. These levels may be helpful in circumstances where response to antimicrobial therapy is poor, in disease due to unusual organisms, and in therapy with unconventional agents.

The first sign of successful therapy often is the patient's increased sense of well being. In uncomplicated IE, fever generally resolves over days to a week or more, and the patient remains afebrile. Immune complex nephritis and arthritis generally parallel the course of the infection, although some patients may be left with residual impairment of renal function. In IE caused by S. aureus, blood cultures may remain positive for several days or more. Many patients can be cured with continuous medical therapy. Persistently positive cultures, however, imply failure to eradicate the initial focus of infection, spread of infection to the myocardium, or metastasis to a distant focus. Persistent fever may be caused by one of these factors, superinfection (eg, of an indwelling intravenous line), or drug fever.

It often is difficult in any one patient to identify with certainty the etiology of persistent or recurrent fever. Repeated examination of the patient, preferably by the same observer, is of paramount importance. The development of a new murmur, a pericardial friction rub, heart failure, or embolic phenomena in such a patient suggests continued active endocarditis. Complaints of bone or joint pain, abdominal pain, or persistent bacteruria should direct attention to a new focus. Repeat echo testing should be considered along with several clinical examinations.

The timing of initial therapy depends on the patient's presentation. In a patient with subacute illness, antibiotic therapy should be withheld until the microbiologic diagnosis can be made securely via blood cultures. In the patient with suspected acute IE, blood cultures should be obtained and empiric antibiotic therapy begun immediately. Isolation of the causative microorganism from blood cultures is critical not only for diagnosis but also for determination of antimicrobial susceptibility and planning of treatment. In the absence of prior antibiotic therapy, a total of 3 blood culture sets, ideally with the first separated from the last by at least 1 hour, should be obtained from different venipuncture sites over 24 hours. If the cultures remain negative after 48 to 72 hours, 2 or 3 additional blood cultures, including a lysis-centrifugation culture, should be obtained, and the laboratory should be asked to pursue fastidious microorganisms by prolonging incubation time and performing special subcultures.

Patients with an acute presentation of IE (often injection drug users) require empiric therapy prior to culture results. For the treatment of native valve endocarditis, empiric treatment awaiting culture results is based on common microbiologic isolates, ie, staphylococci (20-35%) and streptococci (viridans 30% to 40%, other 15% to 25%, and enterococci 5% to 18%) with occasional cases due to gram negative bacilli. The combination of penicillin, a penicillinase-resistant penicillin, and an aminoglycoside will provide effective empiric coverage for a majority of cases. The antibiotics nafcillin and oxacillin and aminoglycosides, eg, gentamicin, may not be adequate coverage for enterococci; hence the addition of penicillin G pending culture results is recommended. Vancomycin should be an alternate drug in situations where community-acquired methicillin-resistant Staphylococcus aureus (MRSA) IE occurs in at least 10% to 15% of cases, for those allergic to penicillin, and in patients who are ill while awaiting culture results.

Once the infecting organism is isolated and antimicrobial susceptibility determined, the antibiotic regimen should be adjusted accordingly. Discussion of therapeutic approaches to the treatment of the more common bacterial isolates follows.

### Nonenterococcal Streptococcal Endocarditis

Approximately 30% to 55% of all cases of IE are caused by penicillin-susceptible streptococci. Streptococcus viridans, a heterogeneous group of organisms, accounts for the majority, with the remainder caused by group G, non-enterococcal group D, and other streptococci.

For these patients, there are several recommended regimens (Table 35-1). For most patients with highly sensitive streptococci (minimal inhibitory concentration [MIC] for penicillin, < 0.1 µg/mL), single drug therapy...
### Table 35-1. Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage* and Route</th>
<th>Duration (wk)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous crystalline Penicillin G sodium</td>
<td>12-18 million U/24 h IV either continuously or in 4 or 6 equally divided doses</td>
<td>4</td>
<td>Preferred in most patient &gt; 65 y or patients with impairment of 8th cranial nerve function or renal function</td>
</tr>
<tr>
<td><strong>Or</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone sodium</td>
<td>2 g/24 h IV/IM in 1 dose</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Pediatric dose†:</strong> penicillin 200 000 U/kg per 24 h IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqueous crystalline Penicillin G sodium</td>
<td>12-18 million U/24 h IV either continuously or in 6 equally divided doses</td>
<td>2</td>
<td>2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of &lt;20 mL/min, impaired 8th cranial nerve function, or <em>Abiotrophia</em>, <em>Granulicatella</em>, or <em>Gemella</em> spp infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 µg/mL and trough serum concentration of &lt;1 µg/mL when 3 divided doses are used; nomogram used for single daily dosing§</td>
</tr>
<tr>
<td><strong>Or</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone sodium</td>
<td>2 g/24 h IV/IM in 1 dose</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Plus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin sulfate‡</td>
<td>3 mg/kg per 24 h IV/IM in 1 dose</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Pediatric dose:</strong> penicillin 200 000 U/kg per 24 h IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose; gentamicin 3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses[</td>
<td></td>
<td>]</td>
<td></td>
</tr>
<tr>
<td>Vancomycin hydrochloride‡</td>
<td>30 mg/kg per 24 h IV in 2 equally divided doses not to exceed 2 g/24 h unless concentrations in serum are inappropriately low <strong>Pediatric dose:</strong> 40 mg/kg per 24 h IV in 2-3 equally divided doses</td>
<td>4</td>
<td>Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 h after infusion completed) serum concentration of 30-45 µg/mL and a trough concentration range of 10-15 µg/mL</td>
</tr>
</tbody>
</table>

Minimum inhibitory concentration \( \leq 0.12 \) µg/mL.

*Dosages recommended are for patients with normal renal function; †Pediatric dose should not exceed that of a normal adult; ‡Other potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis due to viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses. §See reference 280 in full statement of cited source. Although this reference outlines dosing for gentamicin use at 7 mg/kg/dose for treatment in other types of infection syndromes, the Nomogram was selected as an example for use with gentamicin dosing of 3 mg/kg/dose in this table to direct dosing in patients with underlying renal dysfunction. Currently, there is no other formal address of drug concentration monitoring with this gentamicin dosage. ||Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist. ¶Vancomycin dosages should be infused during course of at least 1 h to reduce risk of histamine-release "red man" syndrome.*

for 4 weeks or a combination of penicillin and gentamicin for 2 weeks has replaced 4 weeks of penicillin given with streptomycin for 2 weeks as the conventional therapy. Regimens containing beta-lactam antibiotics achieve cure in at least 98% of cases. Vancomycin appears to be as effective as penicillin when given for 4 weeks in viridans streptococcal IE.

Gentamicin is now preferred to streptomycin in combined regimens because of its broad clinical use, approved intravenous or intramuscular route of administration, and the widespread availability of serum drug levels. Also, streptomycin has become less available for general use. In vitro and clinical data demonstrate the efficacy of gentamicin combined with penicillin in streptococcal IE. Some authorities continue to recommend penicillin for 4 weeks with gentamicin for the initial 2 weeks for sensitive Streptococcus viridans IE if the course is complicated or the duration of disease is longer than 3 months. Consideration of a patient’s age, renal status, eighth cranial nerve function, and drug allergy guide the choice of therapy.

Outpatient treatment, for all or part of therapy, has become feasible with current regimens. The largest experience with outpatient therapy is with ceftriaxone for sensitive S viridans endocarditis; however, staphylococcal, enterococcal, and some gram-negative disease may be suitable for outpatient therapy with a variety of antibiotics. A 2-week regimen of once-a-day ceftriaxone with gentamicin is as efficacious and safe for the treatment of penicillin-susceptible streptococcus endocarditis as a 4-week regimen of ceftriaxone monotherapy.

From 15% to 20% of Streptococcus viridans require more than 0.1µg/mL of penicillin for inhibition. Endocarditis caused by these organisms should be treated with penicillin for 4 weeks, combined with gentamicin for the first 2 weeks, although data are limited and clinical trials showing superior efficacy of the combined regimen over a single agent are lacking. Endocarditis due to penicillin-resistant streptococci (MIC > 0.5 µg/mL) and nutritionally variant streptococci now called Gramicidicella and Abiotrophia species) should be treated with the antibiotic combinations recommended for enterococcal IE.

The significance of antibiotic tolerance for treating Streptococcus viridans IE is controversial. Most streptococci are inhibited and killed by low concentrations of penicillin. Tolerant strains, however, require a much higher concentration (> 32 times) to kill the organism than is required for inhibition of growth. Although in animal models, tolerant strains are killed more slowly than nontolerant ones, differences in treatment outcomes for human IE have not been demonstrated. Therefore, penicillin-tolerant Streptococcus viridans are treated according to the recommendations mentioned earlier based on the determination of penicillin MIC; measurement of the minimum bactericidal concentration (MBC) is usually not necessary.

**Enterococcal Endocarditis**

Enterococci may cause either subacute or acute IE. This occurs most commonly in women of childbearing age after obstetric procedures and in older men. This group of organisms was formerly classified as group D streptococci, but is now considered a separate genus Enterococcus. Enterococci account for 5% to 20% of isolates from patients with IE.

Enterococcal isolates from patients with bacterial IE include Enterococcus faecium, Enterococcus faecalis, and Enterococcus durans. Streptococcus bovis and Streptococcus equinus are group D streptococci that may be confused with enterococci, but these streptococci usually are highly sensitive to penicillin and should be treated the same way as infections caused by S viridans. Treatment recommendations for enterococcal endocarditis are shown in Tables 35-2 to 35-5.

Enterococci are frequently relatively resistant and highly tolerant to penicillin (Table 35-4), exhibiting MICs of 1 to 4 µg/mL and MBCs of equal to or greater than 100 µg/mL. Similar tolerance has been demonstrated for vancomycin (Table 35-5). The cephalosporins are not clinically useful for treating these infections, but some strains of Enterococcus faecalis are susceptible to imipenem-cilastatin (Table 35-5). In view of possible resistance, the MIC for penicillin, ampicillin, and vancomycin should be determined for enterococci causing IE. Beta-lactamase producing strains of enterococci have been identified. Therapy for infections with these organisms would include vancomycin or ampicillin-sulbactam in combination with gentamicin.

Synergistic killing has been demonstrated in vitro for most enterococci with the combination of penicillin and vancomycin or gentamicin. However, enterococcal isolates with high-level (MIC > 500 to 2000 µg/mL) resistance to these aminoglycosides are now isolated with increasing frequency. Bactericidal synergy between a cell wall active antibiotic and aminoglycosides is lost in the presence of high-level resistance. Testing for high-level resistance to gentamicin is currently recommended for enterococcal IE. Therefore, there is an ongoing need for newer aminoglycosides that do not incur resistance.

However, treatment for IE due to strains with high-level aminoglycoside resistance continues to be controversial. The standard recommendations include long-term therapy for 8 weeks or longer with high dose penicillin (20 to 40 million units IV daily in divided doses), ampicillin (2-3 g IV every 4 hours or by continuous infusion) or vancomycin for patients intolerant of beta-lactams. A strong consideration for valve replacement should be given for patients failing medical therapy.
Enterococci resistant to vancomycin (VRE) are an increasing problem in the United States. Infection with these organisms, which are also often resistant to penicillins, has been associated with nosocomial acquisition, severe underlying disease, and previous use of antibiotics. There is no consensus about treatment of IE with multi-resistant enterococci.

The recommended first-line therapy for VRE is a high-dose ampicillin with an aminoglycoside (Table 35-5).

Quinupristin-dalfopristin has been recommended for the treatment of VRE in combination with other antimicrobials such as ampicillin, amoxicillin, doxycycline, and rifampin (Table 35-5). Nevertheless, quinupristin-dalfopristin is still only bacteriostatic, and in vitro resistance is a concern. Another drug approved for the treatment of VRE is the oxazolidinone, linezolid (Table 35-5). When penicillin or vancomycin can be combined with gentamicin or streptomycin, 4 weeks of therapy appears adequate for most patients; 6 weeks is recommended if symptoms have been present for more than 3 months, or infection is on a prosthetic valve; 8 weeks or longer may be needed for VRE infections.

Endocarditis Caused by *Staphylococcus aureus*

*Staphylococcus aureus* generally causes acute bacterial IE in patients with no prior history of valvular disease. It is
the infecting agent in 25% to 45% of IE cases and may be more common at community hospitals than in university referral centers. Among intravenous drug users with IE, staphylococci account for 65% to 82% of the cases.\textsuperscript{15} Standard therapy is a penicillinase-resistant penicillin such as nafcillin or oxacillin or a first-generation cephalosporin (Table 35-6). The penicillins are favored because in vitro, cephalosporins appear more sensitive to beta-lactamases at the high organism densities (inoculum effect) expected in a valvular vegetation. It is not clear that this inoculum effect is important clinically.\textsuperscript{5}

Vancomycin is recommended for patients with severe allergy to beta-lactams. For methicillin-sensitive \textit{Staphylococcus aureus} (MSSA) IE, there is evidence that vancomycin is not as rapidly bactericidal as nafcillin and may have higher failure rates in IE. Vancomycin is the drug of choice for IE due to MRSA, which continues to increase in the United States. The response of patients with MRSA IE appears to be slower than that of patients treated with beta-lactams for MSSA disease.

For MRSA endocarditis refractory to vancomycin, rifampin, or gentamicin (or both) can be added. The licensed combination streptogramin therapy, quinupristin-dalfopristin, has been shown to have a potential benefit combined with a beta-lactam in vitro and in rats with MRSA endocarditis.\textsuperscript{16} The study concluded that quinupristin-dalfopristin plus cefepime could be of use for the treatment of severely ill patients who require multiple-antibiotic therapy. Another combination of quinupristin-dalfopristin and rifampin was found to be effective \textit{in vivo}.

The antibiotic, linezolid, was tested in a staphylococcal endocarditis rabbit model, which indicated that, like

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Table 35-3. Therapy for Native or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Susceptible to Penicillin, Streptomycin, and Vancomycin and Resistant to Gentamicin

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage* and Route</th>
<th>Duration (wk)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin sodium</td>
<td>12 g/24 h IV in 6 equally divided doses</td>
<td>4-6</td>
<td>Native valve: 4-wk therapy recommended for patients with symptoms of illness &lt; 3 mo; 6-wk therapy recommended for patients with symptoms &gt;3 mo</td>
</tr>
<tr>
<td>Or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqueous crystalline Penicillin G sodium</td>
<td>24 million U/24 h IV continuously or in 6 equally divided doses</td>
<td>4-6</td>
<td></td>
</tr>
<tr>
<td>Plus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin sulfate\textsuperscript{†}</td>
<td>15 mg/kg per 24 h IV/IM in 2 equally divided doses</td>
<td>4-6</td>
<td>Prosthetic valve or other prosthetic cardiac material; minimum of 6 wk of therapy</td>
</tr>
<tr>
<td>Pediatric dose\textsuperscript{‡}: ampicillin 300 mg/kg per 24 h IV in 4-6 equally divided doses; penicillin 300 000 U/kg per 24 h IV in 4-6 equally divided doses; streptomycin 20-30 mg/kg per 24 h IV/IM in 2 equally divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin hydrochloride</td>
<td>30 mg/kg per 24 h IV in 2 equally divided doses</td>
<td>6</td>
<td>Vancomycin therapy recommended only for patients unable to tolerate penicillin or ampicillin</td>
</tr>
<tr>
<td>Plus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin sulfate</td>
<td>15 mg/kg per 24 h IV in 2 equally divided doses</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pediatric dose\textsuperscript{‡}: vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; streptomycin 20-30 mg/kg per 24 h IV/IM in 2 equally divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dosages recommended are for patients with normal renal function. †See text for appropriate dosing of streptomycin. ‡Pediatric dose should not exceed that of a normal adult.

vancomycin, linezolid is effective for the treatment of experimental staphylococcal endocarditis in rabbits when plasma drug levels remain above the MIC.

MSSA is killed more rapidly in vitro and in animal models of IE with the combination of a penicillinase-resistant penicillin and gentamicin (Table 35-6). In a large clinical trial, the combination of nafcillin and gentamicin for 2 weeks was associated with a more rapid clearing of bacteremia in staphylococcal IE compared to nafcillin alone but without improved survival and with more renal toxicity. Gentamicin is currently recommended as an optional addition to a beta-lactam agent for the initial 3 to 5 days of treatment. A short course of gentamicin can also be added to vancomycin for MSSA or MRSA IE, although nephrotoxic effects of this combination may be more common.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage* and Route</th>
<th>Duration (wk)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-Lactamase-producing strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>12 g/24 h IV in 4 equally divided doses</td>
<td>6</td>
<td>Unlikely that the strain will be susceptible to gentamicin; if strain is gentamicin resistant, then &gt; 6 wk of ampicillin-sulbactam therapy will be needed</td>
</tr>
<tr>
<td><strong>Plus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin sulfate</td>
<td>3 mg/kg per 24 h IV/IM in 3 equally divided doses</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Intrinsic penicillin resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin hydrochlorides</td>
<td>30 mg/kg per 24 h IV in 2 equally divided doses</td>
<td>6</td>
<td>Vancomycin therapy recommended only for patients unable to tolerate ampicillin-sulbactam</td>
</tr>
<tr>
<td><strong>Plus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin sulfate</td>
<td>3 mg/kg per 24 h IV/IM in 3 equally divided doses</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Pediatric dose:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vancomycin</td>
<td>40 mg/kg per 24 h IV in 2 or 3 equally divided doses</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>gentamicin</td>
<td>3 mg/kg per 24 h IV/IM in 3 equally divided doses</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

*Dosages recommended are for patients with normal renal function. ‡Pediatric dose should not exceed that of a normal adult.

Staphylococcal IE in intravenous drug users usually involves the tricuspid valve and has a significantly better prognosis than left-sided disease from *Staphylococcus aureus* with a mortality < 5%. Two-week antibiotic regimens combining nafcillin and oxacillin and an aminoglycoside have been used successfully in selected stable patients with tricuspid valve IE with cure rates greater than 90%.\(^5\)

There were also two studies that tested the combination of ciprofloxacin plus rifampin orally for 4 weeks for uncomplicated right-sided *Staphylococcus aureus* IE in patients with drug addiction. This study also demonstrated that cure rates were > 90%. There are few clinical data on the

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage* and Route</th>
<th>Duration (wk)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecium</em></td>
<td></td>
<td></td>
<td>Patients with endocarditis caused by these strains should be treated in</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1200 mg/24 h IV/PO in 2 equally divided doses</td>
<td>≥8</td>
<td>consultation with an infectious disease specialist; cardiac valve</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>replacement may be necessary for bacteriologic cure; with anti-microbial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>therapy alone may be &lt; 50%; severe, usually reversible thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>may occur with use of linezolid, especially after 2 wk of therapy</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinupristin-</td>
<td>22.5 mg/kg per 24 h IV in 3 equally divided doses</td>
<td>≥8</td>
<td>Quinupristin-dalfopristin only effective against <em>E. faecium</em> and can</td>
</tr>
<tr>
<td>dalfopristin</td>
<td></td>
<td></td>
<td>cause severe myalgias, which may require discontinuation of therapy; only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>small number of patients have reportedly been treated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td>2 g/24 h IV in 4 equally divided doses</td>
<td>≥8</td>
<td></td>
</tr>
<tr>
<td><strong>Plus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin sodium</td>
<td>12 g/24 h IV in 6 equally divided doses</td>
<td>≥8</td>
<td></td>
</tr>
<tr>
<td><strong>Or</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone sodium</td>
<td>4 g/24 h IV/IM in 2 equally divided doses</td>
<td>≥8</td>
<td></td>
</tr>
<tr>
<td><strong>Plus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin sodium</td>
<td>12 g/24 h IV in 6 equally divided doses [Pediatric dose]: Linezolid 30 mg/kg per</td>
<td>≥8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 h IV/PO in 3 equally divided doses; quinupristin-dalfopristin 22.5 mg/kg per</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 h IV in 3 equally divided doses; imipenem/cilastatin 60-100 mg/kg per 24 h IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>in 4 equally divided doses; ampicillin 300 mg/kg per 24 h IV in 4-6 equally</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 2 equally divided doses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Decreasing order of preference based on published data. *Dosages recommended are for patients with normal renal function. †Pediatric dose should not exceed that of a normal adult.

Table 35-6. Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage* and Route</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxacillin-susceptible strains</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin or oxacillin†</td>
<td>12 g/24 h IV in 4-6 equally divided doses</td>
<td>6 wk</td>
<td>For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk</td>
</tr>
<tr>
<td>with Optional addition of gentamicin sulfate‡</td>
<td>3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses</td>
<td>3-5 d</td>
<td>Clinical benefit of aminoglycosides has not been established.</td>
</tr>
<tr>
<td>For penicillin-allergic (nonanaphylactoid type) patients</td>
<td></td>
<td></td>
<td>Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>6 g/24 h IV in 3 equally divided doses</td>
<td>6 wk</td>
<td>Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.§</td>
</tr>
<tr>
<td>with Optional addition of Gentamicin sulfate</td>
<td>3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses</td>
<td>3-5 d</td>
<td>Clinical benefit of aminoglycosides has not been established.</td>
</tr>
<tr>
<td><strong>Oxacillin-resistant strains</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>30 mg/kg per 24 h IV in 2 equally divided doses</td>
<td>6 wk</td>
<td>Adjust vancomycin dosage to achieve 1-h serum concentration of 30-45 µg/mL and thorough concentration of 10-15 µg/mL.</td>
</tr>
</tbody>
</table>

*Dosages recommended are for patients with normal renal function. †Penicillin G 24 million U/24 h IV in 4 to 6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 µg/mL) and does not produce β-lactamase.
‡Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing. §Pediatric dose should not exceed that of a normal adult.


efficacy of cephalosporins or vancomycin in 2-week regimens, and these drugs are not recommended for short-term use.5

Rifampin is an extremely potent anti-staphylococcal drug that achieves excellent tissue and intracellular concentrations. Resistance emerges rapidly when used as a single agent, but usually not when combined with other effective drugs. In vitro, the effect of rifampin in combination with beta-lactams or vancomycin is variable depending on experimental conditions. There was no advantage to vancomycin and rifampin compared to vancomycin alone in a clinical study of MRSA IE. Rifampin is not recommended...
for native valve staphylococcal endocarditis, although it does have a role in the treatment of prosthetic valve infections in addition to nafcillin and gentamicin.5

Endocarditis Caused by Less Common Pathogens

The optimal therapy for IE resulting from less common causes is still not adequately defined. Recommendations for treating IE caused by HACEK microorganisms (Haemophilus parainfluenzae, Haemophilus aphrophilus, and Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae) are shown in Table 35-7. (Aminoglycosides and fluoroquinolones are bactericidal for Bartonella. However, most patients with reported cases of IE due to Bartonella infections have been treated with a beta-lactam antibiotic and an aminoglycoside. Most patients with IE due to Bartonella have also required valve-replacement surgery for cure. Doxycycline, with a second antimicrobial agent, is often given for 3 to 4 years until IgG antibody titers drop < 1:400 and has been the recommended treatment for IE due to Q fever.

A prospective study among 35 participants with Q fever infective endocarditis suggested that the combination of doxycycline and hydroxychloroquine (median duration, 26 months) was associated with a lower rate of relapse than was therapy with doxycycline and fluoroquinolone for a median of 60 months. Eradication of Q fever IE usually requires valve-replacement surgery, although relapse of infection on the replaced valve may occur.

In the absence of clinical clues to a specific cause, therapy for culture-negative native-valve endocarditis should be individualized and generally includes penicillin, ampicillin, ceftriaxone, or vancomycin, often in combination with an aminoglycoside.17

Table 35-7. Therapy for Both Native and Prosthetic Valve Endocarditis Caused by HACEK* Microorganisms

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage* and Route</th>
<th>Duration (wk)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone† sodium</td>
<td>2 g/24 h IV/IM in 1 dose</td>
<td>4</td>
<td>Cefotaxime or another third- or fourth-generation cephalosporin may be substituted</td>
</tr>
<tr>
<td>Or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin-sulbactam‡</td>
<td>12 g/24 h IV in 4 equally divided doses</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin‡§</td>
<td>1000 mg/24 h PO or 800 mg/24 h IV in 2 equally divided doses</td>
<td>4</td>
<td>Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted; fluoroquinolones generally not recommended for patients &lt; 18 y old; Prosthetic valve: patients with endocarditis involving prosthetic cardiac valve or other prosthetic cardiac material should be treated for 6 wks</td>
</tr>
</tbody>
</table>

*Haemophilus parainfluenzae, Haphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae.
†Patients should be informed that IM injection of ceftriaxone is painful. ‡Dosage recommended for patients with normal renal function.
§Fluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on use of fluoroquinolone therapy for endocarditis caused by HACEK are minimal. ||Pediatric dose should not exceed that of a normal adult.

hemorrhage. Anticoagulant therapy for native-valve endocarditis is restricted to patients with a clear indication separate from IE. In the presence of intracranial hemorrhage or mycotic aneurysm, anticoagulant therapy should be suspended until the complications have resolved. In general, patients with IE involving a prosthetic heart valve that requires maintenance anticoagulation are cautiously continued anticoagulant therapy during treatment of prosthetic-valve endocarditis. However, in the presence of central nervous system emboli with hemorrhage, temporary discontinuation of anticoagulant therapy is appropriate.

Patients with Staphylococcus aureus prosthetic-valve endocarditis who are receiving anticoagulant therapy are particularly susceptible to central nervous system hemorrhage; indirect evidence from uncontrolled studies in a limited number of patients suggests that anticoagulant therapy should generally be suspended in such patients during the acute phase (first 2 weeks) of the illness. If cardiac surgery for IE is planned, warfarin may be discontinued and replaced with heparin to allow more rapid reversal of anticoagulation at the time of surgery. The role (if any) of aspirin in the prevention of embolism in IE is still unproven.

The indications for anticoagulant therapy when systemic embolism occurs during the course of IE involving a native or bioprosthetic heart valve are uncertain. The therapeutic decision should consider comorbid factors, including atrial fibrillation, evidence of left atrial thrombus, evidence and size of valvular vegetations, and particularly the success of antibiotic therapy in controlling the IE.

Endocarditis Prophylaxis

The concept of endocarditis prophylaxis was previously based upon identifying situations in which patients have presumed predisposing factors for the development of endocarditis. Approximately 75% of patients with endocarditis have pre-existing cardiac abnormalities. Although precise figures are lacking, the ranking of risk has been recently assumed to be proportional not simply to the frequency of IE occurrence but also to the relative risk of serious morbidity predisposed by IE occurring in the presence of a particular lesion. Published series regarding endocarditis in patients with congenital heart disease, for example, are underpowered to determine the extent to which a specific form of congenital heart disease is an independent risk factor for morbidity and mortality. Nevertheless, most retrospective case series suggest that patients with complex cyanotic heart disease and those who have postoperative palliative shunts, conduits, or other prostheses have a high lifetime risk of acquiring IE, and these same groups appear at highest risk for morbidity and mortality among all patients with congenital heart disease (Table 35-8).

In addition, previous AHA guidelines and others attempted to stratify invasive procedures according to risk for development of IE despite the lack of firm, evidence-based data to support such categorizations. The newest AHA guidelines, therefore, consider only one group of dental procedures as eligible for secondary prophylaxis against IE: all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa.

Table 35-8. Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prophylaxis Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic Cardiac valve or prosthetic material used for cardiac valve repair</td>
<td>Previous IE</td>
</tr>
<tr>
<td>Congenital heart disease (CHD)*</td>
<td>Unrepaired cyanotic CHD, including palliative shunts and conduits</td>
</tr>
<tr>
<td>Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†</td>
<td>Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†</td>
</tr>
<tr>
<td>Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)</td>
<td>Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)</td>
</tr>
<tr>
<td>Cardiac transplantation recipients who develop cardiac valvulopathy</td>
<td>Cardiac transplantation recipients who develop cardiac valvulopathy</td>
</tr>
</tbody>
</table>

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

**Table 35-9. Prophylactic Regimens for a Dental Procedure**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Regimen: Single Dose 30 to 60 min Before Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin 2 g</td>
<td>Adults 50 mg/kg Children</td>
</tr>
<tr>
<td>Unable to take oral medication</td>
<td>Ampicillin 2 g IM or IV</td>
<td>Adults 50 mg/kg IM or IV Children</td>
</tr>
<tr>
<td>Allergic to penicillins or ampicillin-oral</td>
<td>Cefazolin or ceftriaxone 1 g IM or IV</td>
<td>Adults 50 mg/kg IM or IV Children</td>
</tr>
<tr>
<td>Allergic to penicillins or ampicillin and unable to take oral medication</td>
<td>Cefazolin or ceftriaxone† 1 g IM or IV</td>
<td>Adults 50 mg/kg IM or IV Children</td>
</tr>
</tbody>
</table>

**IM indicates intramuscular; IV , intravenous**

* Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
† Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.


valve IE. Additionally, patients with multiple episodes of native or prosthetic valve IE are at greater risk of additional episodes of endocarditis, each of which is associated with the risk of more serious complication.

Newly developed AHA guidelines for nonvalvular cardiovascular devices, such as atrial septal defect occluders, do not recommend secondary prophylaxis coverage for the vast majority of patients with any implanted device of this type who undergo dental, respiratory, gastrointestinal, or genitourinary procedures. Only very few exceptions are suggested, namely patients in whom less-than-successful device implantation has resulted in the creation or persistence of turbulent blood flow jets.

**Prosthetic Valve Endocarditis**

Prosthetic valve endocarditis (PVE) is a particularly serious problem and can be difficult to treat. Classically, PV infections have been divided into two groups: early and late. In early PVE, the infection becomes manifest within 2 months of insertion of the prosthesis. Due to the significant difference in the organisms found within the first and second year of operation, the cut-off time between late and early PVE should be one year. In general, early PVE is caused by organisms introduced during the surgical procedure or, if the implant replaced an infected valve, residual infection. In contrast, late PVE usually is caused by the introduction of pathogens into the circulation after the time of surgery. Consequently, early PVE more commonly is caused by staphylococcal species (largely *Staphylococcus epidermidis*), gram-negative organisms, and diphtheroids, whereas late disease is similar in microbial spectrum to native valve endocarditis. *Staphylococcus epidermidis* is the most common causative organism in PVE.

The pathology of infection is dependent on the class of valve used. Of 22 participants with infected mechanical valves studied at necropsy by Arnett and Roberts, all had valve ring abscesses. Dehiscence, causing severe valvular regurgitation, occurred in 14 of the 22 participants, and prosthetic valve obstruction by vegetative material occurred in 6. Conversely, in porcine heterografts, the infection frequently developed in the fibrin layer that covers the cusps and can spread to involve the subadjacent collagen; valve ring abscess is infrequent. Regurgitation with porcine valves occurs most often because the valve leaflets are destroyed rather than resulting from suture line dehiscence. There are also reported cases in which fibrinous membranes developed on the atrial surface of a prosthetic mitral valve, leading to fatal obstruction of left ventricular inflow.

The diagnosis of PVE can be elusive, especially when fever and bacteremia complicate the early postoperative period. Even when an extra cardiac source can be identified, the possibility of valve seeding cannot be ignored because virtually any organism can establish a focus of
infection on a newly implanted prosthetic valve. However, in a study of 32 participants who developed bacteremia postoperatively, only 2 (6.3%) were thought to have PVE.23 Bacteremia in a patient with a recently implanted PV is an ominous sign. A review of 6 studies revealed an approximately 50% overall mortality.28

In a large review, the mortality rate for medically treated patients was 61.4%, while for those who also received surgery, it was 38.5%.23 These data were obtained from studies without controls; thus selection bias clearly played some role in determining these figures. The investigators proposed that patients with non-staphylococcal PVE may be managed medically without surgery as long as the patient is hemodynamically stable and closely monitored.

For bacterial PVE, the susceptibility of the etiologic agent to antimicrobial agents is an especially important factor for outcome (Table 35-10). PVE due to organisms resistant to conventional therapy, such as methicillin-resistant staphylococci or gram-negative bacilli, are more likely to require surgery. It also is important to note that many survivors of complicated *Staphylococcus epidermidis* PVE required valve replacement within the ensuing 6 months of bacteriologic cure. In contrast, the somewhat less aggressive endocarditis caused by penicillin-susceptible streptococcal infection is more often cured medically.

A relatively unique situation in PVE is the development of infection caused by methicillin-resistant *Staphylococcus epidermidis*. It has been demonstrated conclusively that these patients were more likely to survive if their antibiotic regimen included vancomycin and, furthermore, the addition of rifampin and gentamicin increased survival.

Sett and colleagues29 reviewed prosthetic valve endocarditis in porcine bioprostheses. In this series, all participants with early PVE died. Ninety-one percent with late PVE survived with a combined medical and surgical approach. The authors recommended that a combined medical and surgical approach in PVE with *Staphylococcus aureus*, *Candida albicans*, or gram-negative organisms.

Fungal PVE, like its counterpart on native valves, is notoriously unresponsive to medical therapy and, therefore, early surgery should be performed once the diagnosis is made.30-31 Even when surgically treated, there is a high incidence of recurrent endocarditis.32 However, it was found that aggressive amphotericin B therapy was an important adjunct to surgery. Central intravascular catheter, previous bacterial endocarditis, prolonged antibiotics, total parental nutrition, and immunosuppression have also been identified as predisposing factors for fungal PVE. *Candida albicans* was found to be the leading causative organism with *Candida parapsilosis* next.

Antimicrobial treatment of PVE is similar to native valve endocarditis treatment with certain concepts to keep in mind. First, due to the larger size of the vegetations, antibiotics need to be given in doses that result in maximum, nontoxic serum concentrations so that the vegetation can be penetrated fully. Also, the duration of treatment is longer and should be determined by the MIC of the most efficient combination of antibiotics and also the size of the vegetation determined by transesophageal echocardiography. When the MIC is ≥ 4 µg/ml, antibiotic sterilization is unlikely.

Coagulase negative staphylococci are difficult to treat medically due to the interaction between the organism and the synthetic material of the valve. An example of this interaction is the irreversible adhesion and production of a biofilm that inhibits host defense mechanisms. This protective mechanism makes antibiotic sterilization difficult. Coagulase negative staphylococci may cause micro-abscesses, and triple therapy with gentamicin (900 mg/day divided into 3 doses) is recommended. Rifampin is apparently effective inside abscesses.

Therapy for culture-negative PVE within the initial 12 months after valve replacement often includes at least vancomycin and gentamicin. For patients with PVE that begins 12 months or more after valve surgery, ceftriaxone or cefotaxime could be added to cover for so-called HACEK organisms. If fever due to IE persists after empirical therapy, valve-replacement surgery for débridement and to obtain material for microbiologic and pathological evaluation may be considered.

Valvular dysfunction caused by incompetence, stenosis of the outflow track, or perivalvular leak is unlikely to respond to medical management and should be treated with prompt surgery prior to hemodynamic compromise. The development of conduction abnormalities suggests an annular abscess. In some studies, 69% of participants with conduction abnormalities and infection of a prosthetic aortic valve have annular abscesses. Many of these participants do not survive despite therapy. It is therefore prudent to follow all participants carefully and to use the earliest sign of valvular destruction, dysfunction, myocardial invasion, or failure of bacteriologic cure as an indication for urgent surgery.

### Implantable Assist Device Infection

The introduction of implanted cardiac assist devices such as pacemakers, automatic implantable cardioverter-defibrillators (AICDs), and left ventricular assist devices (LVADs) has improved survival and quality of life in seriously ill patients. However, similar to prosthetic valves, these foreign materials introduced into the human body are a nidus for infection.33-40a Infection of any of these devices is a serious complication and can be extremely difficult to manage conservatively. Of concern is that bacteria can colonize devices without clinical signs of infection.41-42 The reported incidence of infection is 1% to 12% for pacemakers, 1% to 6% for AICDs, and 13% to 80% for LVADs.43 Most investigators agree that the optimum
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage* and Route</th>
<th>Duration (wk)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxacillin-susceptible strains</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin or oxacillin</td>
<td>12 g/24 h IV in 6 equally divided doses</td>
<td>≥6</td>
<td>Penicillin G 24 million U/24 h IV in 4 to 6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (MIC ≤0.1 µg/mL) and does not produce β-lactamase</td>
</tr>
<tr>
<td><strong>Plus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>900 mg per 24 h IV/PO in 3 equally divided doses</td>
<td>≥6</td>
<td>Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics</td>
</tr>
<tr>
<td><strong>Plus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin†</td>
<td>3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses</td>
<td>2</td>
<td>Cefazolin may be substituted for nafcillin or oxacillin for patients with non-immediate-type hypersensitivity reactions to penicillins</td>
</tr>
<tr>
<td><strong>Pediatric dose:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nafcillin or oxacillin</td>
<td>200 mg/kg per 24 h IV in 4-6 equally divided doses; rifampin 20 mg/kg per 24 h IV/PO in 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Oxacillin-resistant strains** | | | |
| Vancomycin | 30 mg/kg 24 h in 2 equally divided doses | ≥6 | Adjust vancomycin to achieve 1-h serum concentration of 30-45 µg/mL and trough concentration of 10-15 µg/mL |
| **Plus** | | | |
| Rifampin | 900 mg/24 h IV/PO in 3 equally divided doses | ≥6 | |
| **Plus** | | | |
| Gentamicin† | 3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses | 2 | |
| **Pediatric dose:** | | | |
| vancomycin | 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; rifampin 20 mg/kg per 24 h IV/PO in 3 equally divided doses (up to adult dose); gentamicin 3 mg/kg per 24 h IV or IM in 3 equally divided doses | | |

*Dosages recommended are for patients with normal renal function. †Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. ‡Pediatric dose should not exceed that of a normal adult.

management for both pacemaker and AICD infections is explantation of the entire device and prolonged antibiotics. However, there are reported cases of pacemaker infections that were treated successfully by medical therapy alone. Explantation for LVAD infection is not a valid option unless an organ is available for transplant. LVADs are used as a bridge to transplantation. Thus, if no organ is available, the only option is medical management, which is rarely a cure. However, successful transplants have been reported in LVAD-infected individuals controlled with antibiotics.

Pacemaker endocarditis, a relatively rare but serious complication of pacemaker infection, has a mortality rate of 24%. These infections usually involve the pacemaker electrode tip, the tricuspid valve, or endocardial areas in contact with the endocardial lead. The most common organisms involved are the staphylococcal species. Defining/diagnosing criteria are lacking for pacemaker endocarditis, making it difficult to diagnose. Most authors follow criteria for IE.

Two different syndromes of pacemaker endocarditis have been described, metastatic implantation type and the more common foreign body type. The foreign body type results from the extension of a pacemaker generator pocket infection along the pacemaker wire. The implantation type results from damage to the endocardium by the transvenous pacemaker followed by bacteremic implantation. Removal of the entire pacemaker device and prolonged antibiotics for the specific pathogen is the optimum treatment.

At the time of device placement, prophylaxis with an antibiotic that has in vitro activity against staphylococci should be administered intravenously within 1 hour before incision. If vancomycin is given, then it should be administered intravenously within 2 hours of incision.

**Rheumatic Fever**

Prevention of recurrent rheumatic fever depends upon continuous prophylaxis with appropriate antibiotics. The risk of recurrence decreases with time after the previous episode. The risk increases if there are two or more previous attacks of rheumatic fever. The risk also increases in the presence of rheumatic heart disease. Parents of young children, teachers, physicians, nurses, allied medical personnel, military personnel, and other individuals living in crowded conditions have an increased risk of exposure to recurrent streptococcal infection.

The recommendations for treatment of acute streptococcal pharyngitis and prevention of rheumatic fever are summarized in Tables 35-11 to 35-13 (see p. 608). Penicillin remains the treatment of choice for group A streptococcal pharyngitis due to its reliability, safety, and low cost. However, recent studies have shown that a 10-day treatment with once-a-day amoxicillin is as effective as multiple daily doses of penicillin. A slightly higher rate of eradication is reported with cephalosporins, but the cost of these drugs is higher. Other drugs, such as azithromycin, cepuroxime, cefdinir, cefixime, and cefpodoxime at 5 days, have shown results similar to penicillin for 10 days. Cefpodoxime and cefdinir are the only cephalosporins currently approved by the US Food and Drug Administration for less than 10 days of treatment. Cefadroxil (30 mg/kg up to 1000 mg); cefixime (8 mg/kg up to 400 mg); cefdinir (14 mg/kg up to 600 mg); and cefpodoxime (9 mg/kg up to 400 mg) are approved for once-daily, 10-day treatment. However, there is a consideration of cost and development of resistance with these agents. Nevertheless, since poor adherence with antibiotics increases the risk of failure in treatment and the development of acute rheumatic fever, treatment regimens that could improve adherence by decreasing daily frequency or total duration of treatment are being investigated.

*Note: References for this chapter can be found here: www.cvpt3.com*
Table 35-11. Primary Prevention of Rheumatic Fever (treatment of streptococcal tonsillopharyngitis)*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Mode</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Penicillin V (phenoxymethyl penicillin) | Children ≤27 kg (60 lbs): 250 mg 2-3 times a day  
                                          Children >27 kg (60 lbs), adolescents, and adults: 500 mg 2-3 times a day | Oral | 10 days  |
| Amoxicillin                  | 50 mg/kg once daily (max 1 g)              | Oral | 10 days  |
| Benzathine penicillin G      | 600,000 U for patients ≤27 kg (60 lbs)  
                                          1,200,000 U for patients >27 kg (60 lbs) | IM   | Once     |
| **For individuals allergic to penicillin** |                              |      |          |
| Narrow-spectrum cephalosporin† (cephalexin, cefadroxil) | Variable | Oral | 10 days  |
| Clindamycin                  | 20 mg/kg once daily divided in 3 doses (max 1.8 g/d) | Oral | 10 days  |
| Azithromycin                 | 12 mg/kg once daily (max 500 mg)           | Oral | 5 days   |
| Clarithromycin               | 15 mg/kg daily divided BID (max 250 mg bid) | Oral | 10 days  |

For other acceptable alternatives, see text of original citation. The following are not acceptable: sulfonamides, trimethoprim, tetracyclines, fluoroquinolones.

† to be avoided in those with immediate (type I) hypersensitivity to a penicillin

IM = intramuscular; bid = twice daily


Table 35-12. Duration of Secondary Rheumatic Fever Prophylaxis

<table>
<thead>
<tr>
<th>Category</th>
<th>Duration After Last Attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever with carditis and residual heart disease (persistent valvular disease)</td>
<td>10 years or until 40 years of age (whichever is longer); sometimes lifelong prophylaxis</td>
</tr>
<tr>
<td>Rheumatic fever with carditis but no residual heart disease (no valvular disease)*</td>
<td>10 years or until 21 years of age (whichever is longer)</td>
</tr>
<tr>
<td>Rheumatic fever without carditis</td>
<td>5 years or until 21 years of age (whichever is longer)</td>
</tr>
</tbody>
</table>

*Clinical or echocardiographic evidence.


Table 35-13. Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Mode</th>
</tr>
</thead>
</table>
| Benzathine penicillin G       | 600,000 U for children ≤27 kg (60 lbs)  
                                          1,200,000 U for those <27 kg (60 lbs) every 4 weeks* | IM   |
| Penicillin V                  | 250 mg twice daily                         | Oral |
| Sulfadiazine                  | 0.5 g once daily for patients ≤27 kg (60 lbs)  
                                          1.0 g once daily >27 kg (60 lbs) | Oral |
| **For individuals allergic to penicillin and sulfadiazine** | Variable | Oral |

* In high-risk situations, administration every 3 weeks is justified and recommended. See discussion of high-risk situations in source text.

IM, intramuscularly

Myocardial infarction (MI) remains a leading cause of morbidity and mortality throughout the world. Approximately 12 million deaths are attributed to acute MI each year. In the United States alone, 1.3 million cases of MI are reported yearly, making the annual incidence 600 per 100,000 people.¹

Tremendous advances have been made in the diagnosis and treatment of MI over the past 50 years that include the use of beta-adrenergic blockers, thrombolytics, and percutaneous coronary artery interventions. Traditionally, treatment for MI has focused on preserving healthy myocardial cells and those not affected by ischemia. More recently, however, there has been considerable research interest regarding the possibility of replacing damaged and fibrotic myocardium with healthy tissue. More specifically, studies have focused on regenerating myocardial cells by injecting stem cells into the coronary arteries or by direct myocardial injection. Since growth factors play an important role in signaling these stem cells and homing them into the myocardium, the use of cytokines for treating MI has also been explored. This review will focus on several of these cytokines and their potential role in stem cell–mediated therapy for regenerating the diseased myocardium.

Cardiac Remodeling After Infarction

The infarcted myocardium is the target environment for stem cells and growth factors following MI. An understanding of the physiological process of wound healing in the heart is important in understanding stem cell–based therapy and will therefore be discussed here. The remodeling process after MI involves the following: cardiomyocyte death from coagulation necrosis and to a lesser extent apoptosis; inflammation characterized by the accumulation of mast cells, macrophages, and neutrophils, and the subsequent degradation of the extracellular matrix (ECM); formation of granulation tissue; and finally, formation of a scar.² All of these phases of remodeling are tightly regulated by cytokines and growth factors and will be discussed in detail throughout this review.

Moreover, MI stimulates neoangiogenesis, which is important in the maintenance and survival of cardiomyocytes.³ Neoangiogenesis is believed to result from either sprouting or endothelial migration from adjacent vessels⁴ or differentiation of bone marrow stem cells into endothelial cells.⁵ Both mechanisms are greatly influenced by cytokines and growth factors.

Infarction also stimulates mobilization of both mono-nuclear cells expressing cardiac markers and c-met+ stem cells from the bone marrow.⁶,⁷ Several cytokines, especially stromal cell–derived factor-1, have an integral role in this mobilization.⁸,⁹ Thus, it is evident that cardiac remodeling is a complex process that is tightly controlled and influenced by cytokines.

Stem Cell–Mediated Repair and Cardiac Stem Cells

The differentiative and regenerative capabilities of adult stem cells have long been thought to be confined to the tissues in which they reside. Until recently, it was thought that only embryonic stem cells are pluripotent and have the potential to regenerate into a wide range of cell types.¹⁰ These concepts have recently been challenged, and it has been shown that adult stem cells possess plasticity.¹¹,¹² The major reservoir of adult stem cells is the bone marrow, and upon proper stimulation, stem cells are released into the peripheral circulation. Mobilization of bone marrow–derived stem cells involves a complex interaction between stromal cells, ECM, and cytokines.²
Furthermore, the heart has traditionally been thought of as a terminally differentiated organ with no potential for regeneration. This also has been recently invalidated by several studies that have shown the regenerative capacity of myocardial cells. For instance, Beltrami et al reported the presence of proliferating cardiomyocytes in patients who died 4 to 12 days after MI. The same group also demonstrated the presence of Lin-c-kit+ stem cells in the adult rat myocardium. The activation of these cardiac stem cells is influenced by cytokines and may play an important role in cardiac repair post-MI.

Recently, a coronary vascular progenitor cell was identified in the human heart, and angiogenic factors may also play a role in cardiac repair.

The newly discovered plasticity of adult stem cells has caused many investigators to examine the use of stem cell–mediated therapy in post-MI patients. Stem cell–mediated therapy can be employed in 3 different ways: stem cell transplantation, stem cell mobilization, and regulation by growth factors and cytokines. Numerous experimental and clinical reports have been published discussing stem cell transplantation and stem cell mobilization, and therefore, these treatment modalities will not be discussed further. The use of cytokines in stem cell–based therapy will be the focus of this review.

After an ischemic insult, cytokines are released into the peripheral circulation and signal for the mobilization of stem cells. Three components of cardiac repair are important for cytokine-induced cardiac regeneration: the infarcted myocardium, the peripheral circulation, and the bone marrow. The complex interactions among these components are illustrated in Figure 36-1. Several cytokines are involved in stem cell mobilization and cardiac repair. The following cytokines will be discussed in detail: granulocyte colony-stimulating factor (G-CSF), erythropoietin, darbepoetin, and stem-cell factor.

Granulocyte Colony Stimulating Factor

G-CSF is a hematopoietic factor that is involved in the proliferation, maturation, and survival of granulocytes and in the mobilization of granulocytes, stem cells, and progenitor cells from the bone marrow. G-CSF has been traditionally used in oncologic patients to increase the number of circulating neutrophils for prevention of infection and to increase the number of hematopoietic stem cells for bone marrow transplantation. More recently, however, G-CSF has been shown to have a beneficial effect on cardiomyocytes after MI.

G-CSF acts through its receptor, G-CSFR, which is encoded by CSF3R. Under steady-state conditions, the receptor is primarily located in the Golgi apparatus, late endosomes, and lysosomes. There is little expression of G-CSFR on the plasma membrane due to spontaneous internalization caused by G-CSF attachment. The binding of G-CSF to its receptor activates signal transduction via the Jak-STAT pathway. G-CSFR had previously been reported to be located only on mature neutrophils, monocytes, platelets, myeloid leukemia cell lines, leukemia cell lines, and some lymphoid cell lines. Recently, however, reports have established that G-CSFR is located on cardiomyocytes as well. For instance, Harada et al detected expression of the CSF3R gene in the adult mouse heart and cultured neonatal cardiomyocytes using RT-PCR.

In addition to cardiomyocytes, G-CSFR expression was found on cardiac fibroblasts by immunocytochemistry. The group also confirmed that the GSF-R was located in the cytoplasm of cardiomyocytes under steady-state conditions. Similar to myeloid cell lines, G-CSF attachment to its receptor on cardiac cells activated the Jak-STAT pathway, particularly Jak2 and STAT3, and to a lesser extent Jak1. The attachment of GSF to its receptor and the subsequent activation of the Jak-STAT pathway play an integral role in effect of G-CSF and will be discussed in detail later.

The beneficial effect of G-CSF is mainly due to the recruitment of bone marrow–derived stem cells. Other mechanisms, however, also play a role and include the following: recruitment of inflammatory cells and reduction of granulation tissue; prevention of apoptosis; and induction of angiogenesis and collateral vessel growth. Numerous animal studies have provided detail on these mechanisms and will be discussed further.
Animal Studies

Perhaps the most important action of G-CSF is the recruitment of bone marrow–derived stem cells.30 Stem cells recruited by G-CSF possess a certain degree of plasticity, evident by the presence of CD34 on their cell surface.31 Orlic et al was one of the first groups to demonstrate the ability of G-CSF to increase the amount of stem cells in the bone marrow as well as in the peripheral circulation.32-36 In their study, mice were given 200 ug/kg/day of recombinant rat SCF and 50 ug/kg/day of recombinant human G-CSF followed by ligation of a coronary artery. The results of the study showed a 250-fold increase in the amount of Lin− c-kitPOS cells in the peripheral circulation of the treated group.36 In a previous study conducted by Orlic et al, it was shown that Lin− c-kitPOS cells have the ability to differentiate into myocardial cells.34 Furthermore, at 27 days after coronary occlusion, mobilized stem cells in the treated group occupied 76% of the infarct size, proving that stem cells were homed into the myocardium. BrdUrd, which was injected to measure the extent of cell proliferation, and Ki67, a marker for actively cycling cells, were both increased in regenerated cardiomyocytes. This all led to higher survival rates in the cytokine-treated group.

Although Orlic et al used a combination of SCF and G-CSF in their experiments, numerous studies have shown the beneficial effects of using G-CSF alone.37-39 In a study conducted by Yuichiro et al, the hearts of mice that underwent coronary occlusion showed increased amount of side population (SP) cells after G-CSF treatment.38 In a previous study conducted by the same group, SP cells were shown to be Sca-1+/CD45 and derived from the bone marrow.38 Furthermore, Fukuhara et al demonstrated the recruiting capability of G-CSF in a study in which 18 mice were treated with either recombinant human G-CSF or saline following left anterior descending coronary artery ligation.39 The results of the study confirmed previous reports and showed increased bone marrow–derived stem cells in the treated group. Similar to the studies mentioned above, the stem cells in the treated group were significantly more positive for Ki-67. Finally, Minatoguchi et al demonstrated that G-CSF significantly increases bone-marrow derived stem cells in the peripheral circulation.17

Despite these promising animal studies, however, there are reports that G-CSF does not significantly recruit bone marrow–derived stem cells.40-41 One such study was conducted by Dawn et al in which mice underwent a 30-minute coronary occlusion followed by reperfusion and treatment with either G-CSF alone, G-CSF + Flt-3 ligand, or G-CSF + stem cell factor.41 The results of the study showed that G-CSF resulted in only minimal changes in peripheral blood levels of lin−/Sca-1−/c-kit+ cells and induced little cardiomyocyte regeneration. Reports have also claimed that stem cell–induced cardiac repair is merely due to fusion of bone marrow stem cells with cardiomyocytes rather than myocardial regeneration.42

Thus, there is much controversy surrounding G-CSF and stem cell mobilization, and more research needs to be conducted to understand its complexities. Given the discrepancies among these reports, many investigators have suggested that mechanisms other than stem cell recruitment are responsible for the beneficial effects of G-CSF.

Another effect G-CSF has on infarcted myocardium is the reduction of granulation tissue. As described above, granulation and scar tissue play an important role in the adverse ventricular remodeling seen post-MI. It is believed that G-CSF reduces the amount of scar tissue formed by increasing the number of neutrophils recruited to the heart and by increasing the expression of ventricular matrix metalloproteinases (MMPs). Neutrophils appear to decrease the amount of scar tissue via phagocytosis, while MMPs work via proteolysis of excessive collagen.37,43 Minatoguchi et al, in addition to studying G-CSF and stem cell recruitment, investigated the effects of G-CSF on granulation tissue by exposing rabbits to 30 minutes of coronary occlusion followed either by G-CSF treatment or saline infusion.37 The results of the study showed decreased amount of scar tissue in the G-CSF-treated group compared to the control group, as well as increased amounts of neutrophils and macrophages in the treated group 2 days after MI. Interestingly, the number of macrophages and neutrophils were decreased in the G-CSF group in the subacute and chronic phases of the study, suggesting that G-CSF accelerates the healing process of MI as well.

In the same study, Minatoguchi et al found that MMP 9, a gelatinase, and MMP 1, a collagenase, were overexpressed in the G-CSF groups, suggesting that proteolysis of excessive collagen was important in restoring cardiac function.37 This is supported by other studies in which inhibitors of MMP caused cardiac failure,44 targeted deletion of MMP 9 attenuated collagen accumulation and LV remodeling,45 and an increase in MMP-1 by hepatocyte growth factor improved cardiac function post-MI.46

It is important to note, however, that previous reports have shown negative effects of MMP and collagen degradation.47 For instance, Spinali et al showed that overexpression of left ventricular MMPs is an early contributor to left ventricular dilatation and remodeling in congestive heart failure.48 MMPs have also been shown to play a central role in the development of atherosclerosis and restenosis. In fact, studies have shown that MMP inhibitors inhibit the progression of these diseases and may be used as a potential therapy for heart failure.49 Thus, the effect of MMPs on the heart is complex and may involve a balance between these proteinases and their inhibitors. More studies are warranted to understand the complex mechanism of these events.
interaction between MMPs and the myocardium.

Moreover, G-CSF also promotes cardiac repair by preventing apoptosis in cardiac cells. Reactive oxygen species are formed immediately after ischemia and induce apoptosis,56,57 which contributes to adverse cardiac remodeling. In a study conducted by Harada et al, mouse cardiomyocytes were exposed to 0.1 mM of H2O2 in the absence or presence of G-CSF and stained with annexin V to monitor apoptosis.23 The G-CSF group had a significantly lower number of annexin V positive cells, confirming the antiapoptotic properties of G-CSF. Furthermore, pretreatment with G-CSF inhibited the oxidative-induced reduction of the antiapoptotic proteins Bcl-2 and Bcl-xL. It is important to note that the antiapoptotic effects of G-CSF were eliminated when G-CSF was administered to cultured cardiomyocytes with adenovirus encoding dominant-negative STAT3, suggesting the importance of the Jak-STAT pathway in preventing apoptosis.

There have been reports that G-CSF promotes cardiac healing by inducing vasculogenesis.52,53 In fact, Harada et al, in addition to showing the antiapoptotic activities of G-CSF, demonstrated the protective effects of G-CSF on the cardiac vasculature.23 In their study, they showed that G-CSF inhibits apoptosis of endothelial cells and that the Jak-STAT pathway is crucial for the prevention of apoptosis. They also noted that G-CSF treatment significantly increased the number of endothelial cells in the border zone of infarcted hearts.23 Thus, it is evident that G-CSF-induced vasculogenesis plays an important role in cardiac healing post-MI.

In addition to the mechanisms described above, there are several other possible reasons why G-CSF may promote cardiac repair, including activating the Akt and extracellular signal-regulated kinase pathways,54 inhibiting autophagic cardiomyocyte death,55 and acting directly on the heart. It is likely, therefore, that G-CSF works in a variety of ways to promote cardiac repair after ischemic injury.56 A summary of G-CSF’s beneficial effects in reducing cardiac remodeling is shown in Figure 36-2.22 Given the beneficial effects of G-CSF seen in the animal models described above, investigators began testing G-CSF in clinical trials.

**Clinical Trials**

The major clinical trials conducted using G-CSF in the treatment of cardiac disease are discussed below.

One of the first clinical trials evaluating the efficacy of G-CSF in patients with MI was the randomized open label Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intra-Coronary Stem Cell Infusion (MAGIC) trial conducted by Kang et al.57 Twenty-seven patients with MI who underwent coronary stenting were selected for the study and randomized into 3 groups: those receiving intracoronary peripheral blood–stem cell infusion (n = 10); those receiving 10ug/kg/day of GSF alone (n = 10); and those in the control group. Changes in left ventricular function and perfusion were assessed at 6 months. Exercise capacity (measured by mean treadmill exercise time), myocardial perfusion (measured by perfusion defects), and systolic function (measured by left ventricular ejection fraction) all improved in the stem cell infusion group, suggesting the benefits of stem cell–based therapy. However, there was a high rate of in-stent restenosis in the G-CSF group, and consequently, enrollment for the study was discontinued and the study stopped. Some experimental studies suggest that G-CSF could worsen atherosclerosis and the risk of coronary occlusion.58-60

Similar complications were found in a study conducted by Steinwender et al.61 In their nonrandomized open-label study, 20 patients with acute MI and successful primary stenting were treated with 10ug/kg/day of G-CSF on the second postinterventional day for four days. At least 4 days after G-CSF therapy, apheresis and intra-coronary transplantation of peripheral blood stem cells infusion was performed. The ejection fraction improved after stem cell therapy (similar to the MAGIC trial), but again, there was significant in-stent restenosis.60 Complications other than in-stent restenosis have been observed in patients on G-CSF treatment as well. In an observational study conducted by Suarez de Lezo et al.,62 13 patients with anterior wall MI who were revascularized with stents were treated with 10 ug/kg/day
of G-CSF for 10 days. Although mean ejection fraction increased in the patients (mean delta EF = 6.2%), one participant had spontaneous splenic rupture. The investigators of the study hypothesized that massive cell mobilization could have contributed to this complication. Given the results of these trials, doubts have been raised about the safety of G-CSF.

Nevertheless, several other trials have been conducted using G-CSF in post-MI patients. In a nonrandomized, open-label study conducted by Kuethe et al., 14 patients with acute MI received 10ug/kg/d of G-CSF for a mean duration of 7 days following recanalization. Nine patients who initially refused G-CSF treatment were used as the control group. The results of this study were promising. There was a significant improvement in regional wall motion and perfusion in the treatment group, as well as an increased ejection fraction in the treatment group compared to control. Furthermore, there was in-stent restenosis in only one participant, supporting the claim that G-CSF treatment is safe. The investigators of the study attributed the beneficial effect of G-CSF to possible myocardial regeneration and neovascularization. Very similar results were found in a randomized, single-blind, placebo-controlled trial conducted by Valdimir et al. Patients treated with 5 ug/kg/day of G-CSF for 4 days had an increase in ejection fraction at follow-up compared to the control group.

Encouraging results were also found in the larger Front-Integrated Revascularization and Stem Cell Libera
tion in Evolving Acute Myocardial Infarction by Granulocyte Colony-Stimulating Factor (FIRSTLINE-AMI) trial. Fifty patients with ST elevation MI undergoing percutaneous coronary intervention (PCI) with stent and abciximab treatment were selected for the study 85 ± 30 minutes after PCI. Fifteen randomized patients receiving standard care were given 10ug/kg of G-CSF subcutaneously for 6 days, and 15 received standard care alone. All patients were followed for a year. The results of the study showed mobilization of CD34+ cells by G-CSF, as well as an enhancement of resting wall thickening in the infarct zone of the treated group at 4 months and at 12 months. Left ventricular ejection fraction also improved in the G-CSF treated group, and there was no observed remodeling of the left ventricular diastolic diameter. Importantly, there was no evidence of leukocytoclastic effects, accelerated restenosis, or any other adverse effects in the G-CSF treated group.

The promising results of the phase 1 trial described above, however, were not validated by three randomized double-blind placebo-controlled trials. The Double-Blind, Randomized, Placebo-Controlled Stem Cells in Myocardial Infarction (STEMMI) Trial was the first reported double-blind placebo-controlled trial testing G-CSF. In this study, 78 patients with ST elevation MI and PCI were enrolled less than 12 hours after the onset of symptoms. The patients were randomized into two groups: G-CSF group (n = 38 receiving 10 ug/kg/d) and the placebo (n = 35). The primary endpoint of the trial was a change in systolic wall thickening assessed by cardiac magnetic resonance imaging (MRI) from baseline to 6 months. Secondary endpoints included changes in left ventricular ejection fraction, end-systolic and end-diastolic volumes, and infarct size by MRI and echocardiography. The results of the trial showed no difference between the placebo and G-CSF in systolic wall thickening, infarct size, or left ventricular ejection fraction. G-CSF, however, did not increase the rate of in-stent restenosis compared to the placebo.

Similar results were found in the G-CSF-STEMI (Granulocyte Colony-Stimulating Factor ST-Segment Elevation Myocardial Infarction) Trial conducted by Engelmann et al. In this randomized, double-blind, placebo-controlled trial, 44 patients with late revascularized subacute ST-elevation myocardial infarction were treated with either 10ug/kg/d of G-CSF for 5 days or the placebo. Primary endpoints of the study were change of global and regional myocardial function from baseline to 3 months assessed by cardiac MRI. Secondary endpoints included characterization of mobilized stem cell populations, assessment of safety parameters, and myocardial perfusion assessed by MRI. Again, the results of the study showed no improvement in global myocardial function with G-CSF compared to the placebo. Similar to the STEMMI trial, in-stent restenosis was not observed at a higher rate in the G-CSF group.

The largest randomized double-blind placebo-controlled trial testing the efficacy of G-CSF therapy is the Regenerate Vital Myocardium by Vigorous Activation of Bone Marrow Stem Cells (REVIVAL-2) clinical trial, conducted by Zohlnhofer et al. In this study, 112 patients with ST-elevation MI and PCI were randomized into two groups: G-CSF group (n = 56: 10 ug/kg/day for 5 days) and the placebo group (n = 56). The primary endpoint of the study was reduction of left ventricular infarct size using Tc 99 sestamibi scintigraphy. The secondary endpoints were improvement of left ventricular ejection fraction assessed by cardiac MRI and incidence of angiographic restenosis. Similar to the STEMMI trial, G-CSF induced mobilization of CD34+ cells, but there was no improvement on infarct size and left ventricular ejection fraction in the G-CSF group compared to control. Restenosis was not observed at a higher rate in the G-CSF group as well.

In contrast to the three studies described above, data from a recent randomized trial did reveal a benefit on left ventricular function and remodeling using G-CSF in participants undergoing PCI with large MIs and decreased ejection fractions.
The clinical trials using G-CSF were promising at first, but the results of some of the double-blind placebo-controlled trials raised doubts about the efficacy and safety of G-CSF. Although ejection fractions in the STEMMI trial were increased in the G-CSF group at a similar rate to those seen in the FIRSTLINE-AMI trial, these changes were comparable to those seen with the placebo. It is plausible then that the results of the earlier phase 1 clinical trials were merely due to a placebo effect. Furthermore, in the studies conducted by Kuethe et al and Valgimigli et al, improvements in ejection fraction were nonsignificant, raising further questions about the effectiveness of G-CSF therapy.

G-CSF therapy, however, did increase CD34+ stem cell mobilization in most of the clinical trials described above. The fact that stem cell mobilization occurred with no significant change in cardiac function might be related to homing factors. It is plausible that in the double-blind placebo-controlled trials, G-CSF induced mobilization of CD34+ cells from the bone marrow, but these stem cells were not targeted to the heart.

As mentioned earlier, stromal cell–derived factor-1 is an important homing signal in the mobilization of bone marrow stem cells, especially into the injured myocardium. In a study conducted by Wang et al, endogenous plasma stromal cell–derived factor-1 was shown to increase from day 3 to day 28 after MI. Other cytokines, such as VEGF-A and FGF-2, were also shown to have maximal concentrations weeks after infarction. Therefore, the timing of G-CSF administration in the large double-blind trials may have been incorrect. It might have been more efficacious to administer G-CSF weeks, as opposed to days, after infarction where homing factors are at a maximal concentration.

Moreover, many animal studies demonstrated the benefits of administering G-CSF before coronary occlusion. Although it is difficult to apply this to humans, it raises the possibility of using G-CSF as a chronic therapy in patients with coronary disease who are at high risk of developing MI. Administering G-CSF in patients with coronary disease may allow for the accumulation of homing factors, which would be beneficial if an MI takes place in the future. Chronic use of G-CSF, however, has not been tested, and daily subcutaneous injections may not be well tolerated.

Another reason why large clinical trials failed to show improvement with G-CSF may be related to age. It has been shown that aging impairs the beneficial effect of G-CSF in rats. Therefore, G-CSF may not be useful in older patients and may only work in young patients with cardiac disease. Given the low incidence of patients younger than 50 years with MI, trials testing this hypothesis have been difficult to conduct. Nevertheless, the age of the patient is something that may be considered when administering G-CSF.

Finally, the results of the MAGIC trial and the study conducted by Steinwender et al have raised concerns about the safety of G-CSF. No complications were found in the larger placebo-controlled, double-blind studies, suggesting that G-CSF is safe to use. In July 2006, results were reported for the MAGIC-3 Drug-Eluting Stents (MAGIC-3 DES) trial. In the cell infusion groups, peripheral blood stem cells were mobilized by G-CSF for 3 days and delivered to the infarcted myocardium via intracoronary infusion. There was no evidence of restenosis after G-CSF therapy and cell infusion, which had been a concern based on the results of the original MAGIC trial which did not use DES. Nevertheless, in the future, patients started on G-CSF should be monitored carefully for in-stent restenosis and other possible complications.

In summary, G-CSF is a potent hematopoietic factor that has recently been shown in animal studies to induce stem cell mobilization and cardiac regeneration. G-CSF also has the ability to induce vasculogenesis, prevent apoptosis, and decrease scar formation. Clinical trials, promising at first, have generally failed to show the benefits of administering G-CSF in post-MI patients. This may be due to the timing of the administration or the age of the patients studied. Nevertheless, G-CSF therapy continues to be an exciting area of research and more studies need to be conducted in the future to see whether G-CSF can be a helpful adjunctive therapy in patients undergoing treatment for MI.

**Erythropoietin and Darbepoetin**

Erythropoietin (EPO) is a hypoxia-induced hormone that stimulates hematopoiesis in the bone marrow. EPO is predominantly located in the kidneys, however, expression of erythropoietin mRNA has recently been found in other cell types such as activated macrophages. EPO has been traditionally viewed as a hematopoietic hormone that inhibits the apoptosis of erythroid precursor cells and promotes the proliferation and maturation of erythroid progenitor cells. Therefore, EPO has long been used to treat anemia in patients with chronic kidney disease. Moreover, the receptor for EPO was thought to be confined to hematopoietic progenitor cells; however, new studies have shown the presence of the EPO receptor on various cell types including neurons, endothelial cells, and trophoblasts. The EPO receptor has also been found in the heart, mainly on endothelial cells, smooth muscle cells, and cardiomyocytes in the epicardium and pericardium. The discovery of EPO receptors in the cardiac system has prompted many investigators to study the effectiveness of EPO treatment in cardiac disease. Several animal studies have been published and have provided detail on the mechanisms underlying the effect of EPO.
in the heart. These reports, along with the major clinical studies on EPO, will be reviewed here.

**Animal Studies**

Many animal reports have been recently published describing the beneficial effects of EPO on the heart. The following mechanisms have been proposed: prevention of apoptosis, stimulation of neangiogenesis, and increasing nitric oxide synthase (eNOS) activity. EPO has also been shown to enhance the therapeutic potency of autologous bone marrow–derived stromal cells.

Apoptosis is a major contributor to adverse cardiac remodeling as stated above. In vitro and in vivo studies have confirmed the antiapoptotic activities of EPO. In an in vitro study conducted by Ye et al on neonatal rats, recombinant human EPO (rhEPO) significantly downregulated apoptosis of cardiomyocytes that underwent hypoxia. An in vivo experiment conducted by the same group confirmed these results. Thirty-two rats were randomized into three groups: sham operation group, acute MI group, and treated group (MI + EPO). The treated group was given 5000 units/kg of EPO for 6 days following coronary artery ligation. Hemodynamic measurements were taken at day 14 followed by execution and staining for Bcl-2 and Bax. rhEPO downregulated the proapoptotic protein Bax and upregulated the antiapoptotic protein Bcl-2, leading to improved hemodynamic function in the hearts of the treated rats. Numerous other studies have also demonstrated the antiapoptotic properties of EPO.

EPO also offers cardioprotection by inducing angiogenesis. Angiogenesis is a direct result of EPO-induced mobilization of endothelial progenitor cells into the heart. Endothelial progenitor cells have been shown to enhance neovascularization in the setting of myocardial ischemia. In a study conducted by Hirata et al, dogs exposed to EPO after coronary ligation showed mobilization of CD34+ mononuclear cells and increased capillary density and myocardial blood flow in the ischemic region. Nishiya et al also demonstrated the neovascularization induced by EPO in a study conducted in Wistar rats. The importance of angiogenesis in cardiac repair was illustrated in a study in which the reduction of MI size by EPO was found only at doses that stimulated endothelial progenitor cell mobilization and vasculogenesis.

Moreover, many studies have reported the beneficial effect of administering EPO along with bone marrow–derived stromal cells. In a study conducted by Zhang et al, rats exposed to EPO and bone marrow mesenchymal stem cells showed smaller left ventricular diastolic dimensions and a higher left ventricular fractional shortening compared to saline infusion and stem cell transplantation alone. The same group found that EPO enhances the effectiveness of bone marrow–derived stromal cells via the PI3-K/Akt pathways. Thus, the beneficial effects of EPO may be enhanced by simultaneous injection of stem cells. Other mechanisms explaining the beneficial effects of EPO have been proposed as well, including cardiomyocyte proliferation and enhanced phosphorylation of glycogen synthase kinase-3 beta.

Moreover, many studies have looked at the therapeutic window and optimal dose of EPO administration. Moon et al, in a study conducted in rats, showed that EPO administration decreased apoptosis and reduced the size of infarction when given immediately following MI and when delayed for 4, 8, or 12 hours. EPO therapy, however, was not effective after a 24-hour delay, suggesting that EPO administration should be started within a day after infarction. The same group also demonstrated that 150 IU/kg of EPO decreased cell death, final MI size, and myocardial remodeling when given during the first 4 hours after the ischemic event. Higher doses were required to extend the therapeutic window up to 12 hours. They also found that multiple doses of EPO were just as effective as a single bolus. Although doses will be different in clinical trials, these studies can be helpful as an approximate guideline to EPO treatment in humans.

**Clinical Trials**

Large clinical trials have yet to be published testing the efficacy of EPO in acute MI. However, a large, double-blind, placebo-controlled trial is currently under way. Nevertheless, there has been a pilot study conducted on erythropoetin, which has provided insight onto the effects of EPO in humans. The single-center, investigator-initiated, prospective study conducted by Lipsic et al evaluated the safety and tolerability of EPO treatment in nonanemic patients with acute MI. Twenty-two patients with acute MI were randomized to one bolus of 300 ug of darbepoetin alfa or to no additional medication before percutaneous coronary intervention. The results of the study showed a larger increase in endothelial progenitor cells (CD34+/CD45-) in the treatment group compared to control (2.8 versus 1.0 cells). Only small and nonsignificant changes in hematocrit levels were seen in the darbepoetin group.

Importantly, no adverse events were observed during the 30-day follow up. Left ventricular ejection fraction, however, was similar between the two groups after 4 months (52 ± 3% in darbepoetin versus 48 ± 5% in control). The results of the study showed that intravenous single high-dose darbepoetin alfa in acute MI is both safe and well tolerated. Improved cardiac function, however, was not observed with EPO therapy, and larger clinical trials are required to determine the efficacy of EPO and darbepoetin in cardiac patients.

The safety of using both darbepoetin and EPO has been raised. In patients with type 2 diabetes mellitus and chronic kidney disease, darbepoetin therapy was...
associated with an increased risk of stroke. In a study using EPO in patients with chronic renal disease who had their hemoglobin level targeted to 13.5 mg/dL, the drug was associated with an increased cardiovascular mortality rate compared to that of patients targeted to a lower hemoglobin level.

In summary, EPO is a hematopoietic hormone that has recently been found to have a beneficial effect on the heart after ischemic events. EPO has antiapoptotic properties and has been shown both in vitro and in vivo to stimulate neoangiogenesis. EPO is also a potent factor in stem cell–mediated repair. Animal studies have been promising thus far showing the positive effects of EPO treatment in infarcted myocardium. The first pilot study on EPO showed that it is safe and well tolerated but did not show any beneficial effects of EPO on cardiac function. Future large, double-blind, placebo-controlled trials are warranted to test the efficacy of administering EPO as an adjunctive therapy in post-MI patients, taking into consideration potential risks in patients with a history of neoplasia and a possible increased risk of stroke.

**Stem Cell Factor**

Stem cell factor, also known as c-kit ligand, is a hematopoietic factor that is involved in the proliferation, differentiation, and survival of bone marrow–derived stem cells. C-kit, the receptor for stem cell factor, is mainly expressed on the surface of stem and progenitor cells; however, recent studies have also demonstrated its location in the adult human heart. Expression of stem cell factor mRNA has been found in the normal heart. However, there is downregulation of stem cell factor mRNA following infarction, suggesting a specific role of stem cell factor in ischemic heart disease. Given the localization of stem cell factor and its receptor in the cardiovascular system, stem cell factor has been studied in animal models as a possible treatment modality for ischemic heart disease.

**Animal Studies**

Stem cell factor works in a variety of ways to offer cardioprotection in the setting of ischemia, including mobilization of bone marrow stem cells, stimulation of neoangiogenesis, proliferation of cardiomyocytes, reduction in apoptosis, and recruitment of mast cells. One of the first animal reports looking into the cardiac effects of stem cell factor was the study conducted by Orlic et al that was described previously. In their study a combination of stem cell factor and G-CSF caused mobilization of bone marrow stem cells into the peripheral circulation as well as proliferation of cardiomyocytes. The results of their study, however, may be difficult to reproduce clinically since the cytokines were delivered before the MI. In a study conducted by Lin et al, however, cytokine delivery after infarction resulted in attenuation of ventricular remodeling and improved outcomes after MI. Similar results were seen in a study conducted by Kanellakis et al, where MI was induced in mice followed by administration of both stem cell factor and G-CSF for 5 days. The results of the study showed improved cardiac function after delivery of the cytokine combination. The investigators attributed these improvements to an increase in the number of blood vessels and cardiomyocytes. Interestingly, the cardiomyocytes were of myocardial rather than of bone marrow origin, suggesting that resident cardiac stem cells exist and are stimulated by cytokines.

These studies are promising; however, a combination of cytokines were used making it difficult to elucidate the importance of stem cell factor alone. Ayach et al clarified the important contribution of stem cell factor in cardiac repair in a study conducted in c-kit deficient mice. Moreover, Ayach et al showed that mobilization of natural killer cells was important in c-kit mediated cardiac repair. Mesenchymal stem cell implantation after experimental MI in mice was shown to facilitate functional cardiac regeneration, an effect enhanced by concomitant administration of stem cell factor.

Although the animal studies discussed above show the beneficial effects of stem cell factor, more studies are warranted using stem cell factor alone in the setting of ischemic heart disease. A recent study in mice showed that cardiomyocyte-specific overexpression of stem cell factor improved myocardial function and survival after an MI.

**Clinical Trials**

Large clinical trials looking into the efficacy of SCF have yet to be published.

In summary, stem cell factor is a potent cytokine that induces mobilization of bone marrow–derived stem cells, angiogenesis, and recruitment of inflammatory cells. Animal studies have been promising, showing the beneficial effects of stem cell factor; however, most studies have looked at using stem cell factor in combination with other cytokines. More animal studies need to be performed administering stem cell factor alone. Given the positive results of animal studies described above, it is likely that stem cell factor will be a useful adjunct to stem cell–mediated therapy in future clinical trials.

**Conclusion**

The use of cytokines in stem cell–mediated therapy has become a new and exciting area of cardiovascular pharmacotherapeutics.
research. The results of animal studies have been promising, suggesting the beneficial effects of using different cytokines in MI. Clinical studies, however, have been inadequate in showing the efficacy of cytokines used alone in post-MI patients. This may be due to the incorrect timing of cytokine administration, incorrect doses, or an insufficient homing effect of cytokines. In addition, a cocktail of cytokines may prove to be more beneficial than any one cytokine alone.

In the future, large, double-blind, placebo-controlled trials need to be conducted that look more specifically at the correct timing and dosing of cytokine therapy. Despite the less-than-ideal results of major clinical trials reported to date, cytokine therapy continues to be studied as a possible treatment for MI. However, its safety also needs to be established. Given the vast amount of information that is constantly being learned about cytokines, the future of cytokine-based therapy with and without stem cell therapy still looks promising.

Note: References for this chapter can be found here: www.cvpt3.com
Cardiovascular disease and cerebrovascular disease remain major causes of cardiovascular mortality and morbidity in the United States. Intensive efforts over the past 45 years to develop important pharmacologic treatments have reduced cardiovascular risk dramatically.1,2

In recent years, since the publication of the second edition of this book, new classes of drugs have been introduced, including endothelin inhibitors and phosphodiesterase inhibitors for pulmonary hypertension (Chapter 25, Prostacyclins, Endothelin Inhibitors, and Phosphodiesterase-5 Inhibitors in Pulmonary Hypertension); vasopressin antagonists for hyponatremia (Chapter 28, Vasopressin and Vasopressin Receptor Antagonists); and a direct renin inhibitor for systemic hypertension (Chapter 10, The Renin Angiotensin Axis: Direct Renin Inhibition).

A new calcium channel blocker was introduced for the treatment of hypertensive emergencies (Chapter 8, Calcium Channel Blockers), as was a new antiarrhythmic for the treatment of arrhythmias (Chapter 17, Antiarrhythmic Drugs). An entirely new class of drugs was introduced for the treatment of angina pectoris (Chapter 15, Ranolazine: A Piperazine Derivative), and drug-eluting coronary stents may replace bare metal stents for patients with coronary artery disease (Chapter 29, Drug-Eluting Stents).

There are currently over 100 pharmacologic treatments under investigation for the management of cardiovascular disease, many of them encompassing new technologies and pharmacologic classes.3 Various gene therapies and cell therapies are being evaluated for patients with coronary artery disease, peripheral arterial disease, myocardial infarction, and myocardial failure.4 Entire new classes of antiplatelet and anticoagulant drugs are being developed and evaluated for treatment patients with venoembolic diseases, unstable coronary syndromes, and as prophylactic agents in patients with atrial fibrillation (Table 37-1; Chapter 17, Antiarrhythmic Drugs).5,8

New treatments are under investigation for treating post-angioplasty restenosis and angina (Table 37-3). Entire new classes of agents are being studied in patients to prevent atherosclerosis, which include phospholipase inhibitors;5,6 p38 kinase inhibitors; liver X agonists;6 niacin receptor agonists (see Table 37-8); inhibitors of toll-like receptors;11 and stimulators of heme oxygenase.12 New drugs in development for the treatment of hyperlipidemia include apolipoprotein A mimetics13 (see Table 37-5); new CETP inhibitors;14 thyroid mimetic drugs;15 and anti-sense technology agents.16 Stem cell therapies are being evaluated in patients with myocardial infarction (see Table 37-9). Heart failure is a growing problem in the United States, and investigations utilizing new drugs include vasopressin antagonists, relaxin,18 direct renin inhibitors, adenosine agonists,19,20 cell-based treatment, and gene therapies.

For the treatment of systemic hypertension, vaccines are in development,21 as well as new classes of drugs20-24 and new combinations of already approved agents (Table 37-7, Chapter 21, New Aspects of Combination Therapy: Focus on Hypertension).

Innovative drug therapies that are being evaluated for peripheral vascular diseases (Table 37-10), pulmonary hypertension (Table 37-11), and cerebrovascular disease (Table 37-12) include stimulators of soluble guanylate cyclase25 and nitric oxide. In addition, various gene therapy treatment approaches and endothelial cell therapy26 are being studied (Tables 37-10, 37-11).

These new therapies, many of which were developed out of recent scientific advances in molecular biology, molecular pharmacology, and translational research, show great promise in continuing the remarkable progress being made against cardiovascular disease and stroke. We predict that many of the new treatments being discussed in this chapter will have become standard therapies by the time the fourth edition of this book is published.
### Table 37-1. New Antiplatelet and Anticoagulant Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action and Indication</th>
<th>US Food and Drug Administration (FDA) Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Oral factor Xa inhibitor for DVT, ACS, AF prophylaxis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AZD0837</td>
<td>Oral direct thrombin inhibitor for prevention of stroke</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Orally active Xa inhibitor for venoembolic disease and UCS</td>
<td>Phase 2</td>
</tr>
<tr>
<td>BIBT986</td>
<td>Inhibitor of thrombin and factor Xa</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Bivalirudin (Angiomax)</td>
<td>Direct thrombin inhibitor for ACS</td>
<td>Application submitted</td>
</tr>
<tr>
<td>BV1-0007</td>
<td>Reduces platelet production; thrombopoietin antagonist without affecting platelet function</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Intravenous reversible P2Y12 platelet receptor antagonist for UCS</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Oral factor X on inhibitor for ACS</td>
<td>Approved for use</td>
</tr>
<tr>
<td>DU 176b</td>
<td>Orally active factor Xa inhibitor for veno-embolic disease and UCS</td>
<td>Phase 2</td>
</tr>
<tr>
<td>DX9065a</td>
<td>Specific factor Xa inhibitor as fibrinolytic</td>
<td>Phase 1</td>
</tr>
<tr>
<td>E5555</td>
<td>Oral platelet thrombin receptor antagonist for ACS</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Eptifibatide (Integril)</td>
<td>Intravenous GP IIb/IIIa receptor, platelet inhibitor, for ACS</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Erixaban</td>
<td>Orally active factor Xa inhibitor with extended duration of action</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Factor Ila/Xa inhibitors</td>
<td>for ACS</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra)</td>
<td>Intravenous factor Xa inhibitor for ACS</td>
<td>Application submitted</td>
</tr>
<tr>
<td>Idrabiotaparinux</td>
<td>Factor Xa inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Idraparinux</td>
<td>Factor Xa inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ISIS-FXI1ax</td>
<td>Antisense drug that targets factor X1</td>
<td>Phase 1</td>
</tr>
<tr>
<td>K-134</td>
<td>Phosphodiesterase inhibitor, antiplatelet agent</td>
<td>Phase 1</td>
</tr>
<tr>
<td>LY517717</td>
<td>Oral factor Xa inhibitor for DVT</td>
<td>Phase 2</td>
</tr>
<tr>
<td>MER102</td>
<td>Oral fondaparinux to prevent DVT</td>
<td>Phase 1</td>
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<tr>
<td>MPC-0920</td>
<td>Orally available direct thrombin inhibitor</td>
<td>Phase 1</td>
</tr>
<tr>
<td>NAPc2</td>
<td>Recombinant nematode anticoagulant</td>
<td>Phase 2</td>
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<tr>
<td>Otamixaban (XRP0673)</td>
<td>Intravenous factor Xa inhibitor for UCS</td>
<td>Phase 3</td>
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<tr>
<td>PRT060128</td>
<td>Intravenous and oral platelet ADP receptor antagonist that acts directly on P2Y12 receptor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Oral factor Xa inhibitor for VT, UCS, AF prophylaxis</td>
<td>Application submitted</td>
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<tr>
<td>SCH530348 (Vorapaxar)</td>
<td>Oral platelet thrombin receptor antagonist for ACS</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Sitaxsentan (Thelin)</td>
<td>Oral endothelin antagonist for UCS</td>
<td>Studies discontinued</td>
</tr>
<tr>
<td>TAK-442</td>
<td>Oral factor Xa inhibitors for VTE disease and ACS</td>
<td>Phase 3</td>
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<tr>
<td>Terutroban (S-18886)</td>
<td>Selective antagonist of thromboxane receptors for development</td>
<td>Phase 3</td>
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<tr>
<td>Ticagrelor AZD6140</td>
<td>Orally active platelet P2Y12 inhibitors for ACS</td>
<td>Application recently rejected</td>
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<tr>
<td>Vernalis CV-10153</td>
<td>Recombinant plasminogen activator stimulator of UCS</td>
<td>Phase 2</td>
</tr>
<tr>
<td>YM-150</td>
<td>Orally active Xa inhibitor for venoembolic disease and UCS</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; UCS = unstable coronary syndrome; DVT = deep vein thrombosis; AF = atrial fibrillation; ADP = adenosine phosphatase; VT = venous thrombosis; VTE = venous thromboembolic

See also Chapter 17, Antiarrhythmic Drugs.
### Table 37-2. Other Antithrombotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD791</td>
<td>Oral and selective inverse antagonist of the 5-HT2a receptor on platelets for preventing thrombosis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ARC1779</td>
<td>Binds to vWF on platelets to prevent clots</td>
<td>Phase 2</td>
</tr>
<tr>
<td>AVE-5026</td>
<td>Ultra-low-molecular-weight heparin</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Certoparin</td>
<td>Low-molecular-weight heparin</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Diaplasinin (PAI-749)</td>
<td>Selective and reversible PAI-1 antagonist that preserves tPA activity</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Elaparin (oral heparin)</td>
<td>DVT</td>
<td>Phase 1</td>
</tr>
<tr>
<td>M118</td>
<td>Low-molecular-weight heparin</td>
<td>Phase 2</td>
</tr>
<tr>
<td>NU 172</td>
<td>Rapid acting direct thrombin inhibiting aptamer for thrombosis</td>
<td>Phase 1</td>
</tr>
<tr>
<td>PCI-27483</td>
<td>Factor VIIa inhibitor for inhibition of tumor growth and associated thrombolic disease</td>
<td>Phase 1</td>
</tr>
<tr>
<td>PSI-697/WAY-197697</td>
<td>Oral P-selectin inhibitor of thrombosis</td>
<td>Phase 1</td>
</tr>
<tr>
<td>RB006/RB007</td>
<td>Factor IXa antagonist and its oligonucleotide active control agent for arterial thrombosis</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Saratin</td>
<td>Inhibits platelet adhesion to collagen for anti-platelet effects and reducing intimal hyperplasia</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Tecafarin (ATI-5923)</td>
<td>Vitamin K epoxide reductase inhibitor to prevent thrombosis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>TTP3389</td>
<td>Orally active partial inhibitor of factor IXa for preventing VT</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

vWF = von Willebrand factor; PAI-1 = plasminogen activator inhibitor-1; tPA = tissue plasminogen activator; DVT = deep vein thrombosis; VT = venous thrombosis

See also Chapter 18, Antiplatelets and Antithrombotics.

### Table 37-3. New Drugs for Angina Pectoris

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action</th>
<th>FDA Development Status</th>
</tr>
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<tbody>
<tr>
<td>Acclaim ISMN/arginine</td>
<td>Combination nitrate and nitric oxide precursor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>FGF-1</td>
<td>Fibroblast growth factor (angiogenesis)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Select I, inhibitor for angina; bradycardic agent</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

ISMN = isosorbide mononitrate

*Tables continued on p. 622.*
Table 37-4. New Drugs for Arrhythmias

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amio-Aqueous (aqueous amiodarone)</td>
<td>Intravenous amiodarone (class III anti-arrhythmic) for atrial and ventricular arrhythmias</td>
<td>Phase 3</td>
</tr>
<tr>
<td>ATPace (ATP injection)</td>
<td>Diagnosis of bradycardia, treatment of SVT</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Avapro (irbesartan)</td>
<td>ARB for prevention of AF</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AZD 1305</td>
<td>Ion channel blocker for AF and flutter</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Budiodarone (AT-2042)</td>
<td>Class III oral antiarrhythmic for AF and flutter</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Capadenoson (BAY-68-4986)</td>
<td>A1 adenosine receptor agonist for AF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Celivarone (SSR 149744)</td>
<td>Class III antiarrhythmic for AF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>GAP-134</td>
<td>Arrhythmia</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Lipitor (atorvastatin)</td>
<td>Statin for AF</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Lovaza</td>
<td>Fish oil for AF (omega-3 ethyl ester concentrate)</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Nifekalant</td>
<td>Class III antiarrhythmic for paroxysmal AF and ventricular arrhythmias</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Sematilide</td>
<td>Oral class III antiarrhythmic for atrial and ventricular arrhythmias</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Stedicor (azimilide)</td>
<td>Class III antiarrhythmic potassium-channel blocker for atrial and ventricular arrhythmias</td>
<td>Submitted for approval</td>
</tr>
<tr>
<td>Tecadenoson</td>
<td>Intravenous A1 adenosine receptor agonist for SVT, AF and flutter</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Vernakalant (RSD1235)</td>
<td>Intravenous and oral atrial selective potassium and sodium channel blocker for AF</td>
<td>Submitted for approval</td>
</tr>
<tr>
<td>YM-758</td>
<td>If current channel inhibitor for AF</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

ATP = adenosine triphosphate; SVT = supraventricular tachycardia; ARB = angiotensin receptor blocker; AF = atrial fibrillation
See also Chapter 17, Antiarrhythmic Drugs.
Table 37-5. New Drugs for Prevention of Atherosclerosis

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>568859</td>
<td>Lp-PLA2 inhibitor; lowers LDL</td>
<td>Phase 1</td>
</tr>
<tr>
<td>681323</td>
<td>p38 kinase inhibitor; prevents atherosclerosis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>856553</td>
<td>p38 kinase inhibitor; prevents atherosclerosis</td>
<td>Phase 1</td>
</tr>
<tr>
<td>AG-1067</td>
<td>VCAM inhibitor antagonist</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Anacetrapib (MK-0859)</td>
<td>CETP-inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Apo AI Milano (ETC-216)</td>
<td>Synthetic HDL containing recombinant Apo AI (Milano)</td>
<td>Phase 1</td>
</tr>
<tr>
<td>CER-002</td>
<td>PPAR receptor delta-specific agonist</td>
<td>Phase 1</td>
</tr>
<tr>
<td>CP-800569</td>
<td>CETP inhibitor</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Darapladib</td>
<td>Lp-PLA2 inhibitor; lowers LDL</td>
<td>Phase 3</td>
</tr>
<tr>
<td>ISIS-CRP</td>
<td>Antisense drug that targets C-reactive protein</td>
<td>Phase 1</td>
</tr>
<tr>
<td>K-604</td>
<td>Acyl-coenzyme 2 transferase inhibitor</td>
<td></td>
</tr>
<tr>
<td>JTT-705</td>
<td>CETP inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Liver XR agonists</td>
<td>For modulating atherosclerosis</td>
<td>Phase 1</td>
</tr>
<tr>
<td>L-4F, D-4F</td>
<td>Apo-AI mimic</td>
<td>Phase 2</td>
</tr>
<tr>
<td>LY 518674</td>
<td>Atherosclerosis and PPAR alpha agonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>MK-0524B</td>
<td>Prostaglandin D₂ antagonist</td>
<td>Phase 3</td>
</tr>
<tr>
<td>MLN 1202</td>
<td>Chemokine receptor 2 (CCR2) antagonist, anti-inflammatory</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Nicotine receptor agonist (MM74A)</td>
<td>Reductions in VLDL and LDL</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Rifalazil</td>
<td>RN polymerase inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Rilapladib</td>
<td>Lp-PLA2 inhibitor; lowers LDL</td>
<td>Phase 1</td>
</tr>
<tr>
<td>RVX-208</td>
<td>Small molecule that increases Apo-AI and HDL</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Varespladib</td>
<td>sLp-PLA2 inhibitor; lowers LDL</td>
<td>Phase 2</td>
</tr>
<tr>
<td>VIA-2291</td>
<td>Leukotriene synthesis inhibitor; anti-inflammatory</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

Lp-PLA2 = lipoprotein associated phospholipase A2; LDL = low-density lipoprotein; VCAM = vascular cell adhesion molecule; HDL = high-density lipoprotein; CETP = cholesteryl ester transfer protein; PPAR = peroxisome proliferator activated receptor; ACAT = acylcoenzyme A transferase; VLDL = very-low-density lipoprotein

See also Chapter 20, Lipid-Lowering Drugs, and Table 37-8.

*Tables continued on p. 624.*
Table 37-6. New Drugs for Heart Failure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC2592</td>
<td>Glucagon-like peptide identical to incretin for continuous SC infusion for chronic CHF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Adentri</td>
<td>Oral A1 adenosine receptor agonist</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Alagebrium chloride (ALT-711)</td>
<td>Breaks up advanced glycosylated cross-link end-products (AGE) for vascular stiffness</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Anginera (epicardial angiogenesis patch)</td>
<td>Human fibroblast cells for direct cardiac topical use in chronic CHF to cause angiogenesis</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Autologous stem cell therapy</td>
<td>Primitive pluripotential bone marrow stem cells as injection for CHF following acute myocardial infarction</td>
<td>Phase 1</td>
</tr>
<tr>
<td>BAY 60-4552</td>
<td>Soluble guanylate cyclase stimulator for CHF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>BB3</td>
<td>Human growth factor mimetic for cardiac repair and regeneration</td>
<td>Application submitted for approval</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>Non-selective beta blocker for increasing CHF survival</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Cardeva</td>
<td>B-type natriuretic peptide</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Carperitide</td>
<td>Atrial natriuretic peptide</td>
<td>Phase 2</td>
</tr>
<tr>
<td>CD-NP</td>
<td>C-type natriuretic peptide combined with dendoaspis natriuretic peptide</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Cinaciguat (BAY 58-2667)</td>
<td>Soluble guanylate cyclase activator for acute CHF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>CK 1827452</td>
<td>Selective cardiac myosin activator for acute CHF (inotrope)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>Growth factor for anemia of HF</td>
<td>Phase 3</td>
</tr>
<tr>
<td>FX 1006A</td>
<td>Familial amyloid; cardiomyopathy</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Icodextrin solution</td>
<td>Reduction of LVH by increasing ultra-filtration in peritoneal dialysis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>INOmax (nitric oxide inhalation)</td>
<td>Nitric oxide for CHF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Istaroxime</td>
<td>SERCA2a agonist for CHF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Sinus node inhibitor for LV dysfunction (I1 channel inhibitor)</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Mydicar AAV1/SERCA2a therapy</td>
<td>Genetically targeted enzyme replacement of sarcoplasmic reticulum calcium ATPase for improving contractile function</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Myoblast cell</td>
<td>Myoblast stem cell therapy for CHF transplantation</td>
<td>Phase 1</td>
</tr>
<tr>
<td>MyoCell</td>
<td>Autologous skeletal myoblast therapy for CHF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Natrecor (nesiritide)</td>
<td>SC B-type natriuretic peptide for CHF</td>
<td>Phase 1</td>
</tr>
<tr>
<td>NeoFuse</td>
<td>Mesenchymal stem cell therapy for cardiac regeneration</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Recombinant relaxin</td>
<td>Relaxin use for acute CHF</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Renormax (spirapril)</td>
<td>ACE inhibitor for chronic HF</td>
<td>Application submitted for approval</td>
</tr>
<tr>
<td>Rolofylline</td>
<td>Selective A1 adenosine receptor antagonist for acute CHF</td>
<td>Withdrawn because of lack of benefit versus placebo</td>
</tr>
<tr>
<td>Samska (tolvaptan)</td>
<td>Oral vasopressin (V2) receptor blocker for CHF</td>
<td>Application submitted for approval</td>
</tr>
<tr>
<td>SLV320</td>
<td>A1 adenosine receptor antagonist for chronic CHF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Tekturna (aliskiren)</td>
<td>Direct renin inhibitor for chronic CHF</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Thelin (sitaxsentan)</td>
<td>Endothelin inhibitor for chronic CHF</td>
<td>Studies discontinued</td>
</tr>
<tr>
<td>Urodlatin (ularitide)</td>
<td>Renal natriuretic peptide for acute CHF</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Urocortin 2</td>
<td>Corticotropin-releasing factor (CRF)-related peptide through CRF receptor 2 stimulation in HF</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

SC = subcutaneous; CHF = chronic heart failure; LVH = left ventricular hypertrophy
See also Chapter 13, Current and New Inotropes.
## Table 37-7. New Drugs for Hypertension

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADX-415 Altace HCT Ramipril/HCTZ</td>
<td>Central acting alpha agonist for HTN&lt;br&gt;Combination of diuretic relief of HTN</td>
<td>Phase 2&lt;br&gt;Phase 3</td>
</tr>
<tr>
<td>Angeliq Estradiol/Drospirenone</td>
<td>Combination drospirenone, a progestin with antimineralocorticoid activity and 17 beta-estradiol for HTN in postmenopausal women&lt;br&gt;Soluble epoxide inhibitor for reducing blood pressure and reducing renal injury</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AR9281</td>
<td>Archetype of angiotensin II receptor blocker for HTN&lt;br&gt;Endogenous ouabain inhibitor and Inhibitor of Na+/K+ ATPase</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Azilsartan (TAK-491)</td>
<td>Angiotensin II receptor blocker for HTN&lt;br&gt;Combination of drospirenone with antimineralocorticoid activity and 17 beta-estradiol for HTN in postmenopausal women&lt;br&gt;Soluble epoxide inhibitor for reducing blood pressure and reducing renal injury</td>
<td>Previously approved&lt;br&gt;Phase 1</td>
</tr>
<tr>
<td>ClonIBID (Clonidine CR)</td>
<td>12-h sustained-release formulation of clonidine for HTN&lt;br&gt;Fixed dose combination for HTN</td>
<td>Submitted for approval&lt;br&gt;Phase 3</td>
</tr>
<tr>
<td>Coreg CR (Carvedilol/Lisinopril)</td>
<td>Endogenous ouabain inhibitor and Inhibitor of Na+/K+ ATPase&lt;br&gt;Phase 3</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Daglutril</td>
<td>Vaccine that induces anti-angiotensin II antibodies for angiotensin inhibition for long-term control of blood pressure&lt;br&gt;Orally active mixed endopeptidase/endothelin converting enzyme inhibitor for HTN and heart failure</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Darusentan</td>
<td>Selective inhibitor of endothelin type A receptor (ETA) for HTN&lt;br&gt;Digoxin immune Fab-angiotensin therapeutic vaccine for HTN and treatment of pre-eclampsia</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Coreg CR (Carvedilol/Lisinopril)</td>
<td>Endogenous ouabain inhibitor and Inhibitor of Na+/K+ ATPase&lt;br&gt;Phase 3</td>
<td>Phase 2</td>
</tr>
<tr>
<td>LC1699</td>
<td>Aldosterone synthase inhibitor for hyperaldosteronism&lt;br&gt;Dual acting blocker of angiotensin II receptor and neprilysin (neutral endopeptidase for HTN and heart failure)</td>
<td>Phase 1&lt;br&gt;Phase 3</td>
</tr>
<tr>
<td>Lercanidipine (modified release)</td>
<td>Dihydropyridine calcium blocker for HTN&lt;br&gt;Selective central imidazole receptor agonist for HTN</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Selective central imidazole receptor agonist for HTN&lt;br&gt;Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Naproxcinod</td>
<td>COX-inhibiting nitric oxide donor for blood pressure reduction&lt;br&gt;Nitric oxide-releasing derivative of enalapril for HTN and heart failure</td>
<td>Phase 2</td>
</tr>
<tr>
<td>NCX-899</td>
<td>A-type natriuretic peptide for HTN and heart failure&lt;br&gt;Combination blocker of angiotensin II and endothelin 1 for HTN</td>
<td>Phase 2</td>
</tr>
<tr>
<td>PL-3994</td>
<td>Recombinant Relaxin&lt;br&gt;Peptide hormone that softens the birth canal for HTN and heart failure</td>
<td>Phase 3</td>
</tr>
<tr>
<td>PS-433540</td>
<td>Peptide hormone that softens the birth canal for HTN and heart failure&lt;br&gt;Endogenous ouabain receptor inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>SEA04000</td>
<td>Inhibitor of Na+/Ca++ exchanger&lt;br&gt;Direct renin inhibitors for HTN</td>
<td>Phase 1&lt;br&gt;Phase 1</td>
</tr>
<tr>
<td>SPP635, 676, 1148, 1234, 2745, 600, 800, 1100</td>
<td>Inhibitor of Na+/Ca++ exchanger&lt;br&gt;Direct renin inhibitors for HTN</td>
<td>Phase 1&lt;br&gt;Phase 1</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Oral type 5 PDE inhibitor for HTN</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

HTN = hypertension; ACE = angiotensin converting enzyme inhibitor; HCTZ = hydrochlorothiazide; CR = controlled release; COX = cyclooxygenase; PDE = phosphodiesterase
Table 37-8. Drugs for Lipid Disorders

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGR-427 (implitapide)</td>
<td>Triglyceride transfer protein inhibitor for hypercholesterolemia inhibits protein that produces LDL</td>
<td>Phase 2</td>
</tr>
<tr>
<td>AEGR-733 (lomitapide)</td>
<td>Microsomal triglyceride transfer protein inhibitor for hypercholesterolemia</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Anacetrapib</td>
<td>CETP inhibitor for hypercholesterolemia</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Atorvastatin/Fenofibrate</td>
<td>Combination for hyperlipidemia</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AVE5530</td>
<td>Nonabsorbable cholesterol absorption inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>BI-204</td>
<td>Antibody to oxidized LDL</td>
<td>Phase 1</td>
</tr>
<tr>
<td>BMS-PCSK9_\text{rx}</td>
<td>Antisense drug for reducing LDL</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Certriad</td>
<td>Combination for hyperlipidemia Rosuvastatin/Fenofibrate</td>
<td>Submitted and rejected by FDA</td>
</tr>
<tr>
<td>Cordaptive</td>
<td>Extended-release niacin and laropiprant</td>
<td>Submitted and rejected by FDA</td>
</tr>
<tr>
<td>DB 959</td>
<td>Dual PPAR gamma/delta activator</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Eprotirome</td>
<td>Thyroid hormone analogue to reduce atherogenic lipoproteins (stimulates (TR) B isoform</td>
<td>Phase 3</td>
</tr>
<tr>
<td>ETC-1002</td>
<td>Nuclear receptor activator that reduces fat and cholesterol synthesis and increases fat breakdown</td>
<td>Phase 1</td>
</tr>
<tr>
<td>GSK256073</td>
<td>Niacin receptor activator</td>
<td>Phase 3</td>
</tr>
<tr>
<td>ISIS-APOCIII_\text{rx}</td>
<td>Antisense drug that targets ApoC-III to lower triglycerides</td>
<td>Phase 1</td>
</tr>
<tr>
<td>MBX-8025</td>
<td>PPAR delta action for reducing cholesterol</td>
<td>Phase 3</td>
</tr>
<tr>
<td>MD-0727</td>
<td>Cholesterol absorption inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Mipomersen (ISIS 301012)</td>
<td>Antisense oligonucleotide to apo B to lower very LDL, LDL and Lp(a) levels</td>
<td>Phase 3</td>
</tr>
<tr>
<td>MPC-028</td>
<td>Hyperlipidemia</td>
<td>Application submitted</td>
</tr>
<tr>
<td>PravaFen (Pravastatin/</td>
<td>Combination for hypercholesterolemia</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Fenofibrate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Selective estrogen for hypercholesterolemia</td>
<td>Phase 3</td>
</tr>
<tr>
<td>R1658 (dalcetrapib)</td>
<td>CETP inhibitor to increase HDL levels</td>
<td>Phase 3</td>
</tr>
<tr>
<td>slx 4090</td>
<td>Intestinal specific MTP inhibitor to reduce production of chylomicrons</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Sobetirome (QRX 431)</td>
<td>Thyroid receptor beta activator to reduce cholesterol and Lp(a) levels</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Tredaptive, Cordaptive, or</td>
<td>Extended release niacin and laropiprant, a prostaglandin D2 receptor antagonist to reduce pruritus</td>
<td>Phase 3</td>
</tr>
<tr>
<td>both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIA-662</td>
<td>Flush free niacin derivative</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Urodeoxycholic acid</td>
<td>Bile acid to reduce cholesterol</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein; CETP = cholesteryl ester transfer protein; PPAR = peroxisome proliferator activator receptor; MTP = microsomal transfer protein

See also Table 37-5 and Chapter 20, Lipid-Lowering Drugs.
Table 37-9. New Drugs for Myocardial Infarction and Myocardial Ischemia

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alferminogene</td>
<td>An angiogenic FGF4 gene therapy for myocardial ischemia</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AMR-001</td>
<td>Autologous stem cells to prevent adverse remodeling</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Caldaret</td>
<td>Intracellular Ca++ handling modulator to limit infarct size</td>
<td>Phase 2</td>
</tr>
<tr>
<td>KAI-9803</td>
<td>Inhibitor of delta protein kinase C to limit infarct size</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Multistem</td>
<td>Human stem cells for reducing MI</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Neu 2000</td>
<td>n-methyl-d-aspartate receptor antagonist to limit infarct size</td>
<td>Phase 1</td>
</tr>
<tr>
<td>NX-CP105</td>
<td>Human-derived stem cells following MI</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Prochymal</td>
<td>Mesenchymal stem cell therapy following MI</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Antiarrhythmic post infarct survival</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Tekturna (aliskiren)</td>
<td>Post-infarct remodeling</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Thymosin beta-4</td>
<td>Activator of integrin-linked kinase to promote cardiac cell migration, survival and repair</td>
<td>Phase 1V</td>
</tr>
<tr>
<td>Zoniporide</td>
<td>Na+/H+ inhibitor for myocardial ischemia</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; FGF = fibroblast growth factor
See also Chapter 36, Cytokines and Myocardial Regeneration: A Novel Therapeutic Option for Acute Myocardial Infarction.

Table 37-10. New Drugs for Peripheral Vascular Disease

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult stem cell therapy</td>
<td>Critical limb ischemia</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ANGX-1039</td>
<td>Oral L-citrulline in combination with statins</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Ataciguat (HMR1766)</td>
<td>Activator of soluble guanylate cyclase</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Defibrotide</td>
<td>Polydeoxyribonucleotide that modulates endothelial function and prevents blood clots</td>
<td>Phase 3</td>
</tr>
<tr>
<td>FGF-1</td>
<td>Angiogenesis growth factor for peripheral vascular disease</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Glycine propionyl-L-carnitine</td>
<td>Elevated blood nitric oxide and decreases free radical mediated modifications of blood lipids</td>
<td>Phase 3</td>
</tr>
<tr>
<td>HGF DNA plasmid</td>
<td>Angiogenesis growth factor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>HIF-1alpha gene</td>
<td>Engineered form of the HIF-2alpha gene for angiogenesis administered by injection</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Hypoxia Therapeutic</td>
<td>Trans-sodium crocetinate enhances the diffusion of oxygen into tissues</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Prostacyclin infusion for peripheral ischemia</td>
<td>Phase 3</td>
</tr>
<tr>
<td>INDI-702</td>
<td>Active inhibitor of PDE and thromboxane synthetase</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Liprostat (alprostadil)</td>
<td>Prostaglandin E(1) is a potent vasodilator and inhibitor of platelet aggregation</td>
<td>Phase 2</td>
</tr>
<tr>
<td>NV1FGF (XRP0038)</td>
<td>Plasmid-based angiogenic gene delivery system for local expression of FGF-1–injectable</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Remodulin (treprostinil)</td>
<td>Stable structural analog of prostacyclin</td>
<td>Phase 3</td>
</tr>
<tr>
<td>ReoPro (abciximab)</td>
<td>Glycoprotein IIb/IIIa receptor monoclonal antibody that inhibits platelet function</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Sapropterin (6R BH4)</td>
<td>Helps in formation of nitric oxide</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

Table 37-10 continued on p. 628.
Table 37-10. New Drugs for Peripheral Vascular Disease
(continued)

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarpogrelate (MCI 9042)</td>
<td>Specific oral 5HT2 antagonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>SL65, 0472</td>
<td>Mixed 5HT1B/5HT2A receptor antagonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>SPP200</td>
<td>Polyethylene glycol-hirudin/iloprost coating for preserving femoropopliteal grafts</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Vascugel (endothelial cell therapy)</td>
<td>Allogeneic endothelial cell implants to protect arteriovenous grafts</td>
<td>Phase 2</td>
</tr>
<tr>
<td>VM202 (modified hepatocyte growth factor gene therapy)</td>
<td>Plasmid human hepatocyte growth factor by injection</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

FGF = fibroblast growth factor; HGF = human growth factor; HIF = hypoxia induced factor; PDE = phosphodiesterase
See also Chapter 34, Drug Treatment of Peripheral Vascular Disease.

Table 37-11. New Drugs for Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aironite</td>
<td>Nitrite inhalation</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Aviptadil</td>
<td>Vasoactive intestinal peptide (inhalation)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Beraprost Gleevec (imatinib)</td>
<td>Oral prostacyclin analogue PDGF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>INOMAX</td>
<td>NO inhalation</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Macitentan</td>
<td>Oral dual endothelin A/B receptor antagonist</td>
<td>Phase 3</td>
</tr>
<tr>
<td>NO synthase gene therapy</td>
<td>Adenoviral-mediated transfer of the human endothelial synthase gene</td>
<td>Phase 2</td>
</tr>
<tr>
<td>PRX-08066</td>
<td>Selective serotonin (5 HT2B) receptor antagonist</td>
<td>Phase 1</td>
</tr>
<tr>
<td>PulmoLAR (2-methoxyestradiol)</td>
<td>Sustained-release injection for reducing endothelin-1 levels</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Riociguat</td>
<td>Soluble guanylate cyclase inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Inhibitor of multiple kinases</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Thelin (sitasentan)</td>
<td>Endothelin A receptor inhibitor</td>
<td>Studies discontinued</td>
</tr>
</tbody>
</table>

NO = nitric oxide; PDGF = platelet derived growth factor
See Chapter 25, Prostacyclins, Endothelin Inhibitors, and Phosphodiesterase-5 Inhibitors in Pulmonary Hypertension.
Table 37-12. New Drugs for Stroke

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>813893</td>
<td>Direct Factor Xa inhibitor for prevention of stroke in patients with AF</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa inhibitor for prevention of stroke in patients with AF</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Arudic Acid</td>
<td>Astrocyte modulating agent for stroke infusion</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Factor Xa inhibitor for prevention of stroke in patients with AF</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Clazosentan</td>
<td>Intravenous endothelin antagonist for preventing vasospasm after subarachnoid hemorrhage</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Crobenetine</td>
<td>Blocker of voltage-gated sodium channel for central nervous system disorders</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Droxidopa</td>
<td>Synthetic amino acid precursor for neurogenic hypotension</td>
<td></td>
</tr>
<tr>
<td>Desmoteplase</td>
<td>Thrombolytic agent for ischemic stroke</td>
<td>Phase 3</td>
</tr>
<tr>
<td>DU176b (Edoxaban)</td>
<td>Oral factor Xa inhibitor for prevention of stroke</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Oral factor Xa inhibitor for prevention of stroke</td>
<td>Phase 3</td>
</tr>
<tr>
<td>S-0139</td>
<td>Intravenous endothelin A antagonist for stroke</td>
<td>Phase 3</td>
</tr>
<tr>
<td>SUN N8075</td>
<td>Dual blocking action on Na⁺ and T-type Ca²⁺ channel with antioxidant properties to prevent ischemic neuronal damage</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>Thrombolytic for acute stroke</td>
<td>Phase 2</td>
</tr>
<tr>
<td>TS-011</td>
<td>Inhibitor of 20-HETE synthesis that improves focal cerebral ischemia</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Vernalis (V10153)</td>
<td>Vascular endothelial growth factor to prevent intimal hyperplasia and vascular restenosis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Zonampanel (YM872)</td>
<td>α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist for acute stroke and for reducing hematoma size</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; 20-HETE = 20-hydroxyeicosatetraenoic acid
See Chapter 33, Drug Therapy of Cerebrovascular Disease.

Table 37-13. New Therapies for Vascular Restenosis

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCX 140</td>
<td>Chemokine receptor (CCR2) antagonist for treatment of vascular restenosis</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Coroxane</td>
<td>Nanoparticle albumin bound paclitaxel for bare metal stent restenosis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>LT-1951</td>
<td>L-arginine for restenosis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>Suppressor of T and B lymphocyte proliferation post-cardiac transplantation</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>Myolimus</td>
<td>Rapamycin-like prevention of graft restenosis</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>Resten-NG</td>
<td>Antisense drug to prevent restenosis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Trinam (EG004)</td>
<td>Vascular endothelial growth factor D to prevent intimal hyperplasia and vascular restenosis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>VT-111</td>
<td>Proteinase inhibiting anti-inflammatory to prevent restenosis</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

Tables continued on p. 630.
### Table 37-14. New Drug-Eluting Stents in Investigation

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Mechanism of Action and Indication</th>
<th>FDA Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioFREEDOM</td>
<td>Polymer-free paclitaxel drug eluting stent</td>
<td>Phase 3</td>
</tr>
<tr>
<td>BVS</td>
<td>Completely biodegradable everolimus stent</td>
<td></td>
</tr>
<tr>
<td>DIOR DEB</td>
<td>Drug eluting paclitaxel balloon</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Elixir Desyne</td>
<td>Novalimus drug eluting stent</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Endeavor Resolute</td>
<td>Zotarolimus stent with new polymer technology</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Excel Stent</td>
<td>Sirolimus stent with biodegradable polymer</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Infinnium</td>
<td>Paclitaxel stent with biodegradable polymer</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Nevo Stent</td>
<td>Drug eluting stent with biodegradable polymer</td>
<td>Phase 3</td>
</tr>
<tr>
<td>REV A</td>
<td>Completely biodegradable sirolimus stent</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Supralimus Stent</td>
<td>Sirolimus stent with biodegradable polymer</td>
<td>Phase 3</td>
</tr>
<tr>
<td>VESTAsync</td>
<td>Polymer-free sirolimus stent</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Xience V</td>
<td>Everolimus bioabsorbable stent</td>
<td>Phase 3</td>
</tr>
<tr>
<td>XTENT</td>
<td>Biolimus stent with biodegradable polymer</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

*Note: References for this chapter can be found here: [www.cvpct3.com](http://www.cvpct3.com)*
Part 4

Appendices

Angela Cheng-Lai, PharmD
William H. Frishman, MD
Appendix 1

Pharmacokinetic Properties of Approved Cardiovascular Drugs

(Table begins on page 634.)
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Bioavailability (%)</th>
<th>Protein Binding (%)</th>
<th>Volume of Distribution (liters/kg)</th>
<th>Half-Life (hours)</th>
<th>Urinary Excretion (% unchanged)</th>
<th>Clearance (mL · min⁻¹ · kg⁻¹)</th>
<th>Therapeutic Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>37 ± 12</td>
<td>26 ± 3</td>
<td>1.2 ± 0.3</td>
<td>2.7 ± 0.4</td>
<td>40 ± 11</td>
<td>6.8 ± 0.8</td>
<td>—</td>
<td>Singh BN, Thoden WR, Wahl J. Acebutolol: A review of its pharmacology, pharmacokinetics, clinical uses, and adverse effects. <em>Pharmacotherapy</em>. 1986;6:45–63.</td>
</tr>
<tr>
<td>Alteplase</td>
<td>—</td>
<td>—</td>
<td>0.10–0.17</td>
<td>3–5 min t₁/₂ is ↑ in HI</td>
<td>—</td>
<td>9.8–10.4 Cl is ↓ in HI 0.45 µg/mL</td>
<td>—</td>
<td>Seifried E, Tanswell P, Rijken DC, et al. Pharmacokinetics of antigen and activity of recombinant tissue-type plasminogen activator after infusion in healthy volunteers. <em>Arzneimittelforschung</em>. 1988;38:418–422.</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>ID 99</td>
<td>—</td>
<td>9–15</td>
<td>—</td>
<td>0.27–0.54</td>
<td>—</td>
<td>—</td>
<td>Gilead Sciences. Letairis package insert; 2009.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>46 ± 22</td>
<td>99.98 ± 0.01</td>
<td>66 ± 48</td>
<td>25 ± 12 days</td>
<td>0.9 ± 0.4</td>
<td>1.0–2.5 µg/mL</td>
<td>—</td>
<td>Freeman MD, Somberg JC. Pharmacology and pharmacokinetics of amiodarone. <em>J Clin Pharmacol</em>. 1991;31:1061–1069.</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>74 ± 17</td>
<td>93 ± 1</td>
<td>16 ± 4</td>
<td>39 ± 8 t₁/₂ is ↑ in eld and HI</td>
<td>10</td>
<td>5.9 ± 1.5 Cl is ↓ in eld and HI</td>
<td>—</td>
<td>Abernethy DR. The pharmacokinetic profile of amlodipine. <em>Am Heart J</em>. 1989;118:1100–1103.</td>
</tr>
<tr>
<td>Drug</td>
<td>Cmax (µg/mL)</td>
<td>t1/2 (h)</td>
<td>Vd (L/kg)</td>
<td>Cmin (µg/mL)</td>
<td>Half Life (h)</td>
<td>Comments</td>
<td></td>
<td></td>
</tr>
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<td>--------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anistreplase</td>
<td>—</td>
<td>—</td>
<td>0.084 ± 0.027</td>
<td>0.92 ± 0.36</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>50–100¹</td>
<td>76–90</td>
<td>0.15–0.2</td>
<td>0.18–0.88</td>
<td>150–300 µg/mL</td>
<td>Furst DE, Tozer TN, Melmon KL. Salicylate clearance, the resultant of protein binding and metabolism. Clin Pharmacol Ther. 1979;26:380–389.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>50–60</td>
<td>5–15</td>
<td>0.95 ± 0.15</td>
<td>2.0 ± 0.2</td>
<td>0.1–1 µg/mL</td>
<td>Wadsworth AN, Murdoch D, Brogden RN. Atenolol: A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. Drugs. 1991;42:468–510.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Name</td>
<td>Bioavailability (%)</td>
<td>Protein Binding (%)</td>
<td>Volume of Distribution (liters/kg)</td>
<td>Half-Life (hours)</td>
<td>Urinary Excretion (% unchanged)</td>
<td>Clearance (mL · min⁻¹ · kg⁻¹)</td>
<td>Therapeutic Range</td>
<td>References</td>
</tr>
<tr>
<td>-------------------</td>
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<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Benazepril</td>
<td>37</td>
<td>95–97</td>
<td>0.12</td>
<td>0.6</td>
<td>10–11¹</td>
<td>0.3–0.4</td>
<td>—</td>
<td>Kaiser G, Ackermann R, Brechbukler S, et al. Pharmacokinetics of the angiotensin converting enzyme inhibitor benazepril HCl (CGS 14 824 A) in healthy volunteers after single and repeated administration. Biopharm Drug Dispos. 1989;10:365–376. ¹Active metabolite.</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>85–91</td>
<td>30–35</td>
<td>3.2 ± 0.5</td>
<td>8.2–12 t₁/₂ is ↑ in RI</td>
<td>50–60</td>
<td>3.7 ± 0.7 Cl is ↓ in RI</td>
<td>—</td>
<td>Lancaster SG, Sorkin EM. Bisoprolol: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. Drugs. 1988;36:256–285.</td>
</tr>
<tr>
<td>Bosentan</td>
<td>50</td>
<td>&gt;98</td>
<td>−0.26</td>
<td>5</td>
<td>&lt;3</td>
<td>1.9</td>
<td>—</td>
<td>Actelion. Tracleer package insert. S. San Francisco, CA; 2002.</td>
</tr>
<tr>
<td>Bretylium</td>
<td>23 ± 9</td>
<td>0–8</td>
<td>5.9 ± 0.8</td>
<td>5–10 t₁/₂ is ↑ in RI</td>
<td>70–80</td>
<td>10.2 ± 1.9 Cl is ↓ in RI</td>
<td>—</td>
<td>Rapaport WG. Clinical pharmacokinetics of bretylium. Clin Pharmacokin. 1985;10:248–256.</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>55–89</td>
<td>99 ± 0.3</td>
<td>0.13 ± 0.03</td>
<td>0.3–1.5 t₁/₂ is ↑ in RI, HI, and CHF</td>
<td>62 ± 20</td>
<td>2.6 ± 0.5 Cl is ↓ in RI, HI, and CHF</td>
<td>—</td>
<td>Cook JA, Smith DE, Cornish LA, et al. Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with congestive heart failure. Clin Pharmacol Ther. 1988;44:487–500.</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Bioavailability (%)</td>
<td>Protein Binding (%)</td>
<td>Volume of Distribution (liters/kg)</td>
<td>Half-Life (hours)</td>
<td>Urinary Excretion (% unchanged)</td>
<td>Clearance (mL · min⁻¹ · kg⁻¹)</td>
<td>Therapeutic Range</td>
<td>References</td>
</tr>
<tr>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Captopril</td>
<td>65–75</td>
<td>30 ± 6</td>
<td>0.81 ± 0.18</td>
<td>2.2 ± 0.5</td>
<td>40–50</td>
<td>12.0 ± 1.4 Cl is ↓ in RI</td>
<td>0.05–0.5 µg/mL</td>
<td>Duchin KL, McKinstry DN, Cohen AI, et al. Pharmacokinetics of captopril in healthy subjects and in patients with cardiovascular diseases. Clin Pharmacokinet. 1988;14:241–259.</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>10–21</td>
<td>20–80</td>
<td>0.20 ± 0.08</td>
<td>1.5 ± 0.2</td>
<td>92 ± 5</td>
<td>4.5 ± 1.7 Cl is ↓ in RI</td>
<td>—</td>
<td>Osmon MA, Patel RB, Irwin DS, et al. Bioavailability of chlorothiazide from 50, 100, and 250 mg solution doses. Biopharm Drug Dispos. 1982;3:89–94.</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>64 ± 10</td>
<td>75 ± 1</td>
<td>0.10 ± 0.04</td>
<td>47 ± 22</td>
<td>65 ± 9</td>
<td>0.04 ± 0.01 Cl is ↓ in eld</td>
<td>—</td>
<td>Williams RL, Blume CD, Lin ET, et al. Relative bioavailability of chlorthalidone in humans: Adverse influence of polyethylene glycol. J Pharm Sci. 1982;71:533–535.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>95</td>
<td>20</td>
<td>2.1 ± 0.4</td>
<td>12–16</td>
<td>40–60</td>
<td>3.1 ± 1.2 Cl is ↓ in RI</td>
<td>0.2–2 ng/mL</td>
<td>Lowenthal DT, Matzek KM, McGregor TR. Clinical pharmacokinetics of clonidine. Clin Pharmacokinet. 1988;14:287–310.</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Bioavailability (%)</td>
<td>Protein Binding (%)</td>
<td>Volume of Distribution (liters/kg)</td>
<td>Half-Life (hours)</td>
<td>Urinary Excretion (% unchanged)</td>
<td>Clearance (mL · min⁻¹ · kg⁻¹)</td>
<td>Therapeutic Range</td>
<td>References</td>
</tr>
<tr>
<td>--------------------</td>
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</tr>
<tr>
<td>Colesevelam</td>
<td>NA¹</td>
<td>NA</td>
<td>NA</td>
<td>0.05</td>
<td>ID</td>
<td>—</td>
<td>—</td>
<td>Wong N. Colesevelam: A new bile acid sequestrant. Heart Dis. 2001;3:63–70. ¹Colesevelam is not hydrolyzed by digestive enzymes and is not absorbed.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>3-7</td>
<td>35</td>
<td>50-70</td>
<td>12-17</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Pradaxa (dabigatran etexilate mesylate). Boehringer-Ingelheim package insert.</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>87</td>
<td>—</td>
<td>0.04–0.06</td>
<td>3–5</td>
<td>0.27–0.41</td>
<td>0.1–0.6 anti-Xa Units/mL</td>
<td>—</td>
<td>Simoneau G, Bergmann JF, Kher A, et al. Pharmacokinetics of a low molecular weight heparin (Fragmin) in young and elderly subjects. Thromb Res. 1992;66:603–607.</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>&gt;90</td>
<td>97 ± 0.5</td>
<td>0.54 ± 0.14</td>
<td>6.7 ± 1.7 days</td>
<td>32 ± 15</td>
<td>0.055 ± 0.018</td>
<td>14–26 ng/mL</td>
<td>Mooradian AD. Digitalis: An update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations. Clin Pharmacokinet. 1988;15:165–179.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>70 ± 1.3</td>
<td>20–25</td>
<td>39 ± 13</td>
<td>60 ± 11</td>
<td>[(0.8 mL/min/kg) (wt in kg) + Clcr¹; in neo, child]</td>
<td>0.5–2 ng/mL</td>
<td>—</td>
<td>Mooradian AD. Digitalis: An update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations. Clin Pharmacokinet. 1988;15:165–179. ¹Total digoxin clearance in patients without CHF (mL/min)</td>
</tr>
<tr>
<td>Drug</td>
<td>Vd (l/kg)</td>
<td>t1/2 (h)</td>
<td>Cl (L/h)</td>
<td>Dose (mg)</td>
<td>Reference</td>
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<tr>
<td>Diltiazem</td>
<td>40–67</td>
<td>70–80</td>
<td>3.1 ± 1.2</td>
<td>3.7–6</td>
<td>12 ± 4</td>
<td>50–200 ng/mL</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cl is ↓ in RI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>NA</td>
<td>1D</td>
<td>0.20 ± 0.08</td>
<td>2.4 ± 0.7 min</td>
<td>0</td>
<td>59 ± 22</td>
<td>40–190 ng/mL</td>
<td>Steinberg C, Noterman DA. Pharmacokinetics of cardiovascular drugs in children: Inotropes and vasopressors. Clin Pharmacokinet. 1994;27:345–367.</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>&gt;90</td>
<td>60–70</td>
<td>3–4</td>
<td>5–13</td>
<td>=64</td>
<td>5.2</td>
<td>—</td>
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<tr>
<td>Dopamine</td>
<td>NA</td>
<td>—</td>
<td>0</td>
<td>2 min</td>
<td>&lt; 5</td>
<td>—</td>
<td>Kulka PJ, Tryba M. Inotropic support of the critically ill patient. Drugs. 1993;45:654–667.</td>
<td></td>
</tr>
<tr>
<td>Doxazosin</td>
<td>63 ± 14</td>
<td>98.9 ± 0.5</td>
<td>1.5 ± 0.3</td>
<td>19–22</td>
<td>—</td>
<td>1.7 ± 0.4</td>
<td>—</td>
<td>Donnelly R, Meredith PA, Elliott HL. Pharmacokinetic-pharmacodynamic relationships of α-adrenoceptor antagonists. Clin Pharmacokinet. 1989;17:264–274.</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>15</td>
<td>&gt;98</td>
<td>20</td>
<td>13–24</td>
<td>6¹</td>
<td>31–36</td>
<td>—</td>
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<tr>
<td>Encainide</td>
<td>25–90¹</td>
<td>75–85</td>
<td>3.6–3.9</td>
<td>1–2²</td>
<td>5²</td>
<td>30²</td>
<td>250 ng/mL</td>
<td>Brogden RN, Todd PA. Encainide: A review of its pharmacological properties and therapeutic efficacy. Drugs. 1987;34:519–538.¹Mainly as metabolites</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Bioavailability (%)</td>
<td>Protein Binding (%)</td>
<td>Volume of Distribution (liters/kg)</td>
<td>Half-Life (hours)</td>
<td>Urinary Excretion (% unchanged)</td>
<td>Clearance (mL · min⁻¹ · kg⁻¹)</td>
<td>Therapeutic Range</td>
<td>References</td>
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<tr>
<td>Enoxaparin</td>
<td>92</td>
<td>—</td>
<td>0.08</td>
<td>4.5 t₁/₂ is ↑ in RI</td>
<td>8–20</td>
<td>0.3 ± 0.1 Cl is ↓ in RI</td>
<td>—</td>
<td>Bendetowicz AV, Begoquin S, Caplain H, et al. Pharmacokinetics and pharmacodynamics of a low molecular weight heparin (enoxaparin) after subcutaneous injection, comparison with unfractionated heparin—a three-way crossover study in healthy volunteers. <em>Thromb Haemost.</em> 1994;71:305–313.</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>69</td>
<td>50</td>
<td>0.61–1.3</td>
<td>4–6</td>
<td>&lt; 5</td>
<td>2.4</td>
<td>—</td>
<td>Pfizer. Inspra package insert. New York; 2008.</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>13</td>
<td>98</td>
<td>≈4.41</td>
<td>5–9</td>
<td>=6</td>
<td>11.5</td>
<td>—</td>
<td>Bottorff MB, Tenero DM. Pharmacokinetics of eprosartan in healthy subjects, patients with hypertension, and special populations. <em>Pharmacotherapy.</em> 1999;19(4 pt 2):735–78S. This value is the population mean steady-state volume of distribution (Vss/F).</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>100</td>
<td>90</td>
<td>—</td>
<td>0.5–1</td>
<td>65</td>
<td>—</td>
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<td>Drug</td>
<td>Peak</td>
<td>Trough</td>
<td>Volume</td>
<td>Half-life</td>
<td>Peak</td>
<td>Trough</td>
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<tr>
<td>Fenofibric acid</td>
<td>81</td>
<td>99</td>
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<td>20</td>
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<tr>
<td>Fenoldopam</td>
<td>5.7</td>
<td>88</td>
<td>0.23–0.66</td>
<td>0.16</td>
<td>1</td>
<td>24.8–38.2</td>
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<td></td>
<td>3.5–14.25 µg/L</td>
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<tr>
<td>Flecaïnide</td>
<td>85–90</td>
<td>40–50</td>
<td>4.9 ± 0.4</td>
<td>12–30</td>
<td>10–50</td>
<td>5.6 ± 1.3</td>
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<td></td>
<td>t1/2 is ↑ in RI, HI, CHF</td>
<td>Cl ↓ in child</td>
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<td></td>
<td></td>
<td>t1/2 is ↑ in HI</td>
<td>Cl ↓ in child</td>
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<tr>
<td>Flecainide</td>
<td>85–90</td>
<td>40–50</td>
<td>4.9 ± 0.4</td>
<td>12–30</td>
<td>10–50</td>
<td>5.6 ± 1.3</td>
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<td>t1/2 is ↑ in RI, HI, CHF</td>
<td>Cl ↓ in child</td>
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<td>t1/2 is ↑ in HI</td>
<td>Cl ↓ in child</td>
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<tr>
<td>Fluvastatin</td>
<td>9–50</td>
<td>98</td>
<td>—</td>
<td>1.2</td>
<td>&lt; 5</td>
<td>—</td>
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<td></td>
<td>t1/2 is ↑ in HI</td>
<td>Cl ↓ in child</td>
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</tr>
<tr>
<td>Fondaparinux</td>
<td>= 100</td>
<td>—</td>
<td>0.10–0.12</td>
<td>13–15</td>
<td>≤ 77%</td>
<td>0.10–0.13</td>
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<td>t1/2 is ↑ in child</td>
<td>Cl ↓ in child</td>
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<td></td>
<td>t1/2 is ↑ in child</td>
<td>Cl ↓ in child</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fosinopril</td>
<td>36 ± 7</td>
<td>= 95</td>
<td>0.13 ± 0.03</td>
<td>11.3 ± 0.7</td>
<td>&lt; 2</td>
<td>0.51 ± 0.10</td>
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<tr>
<td></td>
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<td></td>
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<td>t1/2 is ↑ in child</td>
<td>Cl ↓ in child</td>
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<td></td>
<td>t1/2 is ↑ in child</td>
<td>Cl ↓ in child</td>
<td></td>
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<tr>
<td>Furosemide</td>
<td>61 ± 17</td>
<td>98.8 ± 0.2</td>
<td>0.11 ± 0.02</td>
<td>0.5–1.0</td>
<td>66 ± 7</td>
<td>2.0 ± 0.4</td>
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<td></td>
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<td>t1/2 is ↑ in child</td>
<td>Cl ↓ in child</td>
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<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Bioavailability (%)</th>
<th>Protein Binding (%)</th>
<th>Volume of Distribution (liters/kg)</th>
<th>Half-Life (hours)</th>
<th>Urinary Excretion (% unchanged)</th>
<th>Clearance (mL · min⁻¹ · kg⁻¹)</th>
<th>Therapeutic Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil</td>
<td>98 ± 1</td>
<td>&gt; 97</td>
<td>0.14 ± 0.03</td>
<td>1.1 ± 0.2</td>
<td>&lt; 1</td>
<td>1.7 ± 0.4</td>
<td>—</td>
<td>Todd PA, Ward A. Gemfibrozil, a review of its pharmacodynamic and pharmaco-kinetic properties and therapeutic use in dyslipidaemia. Drugs. 1988;36:314–339.</td>
</tr>
<tr>
<td>Heparin</td>
<td>NA</td>
<td>—</td>
<td>0.058 ± 0.01</td>
<td>1–2¹</td>
<td>≤ 50</td>
<td>0.5–0.6²</td>
<td>—</td>
<td>Estes JW. Clinical pharmacokinetics of heparin. Clin Pharmacokinet. 1980;5:204–220.</td>
</tr>
<tr>
<td>Drug</td>
<td>Method</td>
<td>Half-life (h)</td>
<td>T1/2 (h)</td>
<td>Cl (L/min/m²)</td>
<td>Reference</td>
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<tr>
<td>Iloprost</td>
<td>NA</td>
<td>60</td>
<td>0.7–0.8</td>
<td>20–30 min</td>
<td>Actelion. Ventavis package insert. San Francisco; 2008.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>22 ± 14</td>
<td>28 ± 12</td>
<td>3.9 ± 1.5</td>
<td>1.0 ± 0.5</td>
<td>Fung HL. Pharmacokinetics and pharmacodynamics of organic nitrates. <em>Am J Cardiol.</em> 1987;60:4H–9H.</td>
<td></td>
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<tr>
<td>Isosorbide mononitrate</td>
<td>93 ± 10</td>
<td>&lt; 4</td>
<td>0.73 ± 0.09</td>
<td>4.9 ± 0.8</td>
<td>Abshagen UWP. Pharmacokinetics of isosorbide mononitrate. <em>Am J Cardiol.</em> 1992;70:61G–66G.</td>
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<tr>
<td>Isoxsuprine</td>
<td>100</td>
<td>ID</td>
<td>1.25</td>
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<td>—</td>
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<tr>
<td>Lidocaine</td>
<td>NA</td>
<td>50–70</td>
<td>1.1 ± 0.4</td>
<td>1.8 ± 0.4 t1/2 is F 1 in eld, neo</td>
<td>Thompson PD, Melmon KL, Richardson JA, et al. Lidocaine pharmacokinetics in advanced heart failure, liver disease and renal disease in humans. <em>Ann Intern Med.</em> 1973;78:499–508.</td>
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<tr>
<td>Generic Name</td>
<td>Bioavailability (%)</td>
<td>Protein Binding (%)</td>
<td>Volume of Distribution (liters/kg)</td>
<td>Half-Life (hours)</td>
<td>Urinary Excretion (% unchanged)</td>
<td>Clearance (mL · min⁻¹ · kg⁻¹)</td>
<td>Therapeutic Range</td>
<td>References</td>
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<tr>
<td>Losartan</td>
<td>33 F is in HI</td>
<td>98</td>
<td>0.49</td>
<td>1.5–2.5 6–9¹</td>
<td>4</td>
<td>8.6 Cl is ↓ in HI</td>
<td>—</td>
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<tr>
<td>Mecamylamine</td>
<td>ID</td>
<td>—</td>
<td>—</td>
<td>1D</td>
<td>50¹</td>
<td>—</td>
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<tr>
<td>Methyldopa</td>
<td>42 ± 16</td>
<td>1–16</td>
<td>0.46 ± 0.15</td>
<td>1.8 ± 0.6 t₁/₂ is ↑ in RI, neo</td>
<td>40 ± 13</td>
<td>3.7 ± 1.0 Cl is ↓ in RI</td>
<td>—</td>
<td>Skerjanee A, Campbell NRC, Robertson S, et al. Pharmacokinetics and presystemic gut metabolism of methyldopa in healthy human subjects. J Clin Pharmacol. 1995;35:275–280.</td>
</tr>
<tr>
<td>Metolazone</td>
<td>40–65</td>
<td>95¹</td>
<td>1.6</td>
<td>14</td>
<td>70–95</td>
<td>—</td>
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<tr>
<td>Mexiletine</td>
<td>87 ± 13</td>
<td>50–60</td>
<td>4.9 ± 0.5</td>
<td>9.2 ± 2.1 t₁/₂ is ↑ in MI, CHF, RI, and HI</td>
<td>10</td>
<td>6.3 ± 2.7 Cl is ↓ in MI, RI (Clcr &lt; 10 mL/min), HI</td>
<td>0.5–2.0 µg/mL</td>
<td>Monk JP, Brogden RN. Mexiletine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in the treatment of arrhythmias. Drugs. 1990;40:374–411.</td>
</tr>
<tr>
<td>Drug</td>
<td>Cmax</td>
<td>Range</td>
<td>T1/2</td>
<td>CL</td>
<td>ID</td>
<td>IEF</td>
<td>Notes</td>
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<tr>
<td>Milrinone</td>
<td>0.32</td>
<td>0.02</td>
<td>85</td>
<td>6</td>
<td>70</td>
<td>0.80 ± 0.22 £t1/2 is ↑ in CHF, RI 6.1 ± 1.3 Cl is ↓ in CHF, RI 150–250 ng/mL</td>
<td>Young RA, Ward A. Milrinone: A preliminary review of its pharmacological properties and therapeutic use. Drugs. 1988;36:158–192.</td>
<td></td>
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<tr>
<td>Minoxidil</td>
<td>2.7</td>
<td>0.7</td>
<td>20</td>
<td>24</td>
<td>0</td>
<td>3.1 ± 0.6 £t1/2 is ↑ in CHF, RI 85 ± 10</td>
<td>Fleishaker JC, Andreedis NA, Welshman IR, et al. The pharmacokinetics of 2.5 to 10 mg oral doses of minoxidil in healthy volunteers. J Clin Pharmacol. 1989;29:162–167.</td>
<td></td>
</tr>
<tr>
<td>Moricizine</td>
<td>38</td>
<td>95</td>
<td>&lt; 1</td>
<td>—</td>
<td>—</td>
<td>1.5–3.5 t1/2 is ↑ in HI</td>
<td>Fitton A, Buckley MM. Moricizine: A review of its pharmacological properties, and therapeutic efficacy in cardiac arrhythmias. Drugs. 1990;40:138–167.</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>34 ± 5</td>
<td>20 ± 4</td>
<td>1.9 ± 0.2</td>
<td>73 ± 4</td>
<td>2.9 ± 0.6 Cl is ↓ in HI</td>
<td>Morrison RA, Singhvi SM, Creasey WA, et al. Dose proportionality of nadolol pharmacokinetics after intravenous administration to healthy subjects. Eur J Clin Pharmacol. 1988;33:625–628.</td>
<td></td>
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<tr>
<td>Nebivolol</td>
<td>12–96</td>
<td>98</td>
<td>17.3–184.0 £t1/2 is ↑ in HI</td>
<td>3.9–156.5</td>
<td>—</td>
<td>—</td>
<td>Sule SS, Frishman W. Nebivolol: New therapy update. Cardiology in Review. 2006;14:259–264. £t1/2 is ↑ in HI.</td>
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<tr>
<td>Nicardipine</td>
<td>18 ± 11</td>
<td>98–99.5</td>
<td>1.1 ± 0.3</td>
<td>&lt; 1</td>
<td>10.4 ± 3.1 Cl is ↓ in HI</td>
<td>Singh BN, Josephson MA. Clinical pharmacology, pharmacokinetics and hemodynamic effects of nicardipine. Am Heart J. 1990;119:427–434.</td>
<td></td>
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<tr>
<td>Nicotinic acid</td>
<td>88</td>
<td>&lt; 20</td>
<td>0.75–1</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>’Increases with dose.</td>
<td></td>
</tr>
<tr>
<td>Generic Name</td>
<td>Bioavailability (%)</td>
<td>Protein Binding (%)</td>
<td>Volume of Distribution (liters/kg)</td>
<td>Half-Life (hours)</td>
<td>Urinary Excretion (% unchanged)</td>
<td>Clearance (mL - min⁻¹ - kg⁻¹)</td>
<td>Therapeutic Range</td>
<td>References</td>
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</tr>
<tr>
<td>Nimodipine</td>
<td>10 ± 4 F is in HI</td>
<td>98</td>
<td>1.7 ± 0.6</td>
<td>1.1 ± 0.3 t₁/₂ iso is ↑ in HI and RI</td>
<td>&lt; 1</td>
<td>19 ± 6 Cl is ↓ in HI and RI</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>3.7 F is in HI</td>
<td>99</td>
<td>4–5</td>
<td>8–9 t₁/₂ iso is ↑ in HI</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral: &lt; 1 SL: 38 ± 26 TOP: 72 ± 20</td>
<td>60</td>
<td>2.9</td>
<td>1–4 min</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>28.6¹</td>
<td>99</td>
<td>≈0.5</td>
<td>10–15</td>
<td>—</td>
<td>0.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>100</td>
<td>80–98</td>
<td>—</td>
<td>5 t₁/₂ iso is ↑ in RI</td>
<td>&lt; 10</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>33 ± 13 F is in HI</td>
<td>0</td>
<td>4.2 ± 0.9</td>
<td>0.9 ± 0.3 t₁/₂ iso is ↑ in eld and HI</td>
<td>0</td>
<td>60 ± 13 Cl is ↓ in eld and HI</td>
<td>—</td>
<td>Ward A, Clissold SP. Pentoxifylline: A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. Drugs. 1987;34:50–97.</td>
</tr>
<tr>
<td>Pindolol</td>
<td>75 ± 9 F is ↓ in RI</td>
<td>40–60</td>
<td>2.3 ± 0.9</td>
<td>3.6 ± 0.6 t₁/₂ iso is ↑ in RI and HI</td>
<td>35–50</td>
<td>8.3 ± 1.8 Cl is ↓ in RI and HI</td>
<td>—</td>
<td>Guerret M, Cheymol G, Aubry JP, et al. Estimation of the absolute oral bioavailability of pindolol by two analytical methods. Eur J Clin Pharmacol. 1983;25:357–359.</td>
</tr>
<tr>
<td>Drug</td>
<td>$t_{1/2}$</td>
<td>$C_{max}$</td>
<td>$AUC_{0-24h}$</td>
<td>$V_d$</td>
<td>$Cl$</td>
<td>Notes</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>11</td>
<td>96</td>
<td>2</td>
<td>11</td>
<td>➥2</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel(^1)</td>
<td>&gt;98</td>
<td>0.63-0.97</td>
<td>68 (as inactive metabolite)</td>
<td>27-40</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>18 ± 8</td>
<td>43–48</td>
<td>1.8 ± 0.8</td>
<td>20</td>
<td>13.5(^5)</td>
<td>Cl is in HI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>48–68</td>
<td>95 ± 1</td>
<td>0.60 ± 0.13</td>
<td>&lt; 1</td>
<td>3.0 ± 0.3</td>
<td>Cl is ↓ in CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probucol</td>
<td>2–8</td>
<td>95</td>
<td>12–500</td>
<td>0</td>
<td>—</td>
<td>23.6 ± 17.2 µg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>83 ± 16</td>
<td>16 ± 5</td>
<td>3.0 ± 0.6</td>
<td>67 ± 8</td>
<td>3.2(^1) &amp; 1.1(^2)</td>
<td>Cl is ↓ in CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>5–50(^1)</td>
<td>85–95</td>
<td>3.6 ± 2.1</td>
<td>&lt; 1</td>
<td>17 ± 8</td>
<td>Cl is ↓ in HI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>26 ± 10</td>
<td>87 ± 6</td>
<td>3–5</td>
<td>&lt; 0.5</td>
<td>11.4–17.1</td>
<td>Cl is ↓ in HI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>60</td>
<td>97</td>
<td>2.2 ± 0.2(^1)</td>
<td>Trace</td>
<td>2.0 ± 0.6</td>
<td>Cl is ↓ in eld and RI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Data refer to active metabolite of prasugrel unless stated otherwise.

\(^5\)Cl is in HI

References:
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Bioavailability (%)</th>
<th>Protein Binding (%)</th>
<th>Volume of Distribution (liters/kg)</th>
<th>Half-Life (hours)</th>
<th>Urinary Excretion (% unchanged)</th>
<th>Clearance (mL · min⁻¹ · kg⁻¹)</th>
<th>Therapeutic Range</th>
<th>References</th>
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<tbody>
<tr>
<td>Reserpine</td>
<td>50</td>
<td>—</td>
<td>—</td>
<td>33</td>
<td>&lt; 1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>&lt; 5</td>
<td>94</td>
<td>1.9</td>
<td>&lt; 0.5</td>
<td>7.6</td>
<td>—</td>
<td>—</td>
<td>Mauro VF, MacDonald JL. Simvastatin: A review of its pharmacology and clinical use. DICP. 1991;25:257–264.</td>
</tr>
<tr>
<td>Drug</td>
<td>Plasma T1/2 (h)</td>
<td>60–70</td>
<td>80.1</td>
<td>2.6 ± 0.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Sotalol</td>
<td>90–100</td>
<td>0</td>
<td>2.0 ± 0.4</td>
<td>7–15</td>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; is ↑ in RI and eld</td>
<td>80.1</td>
<td>2.6 ± 0.5</td>
<td>Cl is ↓ in RI and eld</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>ID</td>
<td>94</td>
<td>1.1</td>
<td>15–35</td>
<td>—</td>
<td>0.38–0.81</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Terazosin</td>
<td>90</td>
<td>90–94</td>
<td>0.80 ± 0.18</td>
<td>9–12</td>
<td>12 ± 3</td>
<td>1.1 ± 0.2</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Ticlopidine</td>
<td>80–90</td>
<td>98</td>
<td>—</td>
<td>4–5 days</td>
<td>trace</td>
<td>8–21</td>
<td>Cl is ↓ in RI</td>
<td>1–2 µg/mL</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>90&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ID</td>
<td>0.06&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3–4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ID</td>
<td>0.4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>—&lt;sup&gt;3&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Bioavailability (%)</td>
<td>Protein Binding (%)</td>
<td>Volume of Distribution (liters/kg)</td>
<td>Half-Life (hours)</td>
<td>Urinary Excretion (% unchanged)</td>
<td>Clearance (mL · min⁻¹ · kg⁻¹)</td>
<td>Therapeutic Range</td>
<td>References</td>
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<tr>
<td>Tocainide</td>
<td>89 ± 5</td>
<td>10–15</td>
<td>3.0 ± 0.2</td>
<td>13.5 ± 2.3</td>
<td>38 ± 7</td>
<td>2.6 ± 0.5 Cl is ↓ in CHF and RI</td>
<td>3–9 µg/mL</td>
<td>Roden DM, Woosley RL. Drug therapy: Tocainide. N Engl J Med. 1986;315:41–45.</td>
</tr>
<tr>
<td>Drug</td>
<td>Cmax (μg/mL)</td>
<td>t_{max} (h)</td>
<td>AUC (μg·h/mL)</td>
<td>t½ (h)</td>
<td>Bioavailability</td>
<td>Note</td>
<td></td>
<td></td>
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<tr>
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</tr>
<tr>
<td>Valsartan</td>
<td>25 (10–35)</td>
<td>95 (94–97)</td>
<td>0.24</td>
<td>&lt; 13</td>
<td>0.48</td>
<td>—</td>
<td></td>
<td></td>
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<tr>
<td>Verapamil</td>
<td>22 ± 8</td>
<td>90 ± 2</td>
<td>5.0 ± 2.1</td>
<td>&lt; 3</td>
<td>15 ± 6</td>
<td>80–300 ng/mL</td>
<td></td>
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<tr>
<td>Warfarin</td>
<td>93 ± 8</td>
<td>99 ± 1</td>
<td>0.14 ± 0.06</td>
<td>&lt; 2</td>
<td>0.045 ± 0.024</td>
<td>—</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↑ = increased; ↓ = decreased; CAD = coronary artery disease; CHF = congestive heart failure; Cl = clearance; Cl.cr = creatinine clearance; eld = elderly; F = bioavailability; HI = hepatic impairment; ID = insufficient data; MI = myocardial infarction; NA = not applicable; neo = neonate; RI = renal impairment; SL = sublingual; t½ = half-life; TOP = topical; Vd = volume of distribution
Appendix 2

Therapeutic Use of Available Cardiovascular Drugs

**Alpha-Adrenergic Blockers**

1. **Doxazosin (doxazosin, Cardura)**

   **Indications**
   - Hypertension
   - Benign prostatic hyperplasia (BPH)

   **Dosage**
   - **Adults**
     As an antihypertensive, initiate at 1 mg/d. Dosage may be increased gradually according to blood pressure response. May increase every 1-2 weeks to 2, 4, 8, and 16 mg/d as needed.

   - **Elderly**
     Initiate at lowest dose and titrate to response.

   - **Children**
     Safety and efficacy have not been established.

   **Preparations**
   - Doxazosin (generic); Cardura (Pfizer): 1, 2, 4, and 8 mg tablets

2. **Prazosin (Prazosin, Minipress)**

   **Indication**
   - Hypertension

   **Dosage**
   - **Adults**
     As an antihypertensive, initiate therapy at 1 mg two to three times daily and slowly increase to the usual maintenance dose of 6-15 mg/d in divided doses. Most patients can be maintained on a twice-daily regimen after initial titration. Doses above 20 mg usually do not have increased effect. Some patients may respond to up to 40 mg/d.

   - **Elderly**
     Initiate at lowest dose and titrate to response.

   - **Children**
     Safety and efficacy have not been established. However, there has been some experience with the use of this drug in children and the following dosage regimen has been suggested: for children younger than 7 years: Initiate at 250 µg (0.25 mg) two to three times daily and adjust to response. For children 7-12 years, initiate at 500 µg (0.5 mg) two to three times daily and adjust to response.

   **Preparations**
   - Prazosin (generic); Minipress (Pfizer): 1, 2, 5 mg capsules.

   **Fixed-Dose Combinations for Treatment of Hypertension**
   - Minizide-prazosin/polythiazide combination tablet: 1 mg/0.5 mg, 2 mg/0.5 mg, 5 mg/0.5 mg

3. **Terazosin (Terazosin, Hytrin)**

   **Indications**
   - Hypertension
   - Benign prostatic hyperplasia (BPH)

   **Dosage**
   - **Adults**
     As an antihypertensive, initiate therapy with 1 mg at bedtime. Dosage may be increased slowly to achieve desired response. There seems to be little benefit in exceeding a dose of 20 mg/d. Usual maintenance dose is 1-5 mg/d.
Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established.

Preparations
Terazosin (generic); Hytrin (Abbott Laboratories): 1, 2, 5, 10 mg capsules

4. Phenoxybenzamine (Dibenzyline)

Indication
Symptomatic management of pheochromocytoma

Dosage
Adults
Initiate with 10 mg twice daily. Dose may be increased every other day by 10 mg until the desired response is obtained. Usual dose range is 20–40 mg two to three times per day. Phenoxybenzamine may be used concurrently with a beta-blocker if troublesome tachycardia coexists.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established. However, there has been some experience with the use of this drug in children, and the following dosage regimen has been suggested: initiate at 0.2 mg/kg once daily (maximum dose of 10 mg/d). Dosage may be increased gradually by 0.2 mg/kg increments until an adequate response is achieved. The usual pediatric maintenance dosage is 0.4–1.2 mg/kg/d given every 6–8 h; higher doses may be needed in some cases.

Preparation
Dibenzyline (Wellspring): 10 mg capsules

5. Phentolamine (Regitine)

Indications
Diagnosis of pheochromocytoma
Prevention/control of hypertensive episodes associated with pheochromocytoma

Prevention/control of hypertensive episodes associated with pheochromocytoma

Adults
Preoperative—5 mg (1 mg for children) administered intravenously (IV) or intramuscularly (IM) 1–2 h before surgery and repeat if indicated.

Intraoperative—5 mg IV (1 mg for children) and repeat as indicated to prevent or control paroxysms of hypertension, tachycardia, respiratory depression, convulsions, or other effects related to epinephrine intoxication.

Elderly
No dosage adjustment is required.

Children
Use lower dose in children as described above.

Prevention/treatment of dermal necrosis and sloughing associated with IV norepinephrine:

Adults
Prevention—10 mg of phentolamine is added to each liter of norepinephrine solution.

Treatment—Initiate within 12 h (as soon as possible) of extravasation; 5–10 mg of phentolamine in 10 mL of 0.9% sodium chloride is infiltrated into the area using a small needle syringe.

Diagnosis of pheochromocytoma (not the first test of choice; all nonessential medications should be withheld for at least 24 h prior to the test):

Adults
5 mg IV or IM (1 mg IV or 3 mg IM for children) is administered. Five milligrams of phentolamine should be dissolved in 1 mL of sterile water for injection before administration. Following the IV dose, blood pressure should be monitored immediately, every 30 s for the first 3 min, and every minute for the next 7 min. Following IM dose, blood pressure should be monitored every 5 min for 30–45 min. A blood pressure decrease of at least 35 mmHg systolic and 25 mmHg diastolic within 2 min after IV or 20 min after IM administration of phentolamine is considered a positive test for pheochromocytoma.

Elderly
No dosage adjustment is required.

Children
Use lower dose in children as described above.

Preparation
Phentolamine mesylate for injection (Bedford); Regitine (Ciba): 5 mg vials
**Alpha₂-Adrenergic Agonists**

1. **Clonidine (clonidine, Catapres, Catapres-TTS, Duraclon)**

   **Indications**
   - Hypertension (oral and transdermal formulations)
   - Severe cancer pain not adequately relieved by opioid analgesics alone (continuous epidural infusion)

   **Dosage**
   **Adults**
   - **Oral**—Initiate therapy at 0.05–0.1 mg twice daily. The dose may be increased by 0.1–0.2 mg daily every few days until the desired response is achieved. For rapid blood pressure reduction in patients with severe hypertension, clonidine 0.1–0.2 mg may be given, followed by 0.05–0.2 mg every hour until a total dose of 0.5–0.7 mg or adequate blood pressure control is achieved. The usual dose range of clonidine is 0.2–2.4 mg/d given in two to three divided doses.
   - **Transdermal**—Initiate with one TTS-1 (2.5 mg) patch; increase to the next largest dose every 1–2 weeks for additional control or use a combination of patches. The maximum dosage is two TTS-3 patches. Note: For patients who are already on oral clonidine, it is recommended that the oral dose be continued for 1–2 days after the first transdermal system is applied.
   - **Intravenous**—Initial dose of clonidine for continuous epidural infusion is 30 \( \mu g/\)h. Dosage may be titrated up or down depending on pain relief and occurrence of adverse events. Experience with dosage rate > 40 \( \mu g/\)h is limited.
   - **Elderly**—Initiate at lowest dose and titrate to response.
   - **Children**—Safety and efficacy have not been established.

   **Preparations**
   - Clonidine (generic); Catapres (Boehringer Ingelheim): 0.1, 0.2, 0.3 mg tablets
   - Transdermal System—Catapres-TTS-1, TTS-2, TTS-3 (Boehringer Ingelheim): delivering 0.1, 0.2, and 0.3 mg/d, respectively
   - Injection, as hydrochloride; Duraclon: 100 \( \mu g/mL \) (10 mL vials)

   **Fixed-Dose Combinations for Treatment of Hypertension:**
   - Combipres—clonidine/chlorthalidone combination tablets: 0.1 mg/15 mg; 0.2 mg/15 mg; 0.3 mg/15 mg

2. **Guanabenz (guanabenz, Wytensin)**

   **Indication**
   - Hypertension

   **Dosage**
   **Adults**
   - Initiate therapy at 4 mg twice daily; dose may be adjusted every 1–2 weeks in increments of 4–8 mg/d until adequate blood pressure control is achieved. The maximum daily dose is 32 mg given in two divided doses.

   **Elderly**
   - Initiate at lowest dose and titrate to response.

   **Children**
   - Safety and efficacy have not been established.

   **Preparations**
   - Guanabenz (generic); Wytensin (Wyeth-Ayerst): 4, 8 mg tablets

3. **Guanfacine (guanfacine, Tenex)**

   **Indication**
   - Hypertension

   **Dosage**
   **Adults**
   - Initiate with 1 mg at bedtime to minimize somnolence. The dose may be increased in 1 mg increments every 3–4 weeks until adequate blood pressure control is achieved. The maximum daily dose is 3 mg once daily.

   **Elderly**
   - Initiate at lowest dose and titrate to response.

   **Children**
   - Safety and efficacy have not been established.

   **Preparations**
   - Guanfacine (generic); Tenex (A.H. Robins): 1, 2 mg tablets

4. **Methyldopa (methyldopa, Aldomet)**

   **Indication**
   - Hypertension

   **Dosage**
   **Adults**
   - **Oral**—Initiate therapy at 250 mg two to three times daily for 2 days. The dose is then increased at intervals
of at least 2 days until adequate blood pressure control is achieved. The maximum oral dose is 3 g/d. Note: In patients who are receiving concomitant antihypertensive therapy other than thiazides, limit the initial dosage to 500 mg/d.

Intravenous (methyldopate)—Add the dose, 250-500 mg, to 100 mL of 5% dextrose or give in 5% dextrose in water in a concentration of 10 mg/mL. Administer intravenously over 30-60 min every 6 h if necessary. Maximum dose is 1 g every 6 h.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established. However, there has been some experience with the use of this drug in children and the following dosage regimen has been suggested:

Oral—Dose should be based on body weight. Initially, give 10 mg/kg/d in two to four divided doses. Dosage should be adjusted in daily increments of 10 mg/kg until adequate blood pressure control is achieved. The maximum daily dose is 65 mg/kg or 3 g, whichever is less.

Intravenous—Dose should be based on body weight: 20-40 mg/kg/d in divided doses every 6 h. The maximum daily dose is 65 mg/kg or 3 g, whichever is less.

Preparations
Methyldopa (generic); Aldomet (Merck): 125, 250, 500 mg tablets
Methyldopate HCl injection (generic); Aldomet injection (Merck): 50 mg/mL, 250 mg/5 mL
Aldomet oral Suspension (Merck): 250 mg/5 mL

Fixed-Dose Combinations for Treatment of Hypertension:
Aldoclor (Merck)—methyldopa/chlorothiazide combination tablets: 250 mg/150 mg; 250 mg/250 mg
Aldoril (Merck)—methyldopa/hydrochlorothiazide combination tablets: 250 mg/15 mg; 250 mg/25 mg
Aldoril D (Merck)—methyldopa/hydrochlorothiazide combination tablets: 500 mg/30 mg; 500 mg/50 mg

Angiotensin-Converting Enzyme Inhibitors

1. Benazepril (benazepril, Lotensin)

Indication
Hypertension

Dosage
Adults
The usual initial dose is 10 mg once daily. Dose can be titrated up to 40 mg/d (in one or two divided doses). The maximum dose is 80 mg/d. In renovascular hypertension, renal failure, or in patients in whom diuretics have not been discontinued, the starting dose should be 5 mg.

Elderly
Dose reduction generally not required.

Children
Safety and efficacy have not been established.

Preparations
Lotensin (Novartis Pharmaceuticals); benazepril (generic): 5, 10, 20, 40 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension:
Lotensin HCT—benazepril hydrochloride/hydrochlorothiazide combination tablets: 5 mg/6.25 mg; 10 mg/12.5 mg; 20 mg/12.5 mg; 20 mg/25 mg
Lotrel—amlodipine/benazepril hydrochloride combination capsules: 2.5 mg/10 mg; 5 mg/10 mg; 5 mg/20 mg; 10 mg/20 mg

2. Captopril (captopril, Capoten)

Indications
Hypertension
Heart failure
Left ventricular dysfunction after myocardial infarction
Diabetic nephropathy

Dosage—Hypertension
Adults
Initiate therapy at 12.5-25 mg two to three times per day. Dosage may be increased according to response to 150 mg/d given in three divided doses. In renovascular hypertension, when diuretics have not been discontinued or in renal impairment, initial dose should be 6.25 mg, titrated cautiously according to response.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established. However, the following regimen has been suggested: Initiate with 0.3 mg/kg three times daily. Dosage may be increased in increments of 0.3 mg/kg at intervals of 8-24 h until adequate blood pressure control is achieved.

Dosage—Heart failure
Adults
Initiate at 6.25-12.5 mg 3 times daily and increase dosage according to clinical response. The target dose is 150
mg/d given in three divided doses.

Dosage—Diabetic nephropathy

Adults
25 mg 3 times daily in type 1 diabetes mellitus

Dosage—Left ventricular dysfunction after myocardial infarction

Adults
Initiate with 6.25 mg, followed by 12.5 mg 3 times daily.
Then increase dose to 25 mg three times per day during
the next several days.
A target dose of 50 mg three times per day may be
achieved over the next several weeks.

Preparations

Captopril (generic); Capoten (Bristol-Myers-Squibb):
12.5, 25, 50, 100 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension:

Capozide (generic)—captopril/hydrochlorothiazide
combination tablets: 25 mg/15 mg; 25 mg/25 mg; 50
mg/15 mg; 50 mg/25 mg

3. Enalapril (enalapril, Vasotec) and Enalaprilat
(Enalaprilat, Vasotec I.V.)

Indications
Hypertension
Heart failure
Left ventricular dysfunction-asymptomatic

Dosage—Hypertension

Adults
Oral—Initiate therapy at 5 mg/d; dosage may be increased
to the usual effective maintenance dose of 10-20 mg/d
(maximum, 40 mg daily given in two divided doses). In
renovascular hypertension or in patients in whom diuretics
have not been discontinued 2 to 3 days previously, the
starting dose should be 2.5 mg.

Intravenous—The usual IV dose in hypertension is
1.25 mg every 6 h administered intravenously over a
5-minute period. An initial dose of 0.625 mg over 5 min
should be used in patients who are sodium- and volume-depleted or who have renal impairment (CrCl < 30 mL/
min). Patients should be observed 1 h after dose to watch
for hypotension. If response is inadequate after 1 h, the
0.625 mg dose may be repeated and therapy continued at
a dose of 1.25 mg every 6 h.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established.

Dosage—Heart failure

Adults
Initiate therapy at 2.5 mg by mouth once or twice per day;
dosage may be titrated according to clinical response.
The usual maintenance dose is 5-40 mg/d given in two
divided doses.

Dosage—Asymptomatic left ventricular dysfunction

Adults
Initiate therapy at 2.5 mg by mouth once or twice per
day; dosage may be titrated according to clinical re-
response. The target daily dose is 20 mg/d given in two
divided doses.

Preparations

Enalapril (generic); Vasotec (Merck): 2.5, 5, 10, 20 mg
tablets
Enalaprilat (generic); Vasotec I.V. (Merck): 1.25 mg/mL
intravenous solution

Fixed-Dose Combinations for Treatment of Hypertension:

Vaseretic—enalapril maleate / hydrochlorothiazide com-
bination tablets: 5 mg/12.5 mg; 10 mg/25 mg
Teczem (Aventis)—enalapril maleate/diltiazem male
extended-release combination tablets: 5 mg/180 mg
Lexxel (Astra Zeneca)—enalapril maleate/felodipine
extended-release combination tablets: 5 mg/2.5 mg, 5
mg/5 mg

4. Fosinopril (fosinopril, Monopril)

Indications
Hypertension
Heart failure

Dosage—Hypertension

Adults
Initiate with 10 mg/d; dosage may be increased to the
usual effective dose of 20-40 mg/d. Some patients may
have a further response to 80 mg/d. The total daily dose
may be divided into two if trough effect is inadequate.
In renovascular hypertension or in patients in whom
diuretics have not been discontinued, the starting dose
should be 5 mg/d.

Elderly
Dose reduction generally not required.

Children
Safety and efficacy have not been established.

Dosage—Heart failure

Adults
The usual initial dose is 10 mg/d. The patient should be observed under medical supervision for at least 2 h for the presence of hypotension or orthostasis following the initial dose of fosinopril. An initial dose of 5 mg may be used in patients with moderate to severe renal impairment or in those who have been vigorously diuresed. Dosage should be increased over a period of several weeks to a dose that is maximal and tolerated. The usual effective dosage range is 20-40 mg once daily.

Preparations
Monopril (Bristol-Myers-Squibb); fosinopril (generic): 10, 20, 40 mg tablets

**Fixed-Dose Combinations for Treatment of Hypertension:**
Monopril HCT—fosinopril/hydrochlorothiazide combination tablets: 10 mg/12.5 mg; 20 mg/12.5 mg

5. Lisinopril (Prinivil, Zestril)

**Indications**
Hypertension
Heart failure
Acute myocardial infarction

**Dosage—Hypertension**

**Adults**
Initiate with 10 mg/d; dosage may be adjusted to the usual effective dose of 10–40 mg/d according to response. In patients with hyponatremia, patients with renal impairment (CrCl ≥ 30 mL/min), or in patients in whom diuretics have not been discontinued, the starting dose should be 2.5 mg/d.

**Elderly**
Initiate at lowest dose and titrate to response.

**Children**
Safety and efficacy have not been established.

**Dosage—Heart failure**

**Adults**
The usual initial dose is 5 mg/d administered under close medical observation, especially in patients with low blood pressure. The usual effective dosage range is 5-20 mg once daily.

**Dosage—Acute myocardial infarction**

**Adults**
In hemodynamically stable patients, give 5 mg of lisinopril within 24 h of the onset of acute MI. Another dose of 5 mg may be given 24 h later, followed by 10 mg at 48 h, then 10 mg once daily thereafter for 6 weeks. Patients should receive, as appropriate, the standard recommended treatments, such as thrombolytics, aspirin, and beta-blockers. Patients with a low systolic blood pressure (≥ 120 mmHg) when treatment is initiated or during the first 3 days after the infarct should be given a lower dose of 2.5 mg. If hypotension occurs (systolic blood pressure ≥ 100 mmHg), a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if necessary.

Preparations
Lisinopril (generic); Prinivil (Merck): 2.5, 5, 10, 20, 40 mg tablets
Lisinopril (generic); Zestril (Astra Zeneca): 2.5, 5, 10, 20, 30, 40 mg tablets

**Fixed-Dose Combinations for Treatment of Hypertension:**
Prinzide—lisinopril/hydrochlorothiazide combination tablets: 10 mg/12.5 mg; 20 mg/12.5 mg; 20 mg/25 mg
Zestoretic—lisinopril/hydrochlorothiazide combination tablets: 10 mg/12.5 mg; 20 mg/12.5 mg; 20 mg/25 mg

6. Moexipril (Univasc)

**Indication**
Hypertension

**Dosage**

**Adults**
The usual initial dose is 7.5 mg once daily in patients not receiving diuretics. Dosage may be increased gradually to a maximum of 30 mg/d (given in one or two divided doses) according to response. In renovascular hypertension, or in patients in whom diuretics have not been discontinued, the recommended starting dose is 3.75 mg once daily given with close medical supervision. Similarly, for patients whose creatinine clearance is ≤ 40 mL/min/1.73², the recommended initial dose is 3.75 mg once daily given with caution. Note: Moexipril should be taken on an empty stomach, preferably 1 h prior to a meal.

**Elderly**
Initiate at lowest dose and titrate to response.

**Children**
Safety and efficacy have not been established.

**Preparations**
Univasc (Schwarz Pharma): 7.5, 15 mg tablets

**Fixed-Dose Combinations for Treatment of Hypertension:**
Uniretic—moexipril hydrochloride/hydrochlorothiazide combination tablets: 7.5 mg/12.5 mg; 15 mg/25 mg

7. Perindopril (Aceon)

**Indication**
Hypertension
Stable coronary artery disease—to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction

Dosage

Adults

Hypertension
The usual initial dose is 4 mg once daily in patients not receiving other antihypertensives. This dose may be titrated up to a maximum of 16 mg/d based on clinical response. The usual maintenance dose is 4-8 mg once daily. For patients older than 70 years and for patients with CrCl of 30-60 mL/min, initiate with 2 mg once daily and titrate according to response to a maximum of 8 mg/d. The safety and efficacy of perindopril have not been established for patients with CrCl of < 30 mL/min.

Stable coronary artery disease
The usual starting dose is 4 mg once daily for 2 weeks. The dose can then be increased as tolerated to a maintenance dose of 8 mg once daily. In elderly patients (> 70 yrs), initiate with a lower dose of 2 mg daily for the first week, followed by 4 mg once daily in the second week and 8 mg once daily for maintenance dose if tolerated.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established.

Preparations
Aceon (Solvay): 2, 4, 8 mg tablets

8. Quinapril (quinapril, Accupril)

Indications
Hypertension
Heart failure

Dosage—Hypertension

Adults
The usual initial dose is 10 or 20 mg once daily in patients not receiving diuretics. This dose may be increased, at intervals of at least 2 weeks, to a maximum of 80 mg/d (given as a single dose or in two divided doses) according to response. In renovascular hypertension, or in patients in whom diuretics have not been discontinued, the starting dose should be 2.5-5 mg/d. For patients with creatinine clearance of 31-60 mL/min, the initial dose should be 5 mg daily. For patients with creatinine clearance of 10-30 mL/min, the initial dose should be 2.5 mg/d.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established.

Dosage—Heart failure

Adults
The usual initial dose is 5 mg twice daily titrated according to clinical response. The usual maintenance dose is 20-40 mg/d in two divided doses.

Preparations
Accupril (Parke-Davis/Pfizer); quinapril (generic): 5, 10, 20, 40 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension:
Accuretic—quinapril/hydrochlorothiazide combination tablets: 10 mg/12.5 mg; 20 mg/12.5 mg; 20 mg/25 mg

9. Ramipril (ramipril, Altace)

Indications
Hypertension
Heart failure post myocardial infarction
Reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes

Dosage—Hypertension

Adults
The usual initial dose is 2.5 mg/d; this dose may be increased gradually to a maximum of 20 mg/d (given as a single daily dose or in two equally divided doses) according to response. In renovascular hypertension or in patients in whom diuretics have not been discontinued, the starting dose should be 1.25 mg/d. For patients with creatinine clearance of < 40 mL/min/1.73 m², the initial dose should be 1.25 mg/d. Dosage may be titrated upward until blood pressure is controlled or to a maximum of 5 mg/d.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established.

Dosage—Heart failure post myocardial infarction

Adults
The usual initial dose is 2.5 mg twice daily. Patients who become hypotensive at this dose may be switched to 1.25 mg twice daily, but all patients should then be titrated toward a target dose of 5 mg twice daily if tolerated. For patients with creatinine clearance of < 40 mL/min/1.73 m², the initial dose should be 1.25 mg daily. Dosage may then be increased to 1.25 mg twice daily up to a maximum dose of 2.5 mg twice daily, depending on clinical response and tolerance.
Dosage—Reduction in risk of MI, stroke, and death from cardiovascular causes

**Adults**
Initiate at 2.5 mg once daily for one week, then increase dose to 5 mg once daily for the next 3 weeks, then increase dose as tolerated to 10 mg once daily (may be given as divided dose).

**Preparations**
Altace (Monarch); ramipril (generic): 1.25, 2.5, 5, 10 mg capsules

10. Trandolapril (Mavik)

**Indications**
Hypertension
Heart failure postmyocardial infarction
Left ventricular dysfunction postmyocardial infarction

**Dosage—Hypertension**

**Adults**
The usual initial dose is 1 mg/d in nonblack patients and 2 mg/d in black patients. Dosage may be increased, according to response, at intervals of \( \leq 1 \) week to a maximum of 8 mg/d. Most patients have required dosages of 2-4 mg/d. There is little experience with doses more than 8 mg/d. Patients inadequately treated with once-daily dosing at 4 mg may be treated with twice-daily dosing. In renovascular hypertension or in patients in whom diuretics have not been discontinued, the starting dose should be 0.5 mg/d. Similarly, for patients with a creatinine clearance < 30 mL/min or with hepatic cirrhosis, the recommended initial dose is 0.5 mg/d.

**Elderly**
Initiate at lowest dose and titrate to response.

**Children**
Safety and efficacy have not been established.

**Preparations**
Mavik (Abbott): 1, 2, 4 mg tablets

**Fixed-Dose Combinations for Treatment of Hypertension:**
Tarka—trandolapril/verapamil hydrochloride extended release tablets: 2 mg/180 mg; 1 mg/240 mg; 2 mg/240 mg; 4 mg/240 mg

**Angiotensin-II Receptor Blockers**

1. Candesartan (Atacand)

**Indication**
Hypertension
Heart failure

**Dosage**

**Adults**

**Hypertension**
The usual initial dose is 16 mg once daily. Dosage may be titrated within the range of 8-32 mg/d according to response. Hydrochlorothiazide has an additive effect.

**Heart failure**
Initiate with 4 mg once daily. The dose should be doubled at approximately 2-week intervals as tolerated. The target dose is 32 mg daily.

**Elderly**
No initial dosage adjustment is required.

**Children**
Safety and efficacy have not been established.

**Preparations**
Atacand (AstraZeneca): 4, 8, 16, 32 mg tablets

**Fixed-Dose Combinations for Treatment of Hypertension:**
Atacand HCT—candesartan cilexetil/hydrochlorothiazide combination tablets: 16 mg/12.5 mg; 32 mg/12.5 mg

2. Eprosartan (Teveten)

**Indication**
Hypertension

**Dosage**

**Adults**
The usual initial dose is 600 mg once daily. Dosage may be titrated within the range of 400-800 mg/d given in one or two divided doses.

**Elderly**
No initial dosage adjustment is required.

**Children**
Safety and efficacy have not been established.

**Preparations**
Teveten (Unimed): 400, 600 mg tablets

*Fixed-Dose Combinations for Treatment of Hypertension:*
Teveten HCT–eprosartan mesylate/hydrochlorothiazide combination tablets: 600 mg/12.5 mg, 600 mg/25 mg

### 3. Irbesartan (Avapro)

**Indications**
Hypertension type 2 diabetes mellitus with nephropathy to prevent end-stage renal disease

**Dosage**

**Adults**
The usual initial dose is 150 mg once daily. Dosage may be titrated to 300 mg once daily according to response in hypertensive patients. Hydrochlorothiazide has an additive effect. In patients with diabetic nephropathy, the target maintenance dose is 300 mg once daily.

**Elderly**
No initial dosage adjustment is required.

**Children**
Safety and efficacy have not been established.

**Preparations**
Avapro (Bristol-Myers Squibb/Sanofi): 75, 150, 300 mg tablets

*Fixed-Dose Combinations for Treatment of Hypertension:*
Avalide—irbesartan/hydrochlorothiazide: 150 mg/12.5 mg, 300 mg/12.5 mg

### 4. Losartan (losartan, Cozaar)

**Indications**
Hypertension
Type 2 diabetes mellitus with nephropathy to prevent end-stage renal disease
Reduction of risk of stroke in patients with hypertension and left ventricular hypertrophy. However, there is evidence that this benefit does not apply to black patients.

**Dosage**

**Adults**
The usual recommended initial dose is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. If further reduction in blood pressure is required after 2 weeks of therapy, the dose may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect.

For hypertensive patients with left ventricular hypertrophy, the usual starting dose is 50 mg once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of losartan should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response.

**Elderly**
No initial dosage adjustment is required.

**Children**
Safety and efficacy have not been established.

**Preparations**
Cozaar (Merck): 25, 50, 100 mg tablets

*Fixed-Dose Combinations for Treatment of Hypertension:*
Hyzaar—losartan/hydrochlorothiazide: 50 mg/12.5 mg, 100 mg/25 mg

### 5. Olmesartan (Benicar)

**Indication**
Hypertension

**Dosage**

**Adults**
The usual recommended initial dose is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. If further reduction in blood pressure is required after 2 weeks of therapy, the dose may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect.

Twice-daily dosing offers no advantage over the same total dose given once daily.

**Elderly**
No initial dosage adjustment is required.

**Children**
Safety and efficacy have not been established.

**Preparations**
Benicar (Sankyo): 5, 20, and 40 mg tablets

*Fixed-Dose Combinations for Treatment of Hypertension:*
Azor: amlodipine/olmesartan: 5 mg/20 mg, 5 mg/40 mg, 10 mg/20 mg, 10 mg/40 mg
Benicar HCT: hydrochlorothiazide/olmesartan: 12.5 mg/20 mg, 12.5 mg/40 mg, 25 mg/40 mg
Tribenzor: amlodipine/HCTZ/olmesartan: 5 mg/12.5 mg/20 mg; 5 mg/12.5 mg/40 mg; 5 mg/25 mg/40 mg; 10 mg/12.5 mg/40 mg; 10 mg/25 mg/40 mg
6. Telmisartan (Micardis)

**Indication**

Hypertension

**Dosage**

*Adults*

The usual initial dose is 40 mg once daily. Dosage may be titrated within the range of 20-80 mg/d according to response. Initiate treatment under close medical supervision for patients with hepatic impairment or biliary obstructive disorders. If intravascular volume depletion is present, correct this condition prior to initiation of telmisartan and monitor closely.

*Elderly*

No initial dosage adjustment is required.

*Children*

Safety and efficacy have not been established.

**Preparations**

Micardis (Boehringer Ingelheim): 40, 80 mg tablets

*Fixed-Dose Combinations for Treatment of Hypertension:*

Micardis HCT—telmisartan/hydrochlorothiazide: 40 mg/12.5 mg; 80 mg/12.5 mg

Twynsta: telmisartan/amlodipine: 40 mg/5 mg; 40 mg/10 mg; 80 mg/5 mg; 80 mg/10 mg

7. Valsartan (Diovan)

**Indication**

Hypertension

Heart failure

Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

**Dosage**

*Adults*

Hypertension

The usual initial dose is 80 mg once daily. Dosage may be increased to 160-320 mg once daily according to response.

*Heart failure*

The usual initial dose is 40 mg twice daily. Dosage should be titrated to 80 mg twice daily and then to 160 mg twice daily as tolerated. Maximum daily dose administered in clinical trials was 320 mg in divided doses.

*Post myocardial infarction*

Valsartan may be started as early as 12 hours after a myocardial infarction. The recommended starting dose is 20 mg twice daily. Patients may be up titrated within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily as tolerated.

*Elderly*

No initial dosage adjustment is required.

*Children*

Safety and efficacy have not been established.

**Preparations**

Diovan (Novartis): 40, 80, 160, 320 mg tablets

*Fixed-Dose Combinations for Treatment of Hypertension:*

Diovan HCT: valsartan/hydrochlorothiazide: 80 mg/12.5 mg; 160 mg/12.5 mg; 320 mg/12.5 mg; 160 mg/25 mg; 320 mg/25 mg.

Exforge: amlodipine/valsartan: 5 mg/160 mg, 5 mg/320 mg, 10 mg/160 mg, 10 mg/320 mg

Exforge HCT: amlodipine/hydrochlorothiazide/valsartan: 5 mg/12.5 mg/160 mg, 5 mg/25 mg/160 mg, 10 mg/12.5 mg/160 mg, 10 mg/25 mg/160 mg, 10 mg/25 mg/320 mg.

Valturna: aliskiren/valsartan: 150 mg/160 mg, 300 mg/320 mg

**Antianginal Agent**

Ranolazine (Ranexa)

**Indication**

Chronic angina pectoris

**Dosage**

*Adults*

The usual initial dose is 500 mg orally twice daily. The dose may be increased to 1000 mg orally twice daily according to response. In patients receiving concomitant therapy with diltiazem, verapamil, erythromycin, fluconazole, or other moderate CYP3A inhibitors, limit the maximum dose to 500 mg twice daily. In patients receiving P-gp inhibitors, such as cyclosporine, the dose of ranolazine may need to be lowered based on clinical response.

*Elderly*

Use normal adult dose with caution. Plasma level increases up to 50% in patients with varying degrees of renal impairment.

*Children*

Safety and efficacy have not been established.

**Preparations**

Ranexa (CV Therapeutics): 500 and 1000 mg extended release tablets
Antiarrhythmic Agents Class IA

1. Disopyramide (disopyramide phosphate, Norpace)

Indications
- Life-threatening ventricular arrhythmias
- Supraventricular arrhythmias (unlabeled use)

Dosage

Adults

The usual loading dose is 300-400 mg by mouth followed by a maintenance regimen of 400-800 mg by mouth daily; the maximum dose is 1.6 g/d. Daily doses can be given in 4 divided doses every 6 hours with non-sustained-release products, or in two equally divided doses every 12 hours with controlled- or extended-release products. For patients < 50 kg, or with hepatic or renal impairment, the loading dose is 150-200 mg by mouth followed by 400 mg/d in two or four divided doses, depending on the dosage form used. The controlled or extended release formulation of disopyramide should not be used initially if rapid plasma concentrations are desired and is not recommended for patients with severe renal impairment.

Maintenance dose (with non-sustained-release products) in patients with severe renal impairment:

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-40</td>
<td>100 mg q 8 h</td>
</tr>
<tr>
<td>15-30</td>
<td>100 mg q 12 h</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>100 mg q 24 h</td>
</tr>
</tbody>
</table>

Elderly

May be more sensitive to adult dose. Dose reduction is required.

Children

Dosing is age-specific. The total daily dose should be given in equally divided doses q 6 h or at intervals according to individual requirements. Pediatric patients should be hospitalized during initial period of therapy to allow close monitoring until maintenance dose is established.

<table>
<thead>
<tr>
<th>Age</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 y</td>
<td>10-30 mg/kg/d</td>
</tr>
<tr>
<td>1-4 y</td>
<td>10-20 mg/kg/d</td>
</tr>
<tr>
<td>4-12 y</td>
<td>10-15 mg/kg/d</td>
</tr>
<tr>
<td>12-18 y</td>
<td>6-15 mg/kg/d</td>
</tr>
</tbody>
</table>

Preparations

Disopyramide phosphate (generic); Norpace (Pharmacia & Upjohn): 100, 150 mg capsules
Disopyramide phosphate extended release (generic); Norpace CR (Pharmacia & Upjohn): 100, 150 mg extended-release capsules

2. Procainamide (procainamide HCl, Pronestyl, Pronestyl SR, Procanbid)

Indications

- Ventricular arrhythmias
- Supraventricular arrhythmias (unlabeled use)
- Atrial fibrillation/atrial flutter (unlabeled use)

Dosage

Adults

Supraventricular arrhythmias

IV: 15-17 mg/kg over 25-60 min, then continuous infusion of 1-4 mg/min (or can convert to oral therapy after initial loading dose).

Oral: The usual dose is 50 mg/kg/d; for immediate release, give in divided doses every 3-6 hours; for extended release preparations (Pronestyl-SR, procainamide HCl extended release), give in divided doses every 6 hours; for extended release (Procanbid), give in divided doses every 12 hours.

Refractory pulseless ventricular tachycardia/ventricular fibrillation

IV: 15-17 mg/kg infused at 30 mg/min (maximum total dose is 17 mg/kg); if stable rhythm is achieved, continuous infusion at 1-4 mg/min may be initiated; convert patient to oral therapy when hemodynamically stable and able to take oral medications.

Stable ventricular tachycardia

IV: 20 mg/min infusion given until arrhythmia suppressed, hypotension occurs, QRS widens by > 50%, or total dose of 17 mg/kg is administered; if stable rhythm is achieved, can initiate continuous infusion at 1-4 mg/min; convert patient to oral therapy when hemodynamically stable and able to take oral medications.

Oral: The usual dose is 50 mg/kg/d; for immediate release, give in divided doses every 3-6 hours; for extended release formulations (Pronestyl-SR, procainamide HCl extended release), give in divided doses every 6 hours; for extended release (Procanbid), give in divided doses every 12 hours.

Elderly

Dosage adjustment is required for reduced renal function and other comorbid conditions (eg, CHF).

Children

Safety and efficacy have not been established. IM injection is not recommended.

Preparations

Capsules or tablets, immediate release (procainamide, Pronestyl)-250, 375, 500 mg
Tablets, extended release (Procainamide HCl extended...
release, Pronestyl SR: dosed every 6 hours)-250 mg, 500 mg, 750 mg, 1000 mg.
Tablets, extended release (Procanbid: dosed every 12 hours)-500 mg, 1000 mg
Injection-100 mg/mL, 500 mg/mL

3. Quinidine (quinidine gluconate, Quinaglute, Dura-Tabs, quinidine sulfate, Quinidex Extentabs)

Indications
Paroxysmal supraventricular tachycardia
Ventricular tachycardia
Atrial fibrillation/flutter
Junctional tachycardia
Premature atrial contractions
Atrial tachycardia

Dosage
Adults
The dosage of quinidine is expressed in terms of the salt: 267 mg of quinidine gluconate or 275 mg of quinidine polygalacturonate is equivalent to 200 mg of quinidine sulfate. The following dosages are expressed in terms of the respective salts. Because of the increased risk of adverse effects, loading doses of quinidine are no longer recommended.

Quinidine sulfate:
*Maintenance of sinus rhythm in patients with atrial fibrillation or flutter*: 200-400 mg by mouth every 6-8 hours or 300-600 mg extended-release tablets by mouth every 8-12 hours.
*Suppression of ventricular tachycardia after cardioversion*: 200-400 mg by mouth every 6 hours or 300-600 mg extended-release tablets by mouth every 8-12 hours.

Quinidine polygalacturonate:
The usual maintenance dose is 275 mg by mouth every 8-12 hours.

Quinidine gluconate:
Oral: 324-648 mg by mouth every 8-12 hours
IV: 5-10 mg/kg at an initial rate up to 0.25 mg/kg/min. There is a high risk for hypotension. Monitor ECG for widening of QRS and prolongation of QT intervals, disappearance of the P wave, symptomatic bradycardia, or tachycardia.

*Note*: Dosage should be adjusted in patients with renal or hepatic impairment.

Elderly
Initiate with lowest dose and titrate to response.

Children
Safety and efficacy have not been established. However, quinidine gluconate used to treat malaria in children has shown an efficacy and safety profile comparable to adults.

Preparations
Tablets (quinidine sulfate)-200, 300 mg
Tablets, quinidine sulfate sustained release (Quinidex Extentabs)-300 mg
Tablets, quinidine gluconate sustained release (Quinaglute Dura-Tabs)-324 mg
Tablets, quinidine polygalacturonate (Cardioquin)-275 mg
Injection (Quinidine gluconate)-80 mg/mL

Class IB

1. Lidocaine (lidocaine HCl, Xylocaine)

Indication
Acute treatment of ventricular tachyarrhythmias (intra-venous formulation)

Dosage
Adults
*Pulseless ventricular tachycardia/ventricular fibrillation*: 1-1.5 mg/kg IV push, may give additional 0.5-0.75 mg/kg IV push in 3-5 min if initial response is inadequate, up to a maximum total dose of 3 mg/kg.

*Stable ventricular tachycardia (left ventricular ejection fraction > 40%)*
1-1.5 mg/kg IV push; may give additional 0.5-0.75 mg/kg IV push in 3-5 min if initial response is inadequate, up to a maximum total dose of 3 mg/kg.

*Stable ventricular tachycardia (left ventricular ejection fraction ≤ 40%)*
0.50-0.75 mg/kg IV push; may repeat every 5-10 min if initial response is inadequate, up to a maximum total dose of 3 mg/kg.

*Maintenance infusion*
1-4 mg/min; a slower infusion rate (1-2 mg/min) should be used for elderly patients, patients < 50 kg, or those with heart failure or hepatic impairment. Lidocaine may also be administered via an endotracheal tube at 2-2.5 times the IV dose.

Elderly
Dose reduction is required due to reduction in patients’ capacity to metabolize the drug.

Children
Safety and effectiveness have not been established; reduce
dosage when used in children.

Preparations
For direct IV injection-10, 20 mg/mL
For preparation of IV continuous infusion-40, 100, 200 mg/mL
For IV infusion-2, 4, 8 mg/mL in 5% dextrose

2. Mexiletine (mexiletine HCl, Mexitil)

Indication
Life-threatening ventricular arrhythmias

Dosage
Adults
Initiate at 200 mg po q 8 h; increase or decrease dosage in increments or decrements of 50-100 mg/dose every 2-3 days as needed. For rapid control of ventricular arrhythmias, loading dose of 400 mg may be administered followed by a maintenance dose of 200 mg po q 8 h. Limit to 1200 mg/d when given q 8 h (ie, 400 mg/dose) or 900 mg/d when given q 12 h (ie, 450 mg/dose).

Patients with CHF or hepatic impairment may require dose reduction. Dosage adjustments should be made no more frequently than every 2-3 days. Some patients may tolerate twice-daily dosing. For patients adequately maintained on a dose of 300 mg or less q 8 h, total daily dose may be given divided q 12 h. Patients not adequately controlled by dosing q 8 h may respond to dosing q 6 h.

Elderly
Dosage adjustment is required due to reduction in patients' capacity to metabolize the drug.

Children
Safety and effectiveness have not been established.

Preparations
Mexiletine (generic); Mexitil (Boehringer Ingelheim): 150, 200, 250 mg capsules

3. Tocainide (Tonocard)

Indication
Life-threatening ventricular arrhythmias

Dosage
Adults
Maintenance dose 400 mg po q 8 h. Usual maintenance dose is 1.2-1.8 g daily. Maximum dose is 2.4 g/d in divided doses. Reduce initial maintenance dose by 50% in patients with hepatic dysfunction. In patients with CrCl of 10-30 mL/min, reduce the dose by 25%. In patients with CrCl < 10 mL/min, reduce the dose by 50%.

Elderly
Dosage adjustment is required due to reduction in patients' capacity to eliminate the drug.

Children
Safety and effectiveness have not been established.

Preparations
Tonocard (Astra Zeneca): 400, 600 mg tablets

Class IC

1. Flecainide (Tambocor)

Indications
Life-threatening ventricular arrhythmias
Supraventricular tachyarrhythmias

Dosage
Adults
For sustained ventricular tachycardia, initiate at 100 mg q 12 h; increase dosage in increments of 50 mg twice daily every 4 days as needed. The usual maintenance dose is 150 mg q 12 h; limit to 400 mg/d. For patients with paroxysmal supraventricular tachycardia and patients with paroxysmal atrial fibrillation/atrial flutter, initiate at 50 mg q 12 h for the maintenance of sinus rhythm. Increase dosage in increments of 50 mg twice daily every 4 days as needed; limit to 300 mg/d.

For patients with severe renal impairment (CrCl < 35 mL/min), reduce initial dose to 50 mg q 12 h; increase doses at intervals of > 4 days if needed and monitor plasma levels frequently to guide dosage adjustment.

Elderly
Lower doses are recommended due to age-related decline in clearance.

Children
Safety and effectiveness have not been established.

Preparations
Tambocor (3M Pharmaceuticals): 50, 100, 150 mg tablets

2. Moricizine (Ethmozine)

Indication
Life-threatening ventricular arrhythmias

Dosage
Adults
Initiate at 200 mg po q 8 h; increase in increments of
150 mg daily every 3 d if needed. The usual maintenance dose is 200-300 mg q 8 h. Maintenance dose should not exceed 600 mg/d in patients with renal or hepatic impairment.

**Elderly**
No dosage adjustment is needed.

**Children**
Safety and effectiveness have not been established.

**Preparations**
Ethmazine (Roberts): 200, 250, 300 mg tablets

### 3. Propafenone (propafenone, Rythmol, Rythmol SR)

**Indications**
Life-threatening ventricular arrhythmias
Maintenance of sinus rhythm in patients with symptomatic atrial fibrillation (Rythmol SR)

**Dosage**

**Adults**

**Immediate release (for ventricular and supraventricular arrhythmias)**
Initiate at 150 mg po q 8 h; increase to 225 mg po q 8 h after 3-4 d if needed. The maximum dose is 300 mg po q 8 h. For conversion to sinus rhythm in patients with atrial fibrillation/flutter, a single oral loading dose of 450-600 mg may be used.

**Sustained release (for maintenance of sinus rhythm in patients with atrial fibrillation)**
Initiate at 225 mg po q 12 h; increase dose to 325 mg po q 12 h after 5 d if needed. Maximum dose is 425 mg po q 12 h.

**Elderly**
Lower doses may be required due to reduction in patients’ capacity to metabolize the drug.

**Children**
Safety and effectiveness have not been established.

**Preparations**
Tablets, immediate release (propafenone, Rythmol)-150, 225, 300 mg
Capsules, sustained release (Rythmol SR)-225 mg, 325 mg, 425 mg

### Class II Beta-Adrenergic Blockers

**Class III**

1. Amiodarone (amiodarone, Cordarone, Pacerone)

**Indications**
Life-threatening ventricular arrhythmias (ventricular fibrillation or hemodynamically unstable ventricular tachycardia)
Supraventricular arrhythmias (not FDA-approved)

**Dosage**

**Adults**

**Atrial fibrillation**
IV: 5-7 mg/kg over 30-60 min, then 1200-1800 mg/d given via continuous infusion; convert to oral therapy when hemodynamically stable and able to take oral medications.

Oral: 800-1200 mg/d in 2-3 divided doses for 1 week until patient receives about 10 g total, then 200 mg po daily.

**Pulseless ventricular tachycardia/ventricular fibrillation**
IV: 300 mg IV push (can be diluted in or followed by 10-20 mL saline); may repeat with 150 mg IV push every 3-5 min if necessary (can be diluted in or followed by 10-20 mL saline); if stable rhythm is achieved, can initiate continuous infusion at 1 mg/min for 6 h, then 0.5 mg/min (maximum dose is 2.2 g/24 h); convert to oral therapy when hemodynamically stable and able to take oral medications.

**Stable ventricular tachycardia**
IV: 150 mg (diluted in 100 mL of 5% dextrose in water or saline) over 10 min; may repeat dose every 10 min if necessary for breakthrough ventricular tachycardia; if stable rhythm is achieved, can initiate continuous infusion at 1 mg/min for 6 h, then 0.5 mg/min (maximum dose is 2.2 g/24 h); convert patient to oral therapy when hemodynamically stable and able to take oral medications.

Oral: 800-1600 mg/d in 2-3 divided doses for 1 week until patient receives about 15 g total, then 300-400 mg po daily.

**Elderly**
No dosage adjustment is needed

**Children**
Safety and effectiveness have not been established. Limited data suggest that amiodarone may be useful in the management of refractory supraventricular or ventricular arrhythmias in selected cases.

**Preparations**
Amiodarone (generic); Cordarone (Wyeth-Ayerst); Pac-
erone (Upsher Smith): 200 mg tablets
Cordarone IV (Wyeth-Ayerst): 3 mL ampule, 50 mg/mL

2. Dofetilide (Tikosyn)

Indications
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation/flutter

Dosage
Adults
The usual recommended dose of dofetilide is 500 µg twice daily. The dose of dofetilide must be individualized according to creatinine clearance and QTc. Prior to administration of the first dose, the QTc must be determined using an average of 5-10 beats. If the QTc is greater than 440 msec (500 msec in patients with ventricular conduction abnormalities), dofetilide is contraindicated. If heart rate is < 60 beats per minute, QT interval should be used. There are no data on use of dofetilide when the heart rate is < 50 beats per minute.

The initial dose of dofetilide is determined as follows:

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dofetilide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 mL/min</td>
<td>500 µg twice daily</td>
</tr>
<tr>
<td>40-60 mL/min</td>
<td>250 µg twice daily</td>
</tr>
<tr>
<td>20 to &lt; 40 mL/min</td>
<td>125 µg twice daily</td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>Dofetilide is contraindicated in these patients</td>
</tr>
</tbody>
</table>

At 2-3 h after administering the first dose of dofetilide, determine the QTc. If the QTc has increased by more than 15% when compared to the baseline, or if the QTc is greater than 500 msec (550 msec in patients with ventricular conduction abnormalities), subsequent dosing should be adjusted as follows:

<table>
<thead>
<tr>
<th>If the Starting Dose Based on Creatinine Clearance Is:</th>
<th>Then the Adjusted Dose (for QTc Prolongation) Is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 µg twice daily</td>
<td>250 µg twice daily</td>
</tr>
<tr>
<td>250 µg twice daily</td>
<td>125 µg twice daily</td>
</tr>
<tr>
<td>125 µg twice daily</td>
<td>125 µg once a day</td>
</tr>
</tbody>
</table>

At 2-3 h after each subsequent dose of dofetilide, determine the QTc (for in-hospital doses 2nd to 5th). No further down titration of dofetilide based on QTc is recommended. If the QTc interval exceeds 500 msec (550 msec in patients with ventricular conduction abnormalities) at any time after the first dosage adjustment, dofetilide should be discontinued. Consult dofetilide package insert for complete prescribing information.

Elderly
Dosage adjustment may be required based on renal function.

3. Dronedarone (Multaq)

Indication
Reduction in the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation or atrial flutter, with a recent episode of atrial fibrillation/atrial flutter and associated cardiovascular risk factors, who are in sinus rhythm, or who will be cardioverted.

Dosage
Adults
The recommended dosage is 400 mg twice daily. Dronedarone should be taken as one tablet with the morning meal and one tablet with the evening meal. Note: Treatment with class I or III antiarrhythmics (eg, amiodarone, flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol) or drugs that are strong inhibitors of CYP3A (eg, ketoconazole) must be stopped before dronedarone is initiated.

Elderly
Use normal adult dose.

Children
Safety and efficacy have not been established.

Preparations
Multaq (Sanofi-aventis): 400 mg film-coated tablets.

4. Ibutilide (Corvert)

Indications
Acute termination of recent-onset atrial fibrillation or atrial flutter

Dosage
Adults
For patients who weigh ≥ 60 kg, give 1 mg intravenously over 10 min. For patients who weigh < 60 kg, give 0.01 mg/kg intravenously over 10 min. If the arrhythmia does not terminate within 10 min after the end of the initial infusion, a second 10-min infusion of equal strength may be administered 10 min after completion of the first infusion.

Elderly
No dosage adjustment is required.

Children
Safety and effectiveness have not been established.

Preparations
Ibutilide (Corvex): 0.5 mg film-coated tablets.
Appendix 2

Children
Safety and effectiveness have not been established.

Preparation
Corvert (Pharmacia and Upjohn): 0.1 mg/mL, 10 mL vials

5. Sotalol (sotalol, Betapace, Betapace AF, Sorine)

Indications
Documented life-threatening ventricular arrhythmias (Betapace, sotalol, Sorine)
Maintenance of sinus rhythm in patients with symptomatic atrial fibrillation or atrial flutter who are currently in sinus rhythm (Betapace AF)
Substitute IV sotalol for oral sotalol in patients who are unable to take sotalol orally

Dosage
Adults

Atrial fibrillation (Betapace AF)
Initiate at 80 mg po twice daily; increase at 3 d intervals to a maximum dose of 160 mg po twice daily, if necessary. Dosing interval must be adjusted in patients with renal insufficiency:

<table>
<thead>
<tr>
<th>CrCl, mL/min</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-60</td>
<td>Every 24 h</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Life-threatening ventricular arrhythmias (sotalol, Betapace, Sorine)
Initiate at 80 mg po twice daily; increase at 2-3 d intervals to a maximum dose of 320 mg po twice daily if necessary; higher doses (480-640 mg/d) should be reserved for patients with drug-refractory ventricular arrhythmias. Dosing interval must be adjusted in patients with renal insufficiency:

<table>
<thead>
<tr>
<th>CrCl, mL/min</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-60</td>
<td>Every 24 h</td>
</tr>
<tr>
<td>10-29</td>
<td>Every 36-48 h</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Individualize dose</td>
</tr>
</tbody>
</table>

Intravenous sotalol must be diluted and infused over 5 hours at a constant rate. The intravenous dose is approximately equal to the oral dose and administered at the same dosing frequency. Intravenous sotalol 75 mg is approximately equal to oral sotalol 80 mg. The initial dose is 75 mg administered twice daily. If CrCl is 40 to 60 mL/min, administer once daily. If CrCl is less than 40 mL/min, intravenous sotalol is not recommended. The dose can be up-titrated to a maximum of 150 mg twice daily under close ECG and QT interval monitoring.

Elderly
Dosage adjustment may be required based on renal function.

Children
Safety and effectiveness have not been established.

Preparations
Tablets (sotalol, Betapace, Sorine): 80, 120, 160, 240 mg
Tablets (Betapace AF): 80, 120, 160 mg
Intravenous sotalol (Academic Pharmaceutical): 150 mg sotalol hydrochloride in 10 mL vial (15 mg/mL) (Must be diluted)

Other

1. Adenosine (Adenocard)

Indications
Conversion to sinus rhythm of paroxysmal supraventricular tachyarrhythmias, including that associated with Wolff-Parkinson-White syndrome

Dosage
Adults

Initiate with 6 mg as a rapid intravenous bolus (administered over 1-2 s). If the first dose does not result in elimination of the supraventricular tachycardia within 1-2 min, give 12 mg as a rapid intravenous bolus. Repeat the 12-mg dose a second time if necessary.

Note: Adenosine injection should be given as a rapid bolus by the peripheral intravenous route. To assure that the medication reaches the systemic circulation, adenosine should be administered either directly into a vein or, if given into an intravenous line, it should be given as close to the patient as possible and followed by a rapid saline flush.

Elderly
Dosage adjustment is not required.

Children
Safety and effectiveness have not been established.

Preparations
Adenocard (Fujisawa): 3 mg/mL, 2 and 5 mL vials

2. Atropine (atropine sulfate)

Indications
Symptomatic sinus bradycardia (intravenous formulation)
Therapeutic Use of Available Cardiovascular Drugs

Treatment of ventricular asystole during CPR (intravenous formulation)

Dosage
Adults

Treatment of bradycardia in advanced cardiac life support during CPR: Usual adult dose is 0.5-1 mg given intravenously; this dose may be repeated every 3-5 min until the desired heart rate is achieved. The maximum total dose is 0.04 mg/kg.

Treatment of ventricular asystole during CPR: 1 mg intravenously; this dose may be repeated in 3-5 min if needed. The total dose usually should not exceed 2.5 mg (0.04 mg/kg) in patients with severe bradycardia or ventricular asystole because a 2.5-mg dose generally results in complete vagal blockade.

Note: When atropine sulfate cannot be administered intravenously for advanced cardiac life support during CPR, the drug may be administered via an endotracheal tube. Some experts recommend that doses administered via endotracheal tube should be 2-2.5 times those administered intravenously and generally should be diluted in 10 mL of 0.9% sodium chloride or sterile water for adults and in 1-2 mL of 0.9% sodium chloride for children. Such dilution may enhance tracheobronchial distribution and absorption of atropine. When atropine sulfate is given intravenously, it should generally be given rapidly because slow injection of the drug may cause a paradoxical slowing of the heart rate.

Elderly
Use usual dose with caution.

Children
Advanced cardiac life support during CPR: 0.02 mg/kg intravenously, with a minimum pediatric dose of 0.1 mg and a maximum single dose of 0.5 and 1 mg in children and adolescents, respectively. The dose may be repeated at 5-minute intervals to a maximum total dose of 1 mg in children and 2 mg in adolescents.

Preparations
Atropine sulfate injection (generic): 0.05, 0.1, 0.3, 0.4, 0.5, 0.8, 1 mg/mL.

Antithrombotics

Anticoagulants

1. Argatroban (Acova)

Indications
As an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT)

As an anticoagulant in patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)

Dosage
Adults

Heparin-Induced Thrombocytopenia (HIT/HITTS)
The usual initial dose is 2 μg/kg/min administered as a continuous infusion (the concentrated drug, 100 mg/mL, must be diluted 100-fold prior to infusion). The dose can be adjusted as clinically indicated and according to steady-state aPTT (1.5-3 times the initial baseline value, not to exceed 100 s) up to 10 μg/kg/min. A lower initial dose of 0.5 μg/kg/min is recommended for patients with moderate hepatic impairment; aPTT should be monitored closely and dosage adjusted as clinically indicated.

PCI in HIT/HITTS (heparin-induced thrombocytopenia and thrombosis syndrome) patients
Give a 350 μg/kg IV bolus (over 3-5 min) with a 25 μg/kg/min IV infusion. Check activated clotting time (ACT) 5-10 min after bolus dose and begin procedure if ACT > 300 s. If ACT < 300 s, administer an additional 150 μg/kg IV bolus and increase infusion to 30 μg/kg/min. The bolus dose may be repeated if ACT remains < 300 s, with the infusion rate increased to 40 μg/kg/min. Recheck aPTT in 5-10 min. If ACT > 450 s, decrease infusion rate to 15 μg/kg/min and check the ACT 5-10 min later. If desired, the argatroban infusion may be continued following the procedure at a lower infusion rate (eg, 2 μg/kg/min with normal liver function).

Conversion to oral anticoagulant therapy
Combination therapy results in higher international normalized ratio (INR) values than warfarin alone. Begin warfarin at the expected daily dose (do not use a loading dose) and, if the dosage of argatroban is > 2 μg/kg/min, temporarily reduce the dosage to 2 μg/kg/min. Measure the INR daily. Discontinue argatroban once the INR is above 4. Measure the INR 4-6 h after argatroban is discontinued. If INR is subtherapeutic, restart argatroban and repeat this procedure daily until INR is in the desired range.

Elderly
Dosage adjustment is not required unless liver function is compromised.

Children
Safety and effectiveness have not been established.

Preparation
Argatroban injection (GlaxoSmithKline): 100 mg/mL, 2.5 mL single-use vials
2. Bivalirudin (Angiomax)

**Indications**
Anticoagulation in conjunction with aspirin in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty.

**Dosage**

**Adults**
Use with aspirin and initiate treatment just prior to PCI. Bolus dose: 1 mg/kg IV; no adjustment needed for renal insufficiency. Maintenance: 2.5 mg/kg/h IV infusion for 4 h, then 0.2 mg/kg/h for up to 20 h if needed. The maintenance dose should be reduced in patients with renal insufficiency and the ACT monitored.

**REPLACE-2 dosing (clinically used but not FDA-approved)**
0.75 mg/kg IV bolus immediately before PCI, followed by 1.75 mg/kg/h IV infusion for the duration of the procedure.

**Elderly**
Dosage adjustment is not required unless patient has renal impairment.

**Children**
Safety and effectiveness have not been established.

**Preparation**
Angiomax (Medicines Company): 250 mg injection, lyophilized.

3. Dabigatran (Pradaxa)

**Indications**
Reduction in the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

**Dosage**

**Adults**
For patients with creatinine clearance (CrCL) > 30 mL/min, the recommended dose is 150 mg twice daily, taken with or without food. For patients with CrCL 15-30 mL/min, the recommended dose is 75 mg twice daily. Dosing recommendations for patients with a CrCL < 15 mL/min or on dialysis cannot be provided.

**Elderly**
Use usual recommended dose based on renal function.

**Children**
Safety and efficacy have not been established.

**Preparations**
Pradaxa (Boehringer Ingelheim Pharmaceuticals): 75 mg and 150 mg capsules.

4. Dalteparin sodium (Fragmin)

**Indications**
Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing hip replacement surgery, in patients undergoing abdominal surgery who are at risk for thromboembolic complications, and in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Prevention of ischemic complications in patients with unstable angina or non-Q-wave myocardial infarction (use with concurrent aspirin therapy).

Extended treatment of symptomatic venous thromboembolism (VTE), to reduce the recurrence of VTE in patients with cancer.

**Dosage**

**Abdominal surgery**
Patients with a low to moderate risk of thromboembolic complications: 2500 IU subcutaneously once daily for 5-10 days starting 1-2 h prior to surgery. Patients with a high risk of thromboembolic complications: 5000 IU subcutaneously once daily for 5-10 days starting the evening before surgery. Alternatively, in patients with malignancy, 2500 IU of dalteparin can be administered subcutaneously 1-2 h prior to surgery followed by 2500 IU subcutaneously 12 h later, and then 5000 IU once daily for 5-10 days postoperatively.

**Hip replacement surgery**
Administer the first dose, 2500 IU, subcutaneously within 2 h before surgery and the second dose of 2500 IU subcutaneously in the evening of the day of surgery (at least 6 h after the first dose). If surgery is performed in the evening, omit the second dose on the day of surgery. Dalteparin 5000 IU is then administered subcutaneously once daily from first postoperative day and continued for 5-10 days. Alternatively, dalteparin 5000 IU can be administered the evening before the surgery, followed by 5000 IU once daily, starting in the evening of the day of surgery and continuing for 5-10 days. Up to 14 days of treatment have been well tolerated in controlled clinical trials.

**Unstable angina/non-Q-wave myocardial infarction**
120 IU/kg (maximum single dose of 10,000 IU) subcutaneously every 12 h with concurrent aspirin therapy for 5-8 days or until the patient is clinically stable.
Medical patients with severely restricted mobility during acute illness
The recommended dose is 5000 IU subcutaneously once daily. The usual duration of therapy is 12-14 days.

Extended treatment of symptomatic VTE in patients with cancer
For the first 30 days of treatment, administer 200 IU/kg total body weight subcutaneously once daily. The total daily dose should not exceed 18,000 IU. For months 2-6 of treatment, administer dalteparin at 150 IU/kg subcutaneously once daily. The total daily dose should not exceed 18,000 IU. Dose reduction or discontinuation of therapy is required for patients with cancer and acute symptomatic VTE who developed thrombocytopenia.

Elderly
No data; dosage adjustment is probably not required.

Children
Safety and effectiveness have not been established.

Preparations
Fragmin (Pharmacia and Upjohn): 2500 anti-Factor Xa IU/0.2 mL; 5000 anti-Factor Xa IU/0.2 mL; 7500 anti-Factor Xa IU/0.3 mL; 10,000 anti-Factor Xa IU/mL, 9.5 mL multiple-dose vials.

5. Desirudin (Iprivask)

Indications
Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.

Dosage
Adults
In patients undergoing hip replacement surgery, the recommended dose is 15 mg every 12 hours administered by subcutaneous injection, with the initial dose given up to 5 to 15 minutes prior to surgery but after induction of regional block anesthesia, if used. Up to 12 days administration (average duration 9 to 12 days) of desirudin has been well tolerated in controlled clinical trials. In patients with CrCL of 31 to 60 mL/min/1.73 m2, initiate therapy at 5 mg every 12 hours by subcutaneous injection, and adjust dosage based on aPTT results. In patients with CrCL < 31 mL/min/1.73 m2, initiate desirudin at 1.7 mg every 12 hours by subcutaneous injection, and adjust dosage based on aPTT results.

Elderly
Dosage should be adjusted based on renal function.

Children
Safety and efficacy have not been established.

Preparations
Iprivask (Canyon Pharmaceuticals): 15.75 mg lyophilized powder, diluent (0.6 mL of mannitol USP [3%] in water for injection)

6. Enoxaparin sodium (Lovenox)

Indications
Prophylaxis of deep vein thrombosis (DVT) in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness

Inpatient treatment of acute DVT with or without pulmonary embolism

Outpatient treatment of acute DVT without pulmonary embolism

Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction

Treatment of acute ST-segment elevation myocardial infarction (STEMI) managed medically or with subsequent percutaneous coronary intervention.

Dosage
Adults
DVT prophylaxis in abdominal surgery
Administer 40 mg subcutaneously once daily up to 12 days.

DVT prophylaxis in knee replacement surgery
Administer 30 mg subcutaneously every 12 hours up to 14 days.

DVT prophylaxis in hip replacement surgery
Administer 30 mg q 12 h or 40 mg once daily by subcutaneous injection. An initial dose of 40 mg once a day subcutaneously may be given approximately 12 h prior to surgery. Following the initial phase of thromboprophylaxis, continued prophylaxis with enoxaparin injection 40 mg once daily for 3 weeks is recommended.

DVT prophylaxis in medical patients
Administer 40 mg subcutaneously once daily for up to 14 days.

Inpatient treatment of acute DVT with or without pulmonary embolism
Administer 1 mg/kg subcutaneously every 12 hours or 1.5 mg/kg subcutaneously once daily (with warfarin) up to 17 days.
Appendix 2

Outpatient treatment of acute DVT without pulmonary embolism
Administer 1 mg/kg subcutaneously every 12 hours (with warfarin) up to 17 days.

Unstable angina and non-Q-wave myocardial infarction
Administer 1 mg/kg subcutaneously every 12 hours (with aspirin) for 2-8 days.

Acute STEMI in patients < 75 years
30 mg single IV bolus plus a 1 mg/kg subcutaneous dose followed by 1 mg/kg subcutaneously every 12 hours for at least 8 days (with aspirin)

Acute STEMI in patients ≥ 75 years
0.75 mg/kg subcutaneously every 12 hours (no bolus) for at least 8 days (with aspirin)

Note: Dosage of enoxaparin must be adjusted in patients with severe renal impairment.

Elderly
Dosage adjustment is not required. However, dosage adjustment should be considered in patients with a creatinine clearance of < 30 mL/min.

Children
Safety and effectiveness have not been established.

Preparations
Lovenox (Sanofi-Aventis): 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL, 120 mg/0.8 mL, 150 mg/1 mL injections

7. Fondaparinux sodium (Arixtra)

Indication
Prophylaxis of DVT in patients undergoing hip fracture surgery (including extended prophylaxis), hip replacement surgery, knee replacement surgery, or abdominal surgery
Treatment of DVT or acute pulmonary embolism when administered in conjunction with warfarin

Dosage
Adults
Prophylaxis of DVT
2.5 mg subcutaneously once daily after hemostasis has been established. The initial dose should be given no earlier than 6-8 hours after surgery and continued for 5-9 days. For patients undergoing hip fracture surgery, extended prophylaxis up to 24 additional days is recommended.

Treatment of DVT and pulmonary embolism
5 mg (body weight < 50 kg), 7.5 mg (50-100 kg), or 10 mg (> 100 kg) subcutaneously once daily. Treatment should continue for at least 5 days until INR of 2-3 is achieved with warfarin.

Elderly
The risk of fondaparinux-associated major bleeding increases with age, with an incidence of 1.8% in patients less than 65 years, 2.2% in those 65-74 years, and 2.7% in those 75 years or older. The kidney substantially eliminates fondaparinux, and the risk of toxic reactions to fondaparinux may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Children
Safety and effectiveness have not been established.

Preparations
Arixtra (GlaxoSmithKline): single-dose, prefilled syringes containing 2.5, 5, 7.5, or 10 mg of fondaparinux.

8. Heparin (heparin Sodium)

Indications
Prophylaxis and treatment of venous thrombosis, pulmonary embolism, atrial fibrillation with thromboembolism, and peripheral arterial embolism
Prophylaxis and treatment of unstable angina, evolving stroke, acute myocardial infarction (not FDA-approved)
Prevention of clotting in cardiac/arterial surgery, blood transfusion, dialysis and other extracorporeal interventions, and disseminated intravascular coagulation

Dosage
Adults
Prophylaxis for deep-venous thrombosis
5000 units subcutaneously q 8 to 12 h until the patient is fully ambulatory.

Treatment guidelines for thromboembolic events
Continuous intravenous administration: 60-100 U/kg loading dose by intravenous injection, followed by an intravenous infusion of 12-20 U/kg/h and adjusted based on coagulation test results.
Deep subcutaneous injections: 10,000-20,000 units loading dose, followed by 8,000-10,000 units q 8 h or 15,000-20,000 units q 12 h. Dose should be adjusted based on coagulation test results.

Open heart and vascular surgery
The minimum initial dose is 150 U/kg for patients undergoing total body perfusion for open heart surgery. For procedures < 60 min, the usual dose used is 300 U/kg. For procedures > 60 min, the usual dose used is 400 U/kg.
Heparin lock
To avoid clot formation in a heparin lock set, inject diluted heparin solution (Heparin Lock Flush Solution, USP; or a 10-100 U/mL heparin solution) via the injection hub to fill the entire set to the needle tip. Replace this solution each time the heparin lock is used. Consult the set manufacturer's instructions.

Elderly
Dosage adjustment is not required.

Children
Dosage adjustment should be made based on weight, age, and coagulation test results.

Preparations
Available in either bovine or porcine origin
Heparin sodium: 10, 100, 1000, 2500, 5000, 7500, 10,000, 20,000, 40,000 U/mL in various volumes as single use or multiple-dose packages.

9. Lepirudin (Refudlan)

Indications
Prevention of further thromboembolic complications in patients with heparin-induced thrombocytopenia and associated thromboembolic disease

Dosage
Adults
Bolus dose 0.4 mg/kg (up to 44 mg) intravenously over 15-20 s

Maintenance dose 0.15 mg/kg/h (up to 16.5 mg/h) as a continuous intravenous infusion for 2-10 days or longer if indicated

Dosage should be adjusted based on aPTT measurements. The first aPTT determination should be made 4 h after initiation of the lepirudin infusion. Follow-up aPTT determinations should be made at least once a day. Adjustments of bolus dose and maintenance dose should be made in patients who are receiving thrombolytic therapy concurrently and in patients with renal impairment. Consult lepirudin package insert for full prescribing information.

Concurrent warfarin therapy Reduce lepirudin dose to reach an aPTT ratio just above 1.5 before administering the first dose of warfarin. Lepirudin infusion should be discontinued once an INR of 2 is achieved.

Elderly
Dosage adjustment should be made based on creatinine clearance.

Children
Safety and effectiveness have not been established.

Preparation
Refudlan (Hoechst-Marion Roussel): 50 mg/vial, powder for injection.

10. Tinzaparin sodium (Innohep)

Indications
Treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin

Dosage
Adults
175 anti-Xa IU/kg, administered subcutaneously once daily for at least 6 days and until the patient is adequately anticoagulated with warfarin (INR ≥ 2 for 2 consecutive days). Use with caution in patients with renal impairment.

Elderly
Dosage adjustment is not required.

Children
Safety and effectiveness have not been established.

Preparation
Innohep (DuPont Pharma): 20,000 IU/mL, 2 mL vials

11. Warfarin (warfarin sodium, Coumadin)

Indications
Prophylaxis and treatment of venous thrombosis, pulmonary embolism, atrial fibrillation with embolization, thromboembolism associated with prosthetic heart valves

Dosage
Adults
Initiate with 2-5 mg/d for 2-4 days; adjust dose to maintain desired therapeutic INRs according to recommendations by the American College of Chest Physicians (ACCP) and the National Heart, Lung and Blood Institute (NHLBI). Warfarin injection provides an alternative administration route for patients who cannot receive oral drugs. The dose of warfarin injection is the same as the oral dose and should only be administered intravenously. The dose should be given as a slow bolus injection over 1-2 min into a peripheral vein.

Elderly
Initiate therapy with a lower dose. Dosing is based on coagulation test results.

Children
Safety and effectiveness have not been established.
Preparations
Warfarin (generic); Coumadin (DuPont): 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg tablets.
Coumadin Injection (DuPont): 5 mg per vial

**Antiplatelet Agents**

1. **Abciximab (ReoPro)**

**Indications**
Prevention of cardiac ischemic complications in patients undergoing PCI or in patients with unstable angina not responding to conventional medical therapy when PCI is planned within 24 h.

**Dosage**

**Adults**
* Percutaneous coronary intervention (PCI)*
0.25 mg/kg intravenous bolus administered 10-60 min prior to the start of PCI, followed by a continuous intravenous infusion of 0.125 μg/kg/min (to a maximum of 10 μg/min) for 12 h.

*Unstable angina with planned PCI within 24 h*
0.25 mg/kg intravenous bolus followed by an 18- to 24-h intravenous infusion of 10 μg/min, concluding 1 h after the PCI.

**Note:** The safety and efficacy of abciximab have only been studied with concomitant administration of heparin and aspirin. The continuous infusion of abciximab should be stopped in cases of failed PCI because there is no evidence for the efficacy of abciximab in that setting. A filter must be used during the administration of abciximab; see package insert for detailed instructions on administration.

**Elderly**
No dosage adjustment is required. However, there may be an increased risk of major bleeding in patients over 65 years. Caution is recommended.

**Children**
Safety and effectiveness have not been established.

**Preparation**
ReoPro (Lilly): 2 mg/mL, 5 mL vials

2. **Aspirin**

**Indications**
Listed below are cardiovascular indications only (not all indications are FDA-approved).

Prevention of arterial and venous thrombosis in:
* Arteriovenous shunt for hemodialysis
* Atrial fibrillation
* Coronary bypass
* Intracoronary stent placement (in combination with clopidogrel, ticlopidine, or warfarin)
* Myocardial infarction (primary/secondary prophylaxis)
* Prosthetic heart valves (with an oral anticoagulant and with or without dipyridamole)
* Transient ischemic attacks
* Transluminal angioplasty of coronary, iliac, femoral, popliteal, or tibial artery (with or without dipyridamole)
* Unstable angina

**Dosage**

**Adults**
* Transient ischemic attacks in men*
160-325 mg chewed for rapid effect

* Acute coronary syndrome*
1300 mg/d in two to four divided doses; doses as low as 300 mg/d may be effective if tolerance is a problem with high doses.

* Coronary artery disease (chronic prophylaxis)*
75-325 mg once daily

**Elderly**
Dosage adjustment is not required.

**Children**
Dosage recommendations are based on age and weight for the analgesic indication. Aspirin is not recommended in children with influenza or chickenpox due to the risk for Reye’s syndrome.

**Preparations**
Available in various strengths and formulations

3. **Cilostazol (Pletal)**

**Indication**
Intermittent claudication

**Dosage**

**Adults**
100 mg twice daily, taken at least 30 min before or 2 h after breakfast and dinner. A lower dose of 50 mg twice daily should be considered during co-administration of CYP3A4 inhibitors (ie, ketoconazole, itraconazole, erythromycin, diltiazem) and CYP2C19 inhibitors (ie,
omeprazole). Because CYP3A4 is also inhibited by grapefruit juice, patients receiving cilostazol should avoid this beverage.

**Elderly**
Dosage adjustment is not required.

**Children**
Safety and effectiveness have not been established.

**Preparations**
Pletal, (Otsuka, America, Pharmaceuticals/Pharmacia, Upjohn): 50, 100 mg tablets

### 4. Clopidogrel (Plavix)

**Indications**
Reduction of thrombotic events in patients with a history of recent myocardial infarction, recent stroke, or established peripheral arterial disease

- Reduction of thrombotic events in patients with acute coronary syndrome

**Dosage**

**Adults**

**Recent myocardial infarction, recent stroke or established peripheral arterial disease**
75 mg once daily

**Acute coronary syndrome**
For patients with non–ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), clopidogrel should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75-325 mg once daily) should be initiated and continued in combination with clopidogrel. In the CURE trial, most patients with acute coronary syndrome also received heparin acutely. For patients with ST-segment elevation acute myocardial infarction, the recommended dose is 75 mg once daily, administered in combination with aspirin, with or without thrombolytics. Clopidogrel may be initiated with or without a 300-mg loading dose.

**Elderly**
Dosage adjustment is not required.

**Children**
Safety and effectiveness have not been established.

**Preparation**
Plavix (Bristol Myers Squibb/Sanofi): 75 mg tablets

### 5. Dipyridamole (dipyridamole, Persantine)

**Indications**
Prophylaxis of thromboembolism after cardiac valve replacement (use as an adjunct to warfarin therapy)
An alternative to exercise during Thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately

**Dosage**

**Adults**

**Adjunctive use in prophylaxis of thromboembolism after cardiac valve replacement**
75-100 mg four times daily (as an adjunct to warfarin therapy).

**Evaluation of coronary artery disease**
Intravenous infusion: 0.14 mg/kg/min for 4 min; not to exceed 60 mg over 4 min). The radiopharmaceutical is injected within 3-5 min after completion of the dipyridamole infusion.

**Elderly**
Dosage adjustment is not required.

**Children**
Safety and effectiveness have not been established in children under 12 years.

**Preparations**
Dipyridamole (generic); Persantine (Boehringer Ingelheim): 25, 50, 75 mg tablets
Persantine Injection (Boehringer Ingelheim): 5 mg/mL (10 mg/2 mL ampule)

### 6. Dipyridamole and aspirin (Aggrenox)

**Indication**
Stroke To reduce the risk of stroke in patients who have had transient ischemia of the brain or complete ischemic stroke due to thrombosis

**Dosage**

**Adults**
Administer 1 capsule twice daily (one in the morning and one in the evening). Capsules should be swallowed whole; do not crush or chew capsule.

**Elderly**
Dosage adjustment is not required.

**Children**
Safety and effectiveness have not been established.
Preparation
Aggrenox (Boehringer Ingelheim): 200 mg extended-release dipyridamole/25 mg aspirin capsules

7. Eptifibatide (Integrilin)

Indications
Prevention of thrombotic complications in patients with acute coronary syndrome (unstable angina/non-ST-elevation myocardial infarction), including patients who are to be managed medically and those undergoing PCI
Treatment of patients undergoing PCI, including those undergoing intracoronary stenting

Dosage
Adults
Acute coronary syndrome
180 μg/kg intravenous bolus (over 1-2 min), followed by 2 μg/kg/min (1.0 μg/kg/min with creatinine clearance < 50 mL/min or serum creatinine > 2.0 mg/dL) continuous infusion for 72 h, until hospital discharge, or until the time of CABG, whichever occurs first. If PCI is performed, the infusion should be continued up to hospital discharge or for up to 18-24 h after the procedure, whichever comes first, allowing for up to 96 h of therapy.

PCI
180 μg/kg IV bolus over 1-2 min, immediately before the procedure, followed by 2.0 μg/kg/min infusion (1.0 μg/kg/min with creatinine clearance < 50 mL/min or serum creatinine > 2.0 mg/dL) and then a second 180 μg/kg bolus given 10 min after the first. The infusion should be continued until hospital discharge or for up to 18-24 h, whichever comes first. A minimum infusion time of 12 h is recommended.

Note: Eptifibatide is recommended to be used concurrently with heparin and aspirin. The maximum bolus dose is 22.6 mg and the maximum infusion rate is 15 μg/h (7.5 μg/h if creatinine clearance < 50 mL/min or serum creatinine > 2.0 mg/dL). The use of this drug is not recommended in patients with serum creatinine > 4.0 mg/dL.

Elderly
Dosage adjustment is not required.

Children
Safety and effectiveness have not been established.

Preparations
Integrilin (Schering-Plough): 0.75 mg/mL, 100 mL vials; 2 mg/mL, 10 mL vials.

8. Prasugrel (Effient)

Indication
Reduction of thrombotic cardiovascular events in patients with acute coronary syndrome who are to be managed with PCI as follows: (1) Patients with unstable angina or, non-ST-elevation myocardial infarction; (2) Patients with ST-elevation myocardial infarction when managed with either primary or delayed PCI.

Dosage
Adults
Initiate treatment as a single 60 mg oral loading dose and then continue at 10 mg orally once daily. For patients < 60 kg, consider 5 mg once daily. Patients taking prasugrel should also take aspirin (75-325 mg) daily.

Elderly
Use normal adult dose with caution. Use of prasugrel is generally not recommended in patients ≥ 75 years due to a higher risk of bleeding and uncertain effectiveness in this population, except in high-risk situations where its effect appears to be greater and its use may be considered.

Children
Safety and efficacy have not been established.

Preparations
Effient (Eli Lilly/Daiichi Sankyo): 5 and 10 mg tablets.

9. Ticlopidine (ticlopidine hydrochloride, Ticlid)

Indication
Prevention of thrombotic stroke in patients with transient ischemic attack or a history of completed thrombotic stroke
Used with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation

Dosage
Adults
250 mg twice daily with food

Elderly
Dosage adjustment is not required.

Children
Safety and effectiveness have not been established.

Preparations
Ticlopidine (generic); Ticlid (Roche): 250 mg tablets
10. Tirofiban hydrochloride (Aggrastat)

Indications
Treatment of acute coronary syndrome (in combination with heparin), including patients who are to be managed medically and those undergoing percutaneous transluminal coronary angioplasty (PTCA), or atherectomy

Dosage
Adults
Administer intravenously, at an initial rate of 0.4 μg/kg/min for 30 min and then continued at 0.1 μg/kg/min. In a clinical trial, PRISM-PLUS, tirofiban was administered in combination with heparin for 48-108 h. The infusion should be continued through angiography and for 12-24 h after angioplasty or atherectomy. Patients with severe renal impairment (creatinine clearance < 30 mL/min) should receive half the usual rate of loading and maintenance infusion.

Note: Tirofiban has been studied in a setting that included aspirin and heparin. The 250 μg/mL injection must be diluted to 50 μg/mL prior to administration.

Elderly
Dosage adjustment is not required.

Children
Safety and effectiveness have not been established.

Preparations
Aggrastat (Medicure Pharma): 50 μg/mL, 100 mL, and 250 mL premixed solution

Thrombolytic Agents

1. Alteplase, recombinant (Activase)

Indications
Acute myocardial infarction
Acute ischemic stroke
Pulmonary embolism

Dosage
Adults
Acute myocardial infarction
Treatment should be initiated as soon as possible after the onset of chest pain.
1. Accelerated Infusion—15 mg intravenous bolus, followed by 0.75 mg/kg (up to 50 mg) infused over the next 30 min, and then 0.5 mg/kg (up to 35 mg) infused over the next 60 min. The maximum total dose is 100 mg for patients who weigh more than 67 kg. The safety and efficacy of this accelerated infusion regimen has only been investigated with concomitant administration of heparin and aspirin.
2. Three-hour infusion—60 mg infused over 60 min (with 6-10 mg administered as a bolus over the first 1-2 min), followed by 20 mg/h infusion for the next 2 h to deliver a total dose of 100 mg. For patients weighing less than 65 kg, a total dose of 1.25 mg/kg given over 3 h is recommended. Although the use of anticoagulants during and following alteplase infusion has been shown to be of unclear benefit, heparin has been given concomitantly for ≤ 24 h in > 90% of patients. Aspirin or dipyridamole has been administered either during or following heparin treatment.

Acute ischemic stroke
0.9 mg/kg (up to 90 mg) administered intravenously over 60 min with 10% of the total dose administered as a bolus over the first minute. Treatment should be initiated within 3 h after the onset of stroke symptoms. Avoid concurrent aspirin and heparin use during the first 24 h after symptom onset.

Pulmonary embolism
Administered 100 mg intravenously over 2 h. Heparin therapy should be instituted or reinstated near the end of or immediately following the alteplase infusion when partial thromboplastin time or thrombin time returns to twice of normal or less.

Note: Alteplase must be reconstituted before administration; consult package insert for detailed instructions.

Elderly
Generally, the adult dose can be used, but body weight should be considered. Patients > 75 years, especially those with suspected arterial degeneration are at an increased risk for unwanted bleeding; monitor closely.

Children
Safety and effectiveness have not been established.

Preparations
Activase (Genentech): 50 mg (29 million IU)/vial, 100 mg (58 million IU)/vial

2. Anistreplase (Eminase)

Indication
Acute myocardial infarction

Dosage
Adults
Thrombolytic therapy should be initiated as soon as possible after the onset of symptoms. The dose of anistreplase is 30 units administered intravenously over 2-5 min.
Reconstitution: Slowly add 5 mL of sterile water for injection into the vial containing anistreplase, directing the stream of water against the side of the vial. Gently roll (do not shake) the vial to mix the powder with the liquid. The reconstituted solution should not be further diluted before administration. No other medication should be added to the vial containing anistreplase.

**Elderly**
Dosage adjustment is not required. Patients older than 75 years, especially those with suspected arterial degeneration, may be at risk for unwanted bleeding; monitor closely.

**Children**
Safety and effectiveness have not been established.

**Preparation**
Eminase (Roberts): 30 U/single-dose vial

3. Reteplase (Retavase)

**Indication**
Acute myocardial infarction

**Dosage**

**Adults**
Treatment should be initiated as soon as possible, preferably within 12 h after the onset of chest pain. Reteplase should be administered as two 10-unit bolus injections each administered over 2 min, the second dose given 30 min after the initiation of the first injection. Patients should also receive adjunctive therapy with heparin and aspirin.

*Note:* Reteplase should be given through an intravenous line in which no other medications (eg, heparin) are being injected or infused. If reteplase is to be administered through an intravenous line containing heparin, the line should be flushed before and after reteplase administration with either 0.9% sodium chloride or 5% dextrose solution. Reteplase should be reconstituted with 10 mL of sterile water for injection (without preservatives) to yield a solution of 1 U/mL. The vial should be swirled gently to dissolve the drug, taking precaution to avoid shaking. Once dissolved, 10 mL should be withdrawn from the vial into a syringe for administration to the patient. Approximately 0.7 mL will remain in the vial due to overfill.

**Elderly**
Dosage adjustment is not required.

**Children**
Safety and effectiveness have not been established.

**Preparation**
Kit-reteplase: 18.1 mg (10.4 U)/vial, in 1- or 2- vial kits that also contain 10 mL sterile water for injection, reconstitution vials, syringes, dispensing pins, needles, and alcohol swabs.

4. Streptokinase (Streptase, Kabikinase)

**Indications**
Acute myocardial infarction
Arterial thrombosis or embolism
Cannula, arteriovenous clearance
Deep-vein thrombosis
Pulmonary embolism

**Dosage**

**Adults**

**Acute myocardial infarction**
Treatment should be initiated as soon as possible after the onset of symptoms.
Intravenous infusion—Administer a total dose of 1,500,000 IU within 60 min.
Intracoronary infusion—Administer 20,000 IU by bolus followed by 2000 IU/min for 60 min (a total dose of 140,000 IU).

**Pulmonary embolism, deep-vein thrombosis, arterial thrombosis, or embolism**
250,000 IU bolus infused intravenously over 30 min, followed by 100,000 IU/h continuous infusion for 24 h for pulmonary embolism, 72 h for deep-vein thrombosis, and 24-72 h for arterial thrombosis or embolism. Treatment should be initiated as soon as possible, preferably within 7 days after onset of the symptoms.

**Arteriovenous cannula occlusion**
Slowly instill 250,000 IU streptokinase in 2 mL solution into each occluded limb of the cannula. Clamp off cannula limb(s) for 2 h and observe closely for adverse effects. After treatment, aspirate contents of infused cannula limb(s), flush with saline, and reconnect cannula.

*Note:* Consult package insert for detailed instructions on reconstitution of streptokinase prior to administration.

**Elderly**
Dosage adjustment is not required. Patients older than 75 years may be more susceptible to unwanted bleeding events.

**Children**
Safety and effectiveness have not been established.

**Preparations**
Streptase (Astra Zeneca): 250,000, 750,000, 1,500,000 IU/vial
5. Tenecteplase (TNKase)

Indication
Acute myocardial infarction

Dosage
Adults
Acute myocardial infarction
Treatment should be initiated as soon as possible after the onset of symptoms. Dosage of tenecteplase is based on patient weight as follows:

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Tenecteplase (mg)</th>
<th>Tenecteplase (mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>≥ 60 to &lt; 70</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>≥ 70 to &lt; 80</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>≥ 80 to &lt; 90</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>≥ 90</td>
<td>50</td>
<td>10</td>
</tr>
</tbody>
</table>

*This is the volume of tenecteplase to be administered as a single bolus dose over 5 s after one vial of tenecteplase (50 mg) is reconstituted with 10 mL of sterile water for injection. Consult tenecteplase package insert for detailed instructions on reconstitution.

Elderly
Dosage determination is based on weight. Elderly patients may be more susceptible to unwanted bleeding events.

Children
Safety and effectiveness have not been established.

Preparation
TNKase (Genentech): 50 mg/vial; sterile water for injection, 10 mL.

Beta-Adrenergic Blockers

Nonselective Beta-Adrenergic Blockers Without ISA

1. Nadolol (nadolol, Corgard)

Indications
Angina
Hypertension

Dosage
Adults
Hypertension
Initiate with 20-40 mg once daily; dosage may be increased gradually in increments of 40-80 mg to a maximum of 240-320 mg/d. Usual maintenance dose is 40-80 mg once daily.

Angina
Initiate with 40 mg once daily; dosage may be increased by 40-80 mg/d every 3-7 days until adequate control of angina is achieved. The usual dose is 40-80 mg/d; up to 160-240 mg/d may be needed.

Note: Because of the long half-life of nadolol, once-daily dosing is sufficient to provide stable plasma concentrations. Adjustments in dosing intervals must be made for patients with renal impairment as follows:

<table>
<thead>
<tr>
<th>CrCl (mL/min/1.73 m²)</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>q 24 h</td>
</tr>
<tr>
<td>31-50</td>
<td>q 24-36 h</td>
</tr>
<tr>
<td>10-30</td>
<td>q 24-48 h</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>q 48 h or longer</td>
</tr>
</tbody>
</table>

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established.

Preparations
Corgard (Monarch): 20, 40, 80, 120, 160 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension:
Corizide 40/5 tablets—40 mg nadolol and 5 mg bendroflumethiazide
Corizide 80/5 tablets—80 mg nadolol and 5 mg bendroflumethiazide

2. Propranolol (propranolol, Inderal, Inderal LA, InnoPran XL)

Indications
Angina
Cardiac arrhythmias
Essential tremor
Hypertension
Hypertrophic subaortic stenosis
Myocardial infarction
Migraine prophylaxis
Pheochromocytoma

Dosage
Adults
Angina
Regular formulation: Initiate with 10-20 mg three to four times per day; dosage may be increased gradually every 3-7 days according to response to a maximum dose of 320 mg/d.

Extended-Release formulation: Initiate with 80 mg once daily; increase dosage gradually every 3 to 7 days as
needed up to a maximum of 320 mg/d.

**Cardiac arrhythmias**
Regular formulation: 10-30 mg three to four times per day given before meals and at bedtime.

**Essential tremor**
Regular formulation: Initiate with 40 mg twice daily; dosage may be titrated according to response to a maximum of 320 mg/d. The usual maintenance dose is 120 mg/d in divided doses.

**Hypertension**
Regular formulation: Initiate with 40 mg twice daily; dosage may be increased gradually according to response to a maximum of 640 mg/d. The usual maintenance dose is 120-240 mg/d given in two to three divided doses. Extended-release formulation: Initiate with 80 mg once daily; dosage may be increased gradually according to response to a maximum of 640 mg/d. The usual maintenance dose is 120-160 mg once daily.

**Hypertrophic subaortic stenosis**
Regular formulation: The usual dose range is 20-40 mg three to four times per day given before meals and at bedtime. Extended-Release formulation: The usual dose range is 80-160 mg once daily.

**Myocardial infarction**
Regular formulation: The usual dose range is 180-240 mg/d given in three to four divided doses.

**Migraine prophylaxis**
Regular formulation: Initiate with 80 mg/d in divided doses; dosage may be increased gradually to the usual range of 160-240 mg/d in divided doses. Extended-release formulation: Initiate with 80 mg once daily. Dosage may be increased gradually to a maximum of 240 mg/d.

**Pheochromocytoma (adjunct therapy to α-adrenergic blocker):** Regular formulation: 60 mg/d in divided doses for 3 days prior to surgery. To prevent severe hypertension caused by unopposed α-adrenergic stimulation, treatment with an α-adrenergic blocking agent must always be started prior to the use of propranolol and continued during propranolol therapy. As an adjunct to prolonged treatment of inoperable pheochromocytoma, 30 mg of propranolol daily in divided doses along with an α-adrenergic blocker is usually sufficient.

Additional administration for life-threatening arrhythmias:
The usual dose is 1-3 mg given under careful monitoring.

Rate of injection should not exceed 1 mg/min. A second dose may be given after 2 min if indicated. Thereafter, do not give additional dose in < 4 h.

**Elderly**
Initiate at lowest dose and titrate to response.

**Children**
Initiate with oral dosage of 0.5 mg/kg twice daily for the treatment of hypertension. Dosage may be increased at 3- to 5-day intervals to usual range of 2-4 mg/kg/d given in divided doses. Intravenous use is not recommended; however, a dose of 0.01 to 0.1 mg/kg/dose to a maximum of 1 mg/dose by slow push has been used for the management of arrhythmias.

**Preparations**
Propranolol (generic); Inderal (Wyeth-Ayerst): 10, 20, 40, 60, 80 mg tablets
Propranolol extended-release capsules (generic); Inderal LA (Wyeth-Ayerst): 60, 80, 120, 160 mg extended-release capsules
InnoPran XL extended release capsules (Reliant, GlaxoSmithKline): 80, 120 mg
Propranolol injection (generic); Inderal injection (Wyeth-Ayerst): 1 mg/mL

**Fixed-Dose Combinations for Treatment of Hypertension:**
Inderide LA 80/50: propranolol 80 mg/hydrochlorothiazide 50 mg capsules
Inderide LA 120/50: propranolol 120 mg/hydrochlorothiazide 50 mg capsules
Inderide LA 160/50: propranolol 160 mg/hydrochlorothiazide 50 mg capsules
Inderide 80/25: propranolol 80 mg/hydrochlorothiazide 25 mg tablets
Inderide 40/25: propranolol 40 mg/hydrochlorothiazide 25 mg tablets
Propranolol 80 mg/hydrochlorothiazide 25 mg tablets
Propranolol 40 mg/hydrochlorothiazide 25 mg tablets

3. **Sotalol (Betapace, Betapace AF)**

See the section on antiarrhythmic agents, beginning on page 663.

4. **Timolol (Timolol, Blocadren)**

**Indications**
Hypertension
Myocardial infarction
Migraine prophylaxis
Open-angle glaucoma (ophthalmic preparation)
Dosage

**Adults**

**Hypertension**
Initiate with 10 mg twice daily; dosage may be increased gradually (at intervals of at least 7 days) to a maximum of 60 mg/d given in two divided doses. The usual maintenance dose is 20-40 mg/d.

**Myocardial Infarction**
Administer 10 mg twice daily for long-term prophylactic use in patients who have survived a myocardial infarction.

**Migraine prophylaxis**
Initiate with 10 mg twice daily. The dose should be adjusted based on clinical response to a maximum of 30 mg/d given in divided doses. Therapy should be tapered and discontinued if a satisfactory response is not achieved after 6-8 weeks of the maximum daily dosage.

**Elderly**
Initiate at lowest dose and titrate to response.

**Children**
Safety and effectiveness have not been established.

**Preparations**
Timolol (generic); Blocadren (Merck): 5, 10, 20 mg tablets
Timolol (generic): 0.25 and 0.50% ophthalmic solution
Timoptic (Merck): 0.25 and 0.50% ophthalmic solution
Timoptic XE (Merck): 0.25 and 0.50% ophthalmic gel

**Fixed-Dose Combinations for Treatment of Hypertension:**
Timolide 10–25: 10 mg timolol/25 mg hydrochlorothiazide tablets

**Beta Selective β-Adrenergic Blockers Without ISA**

1. **Atenolol (atenolol, Tenormin)**

   **Indications**
   Angina
   Hypertension
   Myocardial infarction

   **Dosage**
   **Adults**
   **Angina**
   Initiate with 50 mg once daily; dosage may be increased to 100 mg/d according to response. Some patients may require 200 mg/d.

   **Hypertension**
   Initiate with 50 mg once daily; dosage may be increased (at 1- to 2-week intervals) to 100 mg/d according to response.

   **Myocardial infarction**
   Treatment should be initiated with intravenous atenolol 5 mg administered over 5 min, followed by a second intravenous dose of 5 mg 10 min later. If the patient tolerates the full intravenous therapy, 50 mg of atenolol should be administered orally 10 min after the last intravenous dose, followed by a second 50 mg oral dose 12 h later. Then the patient can receive atenolol orally either 100 mg once daily or 50 mg twice daily for 6-9 days or until discharge from the hospital.

   **Note:** Because atenolol is eliminated mainly in the kidneys as unchanged drug, dosage adjustment should be made in patients with renal impairment.

   **CrCl (mL/min/1.73 m²)**
   **Maximum Dose**
   15-35
   50 mg/d
   < 15
   25 mg/d
   Hemodialysis
   25 or 50 mg post hemodialysis

   **Elderly**
   Initiate at lowest dose and titrate to response.

   **Children**
   Safety and effectiveness have not been established.

   **Preparations**
   Atenolol (generic); Tenormin (Astra Zeneca): 25, 50, 100 mg tablets
   Tenormin injection (Astra Zeneca): 5 mg/10 mL, 10 mL ampules

   **Fixed-Dose Combinations for Treatment of Hypertension:**
   Generic; Tenoretic 50: 50 mg atenolol/25 mg chlorthalidone tablets
   Generic; Tenoretic 100: 100 mg atenolol/25 mg chlorthalidone tablets

2. **Betaxolol (betaxolol, Kerlone)**

   **Indications**
   Hypertension
   Ocular hypertension (ophthalmic preparation)
   Open-angle glaucoma (ophthalmic preparation)

   **Dosage**
   **Adults**
   **Hypertension**
   Initiate with 10 mg once daily (5 mg for elderly patients or
patients with renal impairment). Dosage may be doubled every 2 weeks to a maximum dose of 20-40 mg/d.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Betaxolol (generic); Kerlone: 10, 20 mg tablets

3. Bisoprolol (bisoprolol, Zebeta)

Indications
Hypertension

Dosage
Adults
Hypertension
Initiate with 2.5-5 mg once daily; dosage may be increased according to response to a maximum of 20 mg once daily.

Elderly
Dosage adjustment is not necessary. However, a lower initial dose of 2.5 mg should be used in patients with CrCl < 40 mL/min or in patients with hepatic impairment.

Children
Safety and effectiveness have not been established.

Preparations
Bisoprolol (generic); Zebeta (Lederle): 5, 10 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension:
Generic; Ziac (Barr) bisoprolol/hydrochlorothiazide combination tablets: 2.5 mg/6.25 mg; 5 mg/6.25 mg; 10 mg/6.25 mg

4. Esmolol (Brevibloc)

Indications
Supraventricular tachycardia
Intraoperative and postoperative tachycardia and/or hypertension

Dosage
Adults
Supraventricular tachycardia
The dosage is established by means of a series of loading and maintenance doses. Administer a loading intravenous infusion of 500 μg/kg/min for 1 minute followed by a maintenance intravenous infusion of 50 μg/kg/min for 4 min. If adequate response is not observed at the end of 5 min, repeat sequence with loading intravenous infusion (as above) followed by an increased maintenance infusion rate of 100 μg/kg/min. The sequence is repeated until an adequate response is obtained, with an increment of 50 μg/kg/min in the maintenance dose at each step. As desired endpoint (defined as desired heart rate/unfavorable decrease in blood pressure) is approached, loading dose may be omitted and increments in maintenance dose reduced to 25 μg/kg/min or less. Intervals between titration steps may also be increased from 5-10 min. Established maintenance dose usually does not exceed 200 μg/kg/min (due to the risk of hypotension) and can be given for up to 24 h (up to 48 h of therapy have been given in limited studies). Maintenance doses as low as 25 μg/kg/min and as high as 300 μg/kg/min have been used.

Intraoperative and postoperative tachycardia and/or hypertension: Rapid intraoperative control—Administer an 80-mg (1 mg/kg) intravenous bolus dose over 30 s, followed by a 150 μg/kg/min infusion and titrate the dose to maintain desired heart rate or blood pressure (up to 300 μg/kg/min).

Gradual postoperative control—Dose titration schedule is the same as the treatment in supraventricular tachycardia; however, higher dosages of up to 250-300 μg/kg/min may be needed for adequate blood pressure control.

Note: The 250 mg/mL strength of esmolol hydrochloride injection must be diluted before administration by intravenous infusion. The 10 mg/mL strength may be given by direct infusion.

Concentrations > 10 mg/mL may produce irritation. If a reaction occurs at the infusion site, the infusion should be stopped and resumed at another site. Avoid the use of butterfly needles and very small veins for infusion of esmolol.

Elderly
Initiate with a low dose and titrate according to response.

Children
Safety and effectiveness have not been established.

Preparations
Brevibloc (Baxter Healthcare): 2500 mg/250 mL (10 mg/mL) premixed injection bags

5. Metoprolol (metoprolol tartrate, Lopressor, Toprol XL)

Indications
Angina
Hypertension
Myocardial infarction
Congestive heart failure (metoprolol succinate, Toprol XL)

Dosage
Adults

**Hypertension**

Tartrate salt: Initiate with 100 mg/d in single or divided doses. Dosage may be adjusted at weekly intervals (or longer) until desired blood pressure control is achieved. Effective maintenance dose ranged from 100-450 mg/d. The extended-release tablets (metoprolol succinate) are for once-a-day administration. The usual dose range is 50-400 mg once daily. Begin with 50-100 mg/d and titrate at weekly (or longer) intervals to desired effect.

Angina

Tartrate salt: Initiate with 100 mg/d in two divided doses. Dosage may be increased at weekly intervals until optimum clinical response is achieved. Effective maintenance dose ranged from 100-400 mg/d.

Succinate salt: 100 mg once daily initially, titrate dosage weekly to desired effect.

**Myocardial infarction**

Treatment should be initiated as soon as the patient’s hemodynamic status has stabilized. Three 5-mg intravenous bolus injections of metoprolol should be administered at 2-minute intervals. If the full 15 mg intravenous dose is tolerated by the patient, 50 mg of oral metoprolol (or 25 mg for those who cannot tolerate the full dose) every 6 h should be initiated 15 min after the last intravenous dose and continued for 48 h. Thereafter, the dose may be adjusted to 100 mg twice daily.

**Congestive heart failure**

For NYHA Class II patients start with 25 mg (metoprolol succinate) once daily. For severe heart failure start with 12.5 mg (metoprolol succinate) once daily. Titrate by doubling dose every 2 weeks as tolerated; reduce dose if symptomatic bradycardia occurs. Maximal dose is 200 mg daily.

**Elderly**

Initiate with a low dose and titrate according to response.

**Children**

Safety and effectiveness have not been established.

Preparations

Metoprolol tartrate (generic); Lopressor (Novartis): 25, 50, 100 mg tablets

Toprol XL (Astra Zeneca): 25, 50, 100, 200 mg extended-release tablets

Metoprolol succinate (generic): 25, 50, 100, 200 mg tablets

Metoprolol tartrate injection (generic); Lopressor injection (Novartis): 1 mg/mL

**Fixed-Dose Combinations for Treatment of Hypertension:**

Lopressor HCT tablets (Novartis):

- 50/25—50 mg metoprolol/25 mg hydrochlorothiazide
- 100/25—100 mg metoprolol/25 mg hydrochlorothiazide
- 100/50—100 mg metoprolol/50 mg hydrochlorothiazide

6. **Nebivolol (Bystolic)**

**Indication**

Hypertension

**Dosage**

**Adults**

The usual recommended starting dose is 5 mg once daily. The dose may be increased at 2-week intervals up to 40 mg daily based on response.

**Elderly**

Dose adjustment is not necessary.

**Children**

Safety and efficacy have not been established.

Preparations

Bystolic (Forest Pharmaceuticals): 2.5, 5, 10, and 20 mg tablets

**β-Adrenergic Blockers with ISA**

1. **Acebutolol (Acebutolol, Sectral)**

**Indications**

Hypertension

Ventricular arrhythmia

**Dosage**

**Adults**

**Hypertension**

Initiate with 200-400 mg/d administered in one or two divided doses. Dosage may be increased gradually based on clinical response up to 600 mg twice daily. Most patients require 400-800 mg/d.

**Ventricular arrhythmia**

Initiate with 400 mg once daily or 200 mg twice daily. Dosage may be increased until optimal response is achieved. The usual maintenance dose is 600-1200 mg/d given in two divided doses.

**Note:** The daily dose of acebutolol should be reduced by 50% when CrCl is < 50 mL/min/1.73 m². Reduce dose by 75% when CrCl is < 25 mL/min/1.73 m². Use acebutolol with caution in patients with hepatic impairment.

**Elderly**

Initiate at lowest dose and titrate to response. Avoid doses > 800 mg/d.
Appendix 2

Children
Safety and effectiveness have not been established.

Preparations
Acebutolol (generic); Sectral (Wyeth-Ayerst): 200, 400 mg capsules

2. Carteolol (Cartrol)

Indication
Hypertension

Dosage
Adults

Hypertension
Initiate with 2.5 mg once daily. Dosage may be increased gradually according to response to a maximum of 10 mg once daily. The usual maintenance dose is 2.5 or 5 mg once daily.

Note: Guidelines for dosing intervals in patients with renal impairment are as follows:

<table>
<thead>
<tr>
<th>CrCl (mL/min/1.73 m²)</th>
<th>Dosage Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>24</td>
</tr>
<tr>
<td>20-60</td>
<td>48</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>72</td>
</tr>
</tbody>
</table>

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Cartrol (Abbott): 2.5, 5 mg tablets

3. Penbutolol (Levatol)

Indication
Hypertension

Dosage
Adults

Hypertension
The usual starting and maintenance dose is 20 mg once daily. Doses of 40-80 mg/d have been well tolerated but have not shown greater effect.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparation
Levatol (Schwarz Pharma): 20 mg tablets

4. Pindolol (pindolol, Visken)

Indication
Hypertension

Dosage
Adults

Hypertension
Initiate with 5 mg twice daily. Dosage may be increased by 10 mg/d at 3- to 4-week intervals to a maximum of 60 mg/d if necessary.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Pindolol, Visken (Novartis): 5, 10 mg tablets

Dual-Acting Beta-Blockers

1. Carvedilol (carvedilol, Coreg, Coreg CR)

Indications
Heart failure (mild to severe)
Hypertension
Left ventricular dysfunction following myocardial infarction (in clinically stable patients)

Dosage
Adults

Heart failure
Carvedilol: Dosage of carvedilol must be individualized and closely monitored during the up-titration period. Dosing of digitalis, diuretics, and ACE inhibitors (if used) must be stabilized prior to initiation of carvedilol. Initiate carvedilol with 3.125 mg twice daily for 2 weeks. If this dose is tolerated, it can then be increased to 6.25 mg twice daily. Dosing should then be doubled every 2 weeks to the highest level tolerated by the patient. The maximum recommended dose is 25 mg twice daily in patients weighing < 85 kg and 50 mg twice daily in patients weighing > 85 kg. If bradycardia occurs (pulse rate < 55 beats/min), the dose of carvedilol should be reduced.

Carvedilol phosphate (Coreg CR): Start at 10 mg once daily and increase to 20, 40, and then 80 mg once daily over intervals of at least 2 weeks. Maintain lower doses if
higher doses are not tolerated.

Hypertension
Carvedilol: Initiate with 6.25 mg twice daily. Dosage may be increased to 12.5 mg twice daily after 7-14 days if tolerated and needed. A further increase to 25 mg twice daily may be made after an additional 7-14 days if necessary. The total daily dose should not exceed 50 mg.

Carvedilol phosphate (Coreg CR): Start at 20 mg once daily and increase if needed for blood pressure control to 40 mg. then 80 mg once daily over intervals of 1-2 weeks.

Left ventricular dysfunction following myocardial infarction
Carvedilol: The usual initial dose is 6.25 mg twice daily; dose may be increased after 3-10 days to 12.5 mg twice daily, then again to target maximum dose of 25 mg twice daily.

Carvedilol phosphate (Coreg CR): Start at 20 mg once daily and increase to 40 mg, then 80 mg once daily after intervals of 3-10 days. A lower starting dose or slower titration may be used.

Note: Carvedilol should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic hypotension. Because carvedilol is primarily metabolized in the liver, it should not be given to patients with severe hepatic impairment. In patients with heart failure, slower titration with temporary dose reduction or withdrawal may be required based on clinical assessment; however, this should not preclude later attempts to reintroduce or increase the dose of carvedilol.

Elderly
When switching from higher doses of immediate-release carvedilol to Coreg CR, a lower starting dose should be considered to reduce the risk of hypotension and syncope.

Children
Safety and effectiveness have not been established.

Preparations
Carvedilol (generic): 3.125, 6.25, 12.5, 25 mg tablets
Coreg (GlaxoSmithKline): 3.125, 6.25, 12.5, 25 mg tablets
Coreg CR (GlaxoSmithKline): 10, 20, 40, 80 mg capsules

2. Labetalol (labetalol, Normodyne, Trandate)

Indications
Hypertension
Severe hypertension (intravenous formulation)

Dosage
Adults
Initiate with 100 mg orally twice daily; dosage may be adjusted in increments of 100 mg two times daily every 2-3 days until desired response is reached. The usual maintenance dose is 200-400 mg twice daily. For severe hypertension, oral doses of 1.2-2.4 g daily in two to three divided doses may be needed.

Labetalol may also be administered by repeated intravenous injections. Inject 20 mg (0.25 mg/kg for an 80-kg patient) slowly over 2 min. Additional injections of 20, 40 or 80 mg may be given at 10-minute intervals until the desired blood pressure is reached or a total of 300 mg has been given. Alternatively, an intravenous infusion at a rate of 0.5-2 mg/min may be given (labetalol injection must be diluted properly for intravenous infusion); infusion rate should be adjusted according to response. The infusion should be continued until an adequate response is achieved or a total dose of 300 mg is infused. The infusion is then discontinued and oral therapy is initiated when supine blood pressure begins to increase. Initial oral dose should be 200 mg, followed by an additional oral dose of 200 or 400 mg in 6-12 h based on blood pressure response.

Elderly
Dosage adjustment based on age is not necessary.

Children
Safety and efficacy have not been established.

Preparations
Labetalol HCl (generic); Normodyne (Schering); Trandate (Prometheus): 100, 200, 300 mg tablets
Generic; Normodyne injection (Schering); Trandate injection (Prometheus): 5 mg/mL

Calcium Antagonists

1. Amlodipine (Norvasc)

Indications
Hypertension
Chronic stable angina
Vasospastic (Prinzmetal's or variant) angina

Dosage
Adults
Hypertension
Initiate with 5 mg once daily; dosage may be increased to a maximum of 10 mg once daily based on response. A lower initial dose of 2.5 mg once daily is recommended for elderly patients and patients with hepatic insufficiency.

Angina
The usual dose is 5-10 mg once daily. Use lower dose for elderly patients and patients with hepatic impairment.
Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Norvasc (Pfizer): 2.5, 5, 10 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension:
Exforge: amlodipine/valsartan: 5 mg/160 mg, 5 mg/320 mg, 10 mg/160 mg, 10 mg/320 mg
Exforge HCT: amlodipine/hydrochlorothiazide/valsartan: 5 mg/12.5 mg/160 mg, 5 mg/25 mg/160 mg, 10 mg/12.5 mg/160 mg, 10 mg/25 mg/160 mg, 10 mg/25 mg/320 mg
Lotrel (generic combination also available): amlodipine/benazepril: 2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 10 mg/20 mg, 10 mg/40 mg
Azor: amlodipine/olmesartan: 5 mg/20 mg, 5 mg/40 mg, 10 mg/20 mg, 10 mg/40 mg

Fixed-Dose Combinations for Treatment of Hypertension and Hyperlipidemia:
Caduet: amlodipine/atorvastatin: 2.5 mg/10 mg, 2.5 mg/20 mg, 2.5 mg/40 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg

2. Clevidipine (Cleviprex)

Indication
Reduction of blood pressure when oral therapy is not feasible or not desirable

Dosage
Adults
Intravenous infusion of clevidipine should be initiated at 1-2 mg/h, and titrated by doubling the dose at 90-second intervals initially. Once the target blood pressure range is approached, the dose may be increased by less than double and at longer intervals of 5-10 minutes. The maintenance dose usually ranges between 4-6 mg/h, and can go up to a maximum of 16-32 mg/h for severe hypertension. Due to lipid load restrictions, no more than 1000 mL or an average of about 21 mg/h of clevidipine infusion is recommended per 24-hour period.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and efficacy have not been established

Preparations
Cleviprex (clevidipine butyrate injectable emulsion for intravenous use, Hospira): 0.5 mg/mL, 50 and 100 mL

3. Diltiazem (diltiazem, Cardizem, Cardizem SR, Cardizem CD, Cardizem LA, Cartia, XT, Dilacor XR, Diltia XT, Tiazac)

Indications
Angina
Atrial fibrillation or flutter (Cardizem injectable)
Hypertension
Paroxysmal supraventricular tachycardia (Cardizem injectable)

Dosage
Adults
Short-acting (diltiazem, Cardizem)
As an antianginal agent, the usual initial dose is 30 mg four times daily (before meals and at bedtime). Dosage should be increased gradually at 1- to 2-day intervals. Maximum daily dose is 360 mg.

Extended release (Cardizem LA)
For hypertension, start with 180-240 mg once daily. The usual dose range is 180-480 mg/d.

Sustained-release (Cardizem SR)
As monotherapy for hypertension, start with 60-120 mg twice daily, although some patients may respond well to lower doses. The usual dosage range is 240-360 mg/d.

Sustained-release (Cardizem CD, Cartia XT)
As monotherapy for hypertension, initiate at 180-240 mg once daily. The usual dose range in clinical trials was 240-360 mg/d. Some patients may respond to higher doses of up to 480 mg once daily. For angina, start with 120 or 180 mg once daily. Dosage may be titrated upward every 7-14 days to a maximum of 480 mg once daily if necessary.

Sustained-release (Dilacor XR, Diltia XT)
For hypertension, initiate at 180-240 mg once daily. Adjust dose as needed depending on antihypertensive response. In clinical trials, the therapeutic dose range is 180-540 mg once daily. For angina, initiate at 120 mg once daily. Dosage may be titrated upward every 7-14 days up to a maximum of 480 mg once daily if needed.

Sustained-release (Tiazac)
The usual initial dose is 120-240 mg once daily. Maximum effect is observed after 14 days. Doses up to 540 mg daily were shown to be effective in clinical trials. For angina, initiate with 120-180 mg once daily. Dosage may be
Therapeutic Use of Available Cardiovascular Drugs

increased every 7-14 d as needed to a maximum dose of 540 mg once daily.

Injection (diltiazem IV, Cardizem IV)
Direct intravenous single injections (bolus): Administer 0.25 mg/kg as a bolus over 2 min (20 mg is a reasonable dose for a patient with an average weight). If response is inadequate, a second dose may be administered after 15 min (25 mg or 0.35 mg/kg is a reasonable dose).

Intravenous infusion
An intravenous infusion may be administered for continued reduction of the heart rate (up to 24 h) in patients with atrial fibrillation or atrial flutter. Start an infusion at a rate of 10 mg/h immediately after bolus administration of 0.25 or 0.35 mg/kg. Some patients may maintain response to an initial rate of 5 mg/h. The infusion rate may be increased in 5 mg/h increments up to 15 mg/h as needed. Infusion duration longer than 24 h and infusion rate > 15 mg/h are not recommended (refer to manufacturer’s package insert for proper dilution of diltiazem injection for continuous infusion).

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Tablets (Diltiazem, Cardizem): 30, 60, 90, 120 mg
Tablets, extended release (Cardizem LA): 120, 180, 240, 300, 360, 420 mg
Capsules, sustained release (Cardizem SR): 60, 90, 120 mg
Capsules, extended release (Cardizem CD, Cartia XT): 120, 180, 240, 300 mg
Capsules, extended release (Dilacor XR, Diltia XT): 120, 180, 240 mg
Capsules, extended release (Tiazac): 120, 180, 240, 300, 360 mg
Injection (as hydrochloride): 5 mg/mL (5 mL, 10 mL)

Fixed-Dose Combinations for Treatment of Hypertension:
Teczem—5 mg of enalapril maleate/180 mg of diltiazem malate ER (extended-release) combination tablets

4. Felodipine (Plendil)

Indication
Hypertension

Dosage
Adults
The usual initial dose is 5 mg once daily. Dosage may be increased by 5 mg at 2-week intervals according to response. Maintenance dose range from 2.5-10 mg once daily.

Elderly
A lower initial dose of 2.5 mg once daily is recommended.

Children
Safety and effectiveness have not been established.

Preparations
Plendil (Astra Zeneca): 2.5, 5, 10 mg extended-release tablets

Fixed-Dose Combinations for Treatment of Hypertension:
Lexxel—5 mg of enalapril maleate/5 mg of felodipine ER (extended-release) combination tablets

5. Isradipine (isradipine, DynaCirc, DynaCirc CR)

Indication
Hypertension

Dosage
Adults
Immediate-release (DynaCirc)
Initiate at 2.5 mg twice daily alone or in combination with a thiazide diuretic. Dosage may be adjusted in increments of 2.5-5 mg/d at 2- to 4-week intervals if needed. The maximum daily dose is 20 mg.

Note: Most patients show no further improvement with doses > 10 mg/d; adverse reactions are increased in frequency with doses > 10 mg/d.

Controlled-release (DynaCirc CR)
Initiate at 5 mg once daily alone or in combination with a thiazide diuretic.

Dosage may be adjusted in increments of 5 mg/d at 2- to 4-week intervals if needed. The maximum daily dose is 20 mg. Adverse experiences are increased in frequency at daily dose above 10 mg.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
DynaCirc (Reliant): 2.5, 5 mg capsules
DynaCirc CR (Reliant): 5, 10 mg controlled-release tablets
6. Nicardipine (nicardipine, Cardene, Cardene SR)

Indications
Hypertension (Cardene, Cardene SR)
Short-term treatment of hypertension when oral therapy cannot be given (Cardene IV)
Angina (Cardene)

Dosage
Adults
Immediate-release (Cardene)
As an antianginal or antihypertensive agent, administer 20 mg in capsule form three times daily. The usual maintenance dose is 20-40 mg three times daily. Allow at least 3 days between dose increases. For patients with renal impairment, titrate dose beginning with 20 mg three times daily. For patients with hepatic impairment, titrate dose starting with 20 mg twice daily.

Sustained-release (Cardene SR)
Initiate treatment with 30 mg twice daily. The effective dose ranges from 30-60 mg twice daily. For patients with renal impairment, carefully titrate dose beginning with 30 mg twice daily. The total daily dose of immediate-release product may not automatically be equivalent to the daily sustained-release dose; use caution in converting.

Injection (Cardene IV)
Intravenously administered nicardipine injection must be diluted before infusion. Administer (concentration of 0.1 mg/mL) by slow, continuous infusion. Blood pressure–lowering effect is seen within minutes. For gradual blood pressure lowering, initiate at 50 mL/h (5 mg/h). Infusion rate may be increased by 25 mL/h (2.5 mg/h) every 15 min to a maximum of 150 mL/h (15 mg/h). For rapid blood pressure reduction, initiate at 50 mL/h. Increase infusion rate by 25 mL/h every 5 min to a maximum of 150 mL/h until desirable blood pressure lowering is reached. Infusion rate must be decreased to 30 mL/h (3 mg/h) when desirable blood pressure is achieved. Conditions requiring infusion adjustment include hypotension and tachycardia. The intravenous infusion rate required to produce an average plasma concentration equivalent to a given oral dose at steady state is as follows:

<table>
<thead>
<tr>
<th>Oral Dose (Immediate-Release)</th>
<th>Equivalent IV Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg q 8 h</td>
<td>0.5 mg/h</td>
</tr>
<tr>
<td>30 mg q 8 h</td>
<td>1.2 mg/h</td>
</tr>
<tr>
<td>40 mg q 8 h</td>
<td>2.2 mg/h</td>
</tr>
</tbody>
</table>

Intravenous nicardipine should be transferred to oral medication for prolonged control of blood pressure as soon as the clinical condition permits. If treatment includes transfer to an oral antihypertensive agent other than nicardipine, generally initiate therapy upon discontinuation of the infusion. If oral nicardipine is to be used, administer the first dose of a three times daily regimen 1 h before discontinuation of the infusion.

Elderly
Dosage adjustment is not necessary.

Children
Safety and effectiveness have not been established.

Preparations
Nicardipine HCl (generic); Cardene (Roche): 20, 30 mg capsules
Cardene SR (Roche): 30, 45, 60 mg sustained-release capsules
Cardene IV (Wyeth-Ayerst): 2.5 mg/mL injection, 10 mL ampules (generic IV nicardipine is also available in premixed bags)

7. Nifedipine (nifedipine, Adalat, Adalat CC, Nifedical XL, Procardia, Procardia XL)

Indications
Chronic stable angina (nifedipine, Adalat, Nifedical XL, Procardia, Procardia XL)
Hypertension (Adalat CC, Nifedical XL, Procardia XL)
Vasospastic angina (nifedipine, Adalat, Nifedical XL, Procardia, Procardia XL)

Dosage
Adults
Short-acting (nifedipine, Adalat, Procardia)
As an antianginal, initiate nifedipine in the capsule form at 10 mg three times daily; dosage may be increased gradually over 7-14 days as needed. For hospitalized patients under close supervision, dosage may be increased by 10 mg increments over 4-6 h periods until symptoms are controlled. For elderly patients and patients with hepatic impairment, initiate treatment at 10 mg twice daily and monitor carefully.

Note: Current labeling states that the short-acting product should not be used for hypertension, hypertensive crisis, acute MI, and some forms of unstable angina and chronic stable angina.

Extended-release (Adalat CC)
Initiate with 30 mg once daily and titrate over a 7-14 day period according to response. The usual maintenance dose is 30-60 mg once daily. Titration to doses > 90 mg daily is not recommended.
Extended-release (Nifedical XL, Procardia XL)
Initiate with 30 or 60 mg once daily and titrate over a period of 7-14 days according to response. Titration may proceed more rapidly if the patient is frequently assessed. Titration to doses > 120 mg daily is not recommended. Angina patients maintained on the short-acting formulation (nifedipine capsule) may be switched to the extended-release tablet at the nearest equivalent total daily dose. Experience with doses > 90 mg daily in patients with angina is limited.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Nifedipine (generic); Adalat (Bayer); Procardia (Pfizer): 10, 20 mg liquid-filled capsules
Adalat CC (Bayer): 30, 60, 90 mg sustained-release tablets
Procardia XL (Pfizer): 30, 60, 90 mg sustained-release tablets
Nifedical XL (TEVA) tablets: 30, 60 mg
Generic SR tablets: 30, 60, 90 mg

8. Nimodipine (Nimotop)

Indication
Subarachnoid hemorrhage

Dosage
Adults
The usual dose is 60 mg q 4 h beginning within 96 h of subarachnoid hemorrhage and continuing for 21 days. Dosage should be reduced to 30 mg q 4 h with close monitoring of blood pressure and heart rate in patients with hepatic cirrhosis.

Note: This medication is given preferably not less than 1 h before or 2 h after meals. If the capsule cannot be swallowed (eg, time of surgery, unconscious patient), make a hole in both ends of the capsule with an 18-gauge needle and extract the contents into a syringe. Empty the contents into the patient’s in situ nasogastric tube and wash down the tube with 30 mL of normal saline.

Elderly
Use usual dose with caution.

Children
Safety and effectiveness have not been established.

Preparations
Nimotop (Bayer): 30 mg liquid-filled capsules

9. Nisoldipine (nisoldipine extended release, Sular)

Indication
Hypertension

Dosage
Adults
Coat-core extended-release tablets
Initiate at 20 mg orally once daily; dosage may be increased by 10 mg per week (or at longer intervals) to attain adequate response. The usual maintenance dose is 20-40 mg once daily. Doses greater than 60 mg daily are not recommended. For elderly patients and patients with hepatic function impairment, initiate with a dose not exceeding 10 mg daily. Monitor blood pressure closely during any dosage adjustment.

Hydrogel extended-release tablets
Initiate at 17 mg once daily; dosage may be increased by 8.5 mg per week (or at longer intervals) to attain adequate response. The usual maintenance dose is 17.5-34 mg once daily. The maximum daily dose is 34 mg once daily.

Note: Nisoldipine has been used safely with diuretics, ACE inhibitors, and beta-blockers. Administration of this medication with a high fat meal can lead to excessive peak drug concentration and should be avoided. In addition, grapefruit products should be avoided before and after dosing.

Elderly
Initiate at lower dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Nisoldipine (generic, Astra Zeneca, Sciele Pharma): 20, 30, 40 mg extended release tablets
Sular (Sciele Pharma): 8.5, 10, 17, 20, 25.5, 34, 40 mg extended release tablets


Indications
Angina (all oral immediate-release formulations and Covera-HS)
Arrhythmias (all oral immediate-release formulations)
Hypertension (all oral formulation)
Supraventricular tachyarrhythmias (intravenous formulations)

Dosage

**Adults**

**Immediate-release tablets** *(verapamil, Calan, Isoptin)*
As an antianginal, antiarrhythmic, and antihypertensive, initiate at 80-120 mg three times daily. Dosage may be increased at daily or weekly intervals as needed and tolerated. Limit to 480 mg daily in divided doses.

**Sustained-release capsules** *(Verelan)*
As an antihypertensive, initiate at 120-240 mg once daily. Dosage may be adjusted in increments of 60-120 mg/d at daily or weekly intervals as needed and tolerated. The usual daily dose range is 240-480 mg.

**Sustained-release tablets** *(verapamil SR, Calan SR, Isoptin SR)*
As an antihypertensive, initiate at 120-240 mg once daily with food. Dosage may be adjusted in increments of 60-120 mg/d at daily or weekly intervals as needed and tolerated. The usual total daily dose range is 240-480 mg.

**Extended-release tablets, controlled onset** *(Covera-HS)*
Initiate with 180 mg at bedtime for both hypertension and angina. If response is inadequate, the dose may be titrated upward to 480 mg/d given at bedtime.

**Extended-release capsules, controlled onset** *(Verelan PM)*
Initiate with 200 mg dose at bedtime for hypertension; if response is inadequate, the dose may be titrated upward to 300 or 400 mg/d given at bedtime.

**Injection** *(verapamil IV, Isoptin IV)*
Initiate at 5-10 mg (or 0.075-0.15 mg/kg) slowly over at least 2 min with continuous electrocardiographic and blood pressure monitoring. If response is inadequate, 10 mg (or 0.15 mg/kg) may be administered 30 min after completion of the initial dose.

*Note:* Less than 1% of patients may have life-threatening adverse responses (rapid ventricular rate in atrial flutter/fibrillation, marked hypotension, or extreme bradycardia/asystole) to verapamil injections. Monitor the initial use of intravenous verapamil and have resuscitation facilities available. An intravenous infusion (5 mg/h) has also been used; precede the infusion with an intravenous loading dose.

**Elderly**
Initiate the oral formulation of verapamil at lower dose and titrate to response. Intravenous injections should be given slowly over a longer period of time (at least 3 min) to minimize undesired effects.

Children
Safety and effectiveness have not been established. However, there has been experience with the use of verapamil in the pediatric population.

Preparations

**Tablets, immediate release** *(verapamil, Calan, Isoptin)*:
40, 80, 120 mg

**Capsules, sustained-release** *(Verelan)*:
120, 180, 240, 360 mg

**Tablets, extended-release and controlled onset** *(Covera-HS)*:
180, 240 mg

**Capsules, extended-release and controlled onset** *(Verelan PM)*:
100, 200, 300 mg

**Tablets, sustained-release** *(verapamil)*:
120, 180, 240 mg

**Tablets, sustained-release** *(Calan SR, Isoptin SR)*:
120, 180, 240 mg

**Injection** *(verapamil IV, Isoptin IV)*:
5 mg/2 mL (2- and 4-mL ampules and vials; syringes)

**Fixed-Dose Combinations for Treatment of Hypertension:**
Tarka—trandolapril/verapamil hydrochloride ER combination tablets: 2 mg/180 mg, 1 mg/240 mg, 2 mg/240 mg, 4 mg/240 mg

**Diuretics**

**Loop Diuretics**

1. **Bumetanide** *(bumetanide, Bumex)*

**Indications**
Edema associated with CHF, hepatic cirrhosis, or renal disease, including the nephrotic syndrome

**Dosage**

**Adults**
**Oral formulation**
The usual dose range is 0.5-2 mg/d as a single dose. Higher dosage ( > 1-2 mg/d) may be required to achieve the desired therapeutic response in patients with renal insufficiency. If the initial diuresis is inadequate, repeated doses may be administered q 4-6 h until the desired diuretic response is achieved or until a maximum daily dosage of 10 mg is administered. An intermittent dose schedule, given on alternate days or daily for 3-4 days with rest periods of 1-2 days in between, may be used for the continued control of edema. Dosage should be kept to a minimum with careful adjustments in dosage for patients with hepatic impairment.
Intravenous or intramuscular formulations

Parenteral administration of bumetanide should be reserved for patients in whom GI absorption may be impaired or in whom oral administration is not feasible. Initiate at 0.5-1 mg intravenously or intramuscularly. Intravenous injection should be given over a period of 1-2 min. If the initial diuresis is inadequate, repeated doses may be administered q 2-3 h until the desired diuretic response is achieved or until a maximum daily dosage of 10 mg is administered.

Elderly

Initiate at lowest dose and titrate to response.

Children

Safety and effectiveness have not been established.

Preparations

Bumetanide (generic); Bumex (Roche): 0.5, 1, 2 mg tablets
Bumetanide injection (generic); Bumex injection (Roche): 0.25 mg/mL

2. Ethacrynic Acid (Edecrin, Edecrin Sodium Intravenous)

Indications

Ascites associated with malignancy, idiopathic edema, and lymphedema
Edema associated with CHF, hepatic cirrhosis, or renal disease, including the nephrotic syndrome
Rapid diuresis (eg, in acute pulmonary edema) or when oral administration is not feasible (IV formulation)
Hospitalized pediatric patients with congenital heart disease or the nephrotic syndrome (not indicated for infants)

Dosage

Adults

Oral formulation

Initiate at 25-50 mg (lower doses should be used in patients who are receiving other diuretics concurrently) once daily after a meal. Dosage may be adjusted at 25-50 mg increments daily until the desired response is achieved or until a maximum dose of 100 mg twice daily is given. A dose of 200 mg twice daily may be required to maintain adequate diuresis in patients with severe refractory edema. An intermittent dose schedule, given on alternate days or daily for 3-4 days with rest periods of 1-2 days in between, may be used for the continued control of edema after an effective diuresis is obtained.

Intravenous formulations

Intravenous administration of ethacrynic acid sodium should be reserved for patients in whom a rapid onset of diuresis is desired such as in acute pulmonary edema, or when oral administration is not feasible. The usual adult intravenous dose is 0.5-1 mg/kg (up to 100 mg in a single intravenous dose) or 50 mg for an adult of average size. After reconstitution, ethacrynate sodium solution may be infused slowly (over 20-30 min) through the tubing of a running intravenous infusion or by direct intravenous injection over several minutes. If the desired diuresis is not achieved with the first dose of ethacrynate sodium, a second dose may be given after 2-3 h at a new injection site.

Elderly

No dosage adjustment is required.

Children

Safety and effectiveness have not been established in children for intravenous administration and in infants for oral as well as intravenous administration.

Preparations

Edecrin (Merck): 25, 50 mg tablets
Edecrin Sodium (Merck): 50 mg/vial, powder for injection

3. Furosemide (furosemide, Lasix)

Indications

Edema associated with CHF, hepatic cirrhosis, or renal disease, including the nephrotic syndrome
Hypertension (oral formulation)

Dosage

Adults

Edema (oral formulation)

The usual oral dose is 20-80 mg given as a single dose. The same dose may be repeated, or adjusted in increments of 20-40 mg q 6-8 h until the desired diuresis is achieved. The effective dose may then be given once or twice daily to maintain adequate fluid balance. For chronic maintenance therapy, furosemide given on alternate days or intermittently on 2-4 consecutive days each week is preferred. A maximum oral dose of 600 mg/d has been used in patients with severe fluid overload.

Edema (intravenous formulation)

The usual dose is 20-40 mg given as a single injection. The intravenous route is preferred when rapid diuresis is indicated. The same dose may be repeated or adjusted in 20-40 mg increment q 1-2 h until the desired response is achieved. Each intravenous dose should be administered over a few minutes. Furosemide has also been administered as a continuous intravenous infusion in some patients to maintain adequate urine flow. A bolus of 20-40 mg should be given first, followed by an infusion with an initial rate of 0.25-0.5 mg/min. The infusion rate may be titrated up to a maximum of 4 mg/min according to clinical response.
**Hypertension**

The usual initial dose is 40 mg orally twice daily; dosage should then be adjusted according to clinical response. The maximum dose is 240 mg/d in two to three divided doses. Higher doses may be required for the management of edema or hypertension in patients with renal insufficiency or CHF. These patients should be monitored closely to assure efficacy and avoid undesired toxicity.

**Elderly**

No dosage adjustment is required.

**Children**

Safety and effectiveness have been established in children for the management of edema but not for hypertension.

**Preparations**

- Furosemide (generic); Lasix (Aventis): 20, 40, 80 mg tablets
- Furosemide (generic); Lasix (Aventis): 10 mg/mL, 40 mg/5 mL oral solution
- Furosemide (generic); Lasix (Aventis): 10 mg/mL injection, in 2, 4, and 10 mL single-dose vials

**4. Torsemide (Demadex)**

**Indications**

- Edema associated with CHF, hepatic cirrhosis, or renal disease, including the nephrotic syndrome
- Hypertension (oral formulation)

**Dosage**

**Adults**

**CHF/chronic renal failure**

The usual initial dose is 10-20 mg once daily via oral or intravenous administration. If the diuretic response is inadequate, the dose may be doubled until the desired response is achieved or until a maximum single dose of 200 mg is given.

**Hepatic cirrhosis**

The usual initial dose is 5-10 mg once daily administered orally or intravenously along with an aldosterone antagonist or a potassium-sparing diuretic. If the diuretic response is inadequate, the dose may be doubled until the desired response is achieved or until a maximum single dose of 40 mg is given.

**Note:** Because of high bioavailability, oral and intravenous doses are therapeutically equivalent. Therefore, patients may be switched to and from the intravenous form with no change in dose. The intravenous injection should be administered slowly over a period of 2 min.

**Hypertension**

The usual initial dose is 5 mg orally once daily. If adequate reduction in blood pressure is not achieved in 4-6 weeks, the dose may be increased up to 10 mg once daily. If the blood pressure response is still inadequate, an additional antihypertensive agent should be added.

**Elderly**

No dosage adjustment is required.

**Children**

Safety and effectiveness have not been established.

**Preparations**

- Demadex (Roche): 5, 10, 20, 100 mg tablets
- Demadex injection (Roche): 10 mg/mL

**Thiazide Diuretics**

1. **Bendroflumethiazide (Available only in combination with nadolol-Corzide)**

**Indications**

- Hypertension (Corzide)

**Dosage**

**Adults**

**Hypertension**

The initial dose is 5 mg bendroflumethiazide + 40 mg nadolol once daily, eventually increasing to 5 mg/80 mg once daily if desired.

**Elderly**

No dosage adjustment is required.

**Children**

Safety and effectiveness have not been established.

**Preparations**

- Fixed-Dose Combinations for Treatment of Hypertension: Corzide 80/5—Bendroflumethiazide 5 mg/Nadolol 80 mg
- Corzide 40/5—Bendroflumethiazide 5 mg/Nadolol 40 mg

2. **Benzthiazide (Exna)**

**Indications**

- Edema
- Hypertension

**Dosage**

**Adults**

**Edema**

Initiate at 50-200 mg/d given in one to two doses for a few days until the desired diuresis is achieved (dosages above 100 mg/d should be divided and administered in
two daily doses). The usual maintenance dose is 50-150 mg/d. Electrolyte imbalance may occur less frequently by administering benzthiazide every other day or on a 3-to-5 days per week schedule during maintenance therapy.

**Hypertension**
Initiate at 25-50 mg twice daily after breakfast and lunch; dosage may be titrated up to a maximum of 100 mg twice daily if necessary.

**Elderly**
No dosage adjustment is required

**Children**
Safety and effectiveness have not been established.

**Preparation**
Exna (Robbins): 50 mg tablets

**3. Chlorothiazide (chlorothiazide, Diuril, Sodium Diuril various generics)**

**Indications**
Edema
Hypertension (oral formulation)

**Dosage**
**Adults**
**Edema**
Administer 500-1000 mg once daily in the morning or twice daily orally or intravenously (The intravenous route should be reserved for patients who are unable to take oral medication or for emergency situations). Electrolyte imbalance may occur less frequently by administering chlorothiazide every other day or on a 3-to-5 days per week schedule during maintenance therapy.

**Hypertension**
Initiate at 250-500 mg once daily in the morning or twice daily; dosage may be titrated up to a maximum of 2000 mg (2 g)/d given in divided doses.

**Elderly**
No dosage adjustment is required

**Children**
Safety and effectiveness have been established for the oral formulation, but not for the intravenous formulation.

**Preparations**
Chlorothiazide (generic); Diuril (Merck): 250, 500 mg tablets
Diuril (Merck): 250 mg/5 mL oral suspension
Sodium Diuril (Merck): 500 mg, powder for injection

**Fixed-Dose Combinations for Treatment of Hypertension:**
Chloroserpine—chlorothiazide  500 mg/reserpine 0.125 mg
Chloroserpine—chlorothiazide  250 mg/reserpine 0.125 mg
Aldoclor 250—chlorothiazide  250 mg/methyldopa 250 mg
Aldoclor 150—chlorothiazide  150 mg/methyldopa 250 mg

**4. Chlorthalidone (chlorthalidone, Hygroton, Thalitone)**

**Indications**
Edema
Hypertension

**Dosage**
**Adults**
**Edema**
Administer 50-100 mg (Thalitone, 30-60 mg) daily or 100 mg (Thalitone, 60 mg) on alternate days. Some patients may require doses up to 200 mg (Thalitone, 120 mg) daily.

**Hypertension**
Initiate at 25 mg (Thalitone, 15 mg) once daily. Dosage may be increased gradually to a maximum of 100 mg once daily (Thalitone, 50 mg) if needed.

**Note:** Dosages above 25 mg/d (Thalitone, 15 mg/d) are likely to potentiate potassium waste but provide no further benefit in sodium excretion or blood pressure reduction.

**Elderly**
No dosage adjustment is required.

**Children**
Safety and effectiveness have not been established.

**Preparations**
Chlorthalidone (generic): 25, 50, 100 mg tablets
Thalitone (Monarch): 15 mg tablets, 25 mg tablets
Hygroton (RPR): 50, 100 mg tablets

**Fixed-Dose Combinations for Treatment of Hypertension:**
Combipres 0.1—chlorthalidone 15 mg/clonidine 0.1 mg combination tablets
Combipres 0.2—chlorthalidone 15 mg/clonidine 0.2 mg combination tablets
Combipres 0.3—chlorthalidone 15 mg/clonidine 0.3 mg combination tablets
Tenoretic 50—chlorthalidone 25 mg/atenolol 50 mg combination tablets
Tenoretic 100—chlorthalidone 25 mg/atenolol 100 mg combination tablets
5. Hydrochlorothiazide (hydrochlorothiazide, HydroDIURIL, various other brands and generics)

Indications
Edema
Hypertension

Dosage
Adults

Edema
Administer 25-200 mg/d in one to three divided doses for a few days until the desired diuresis is achieved. The usual maintenance dose is 25-100 mg/d. Electrolyte imbalance may occur less frequently by administering hydrochlorothiazide every other day or on a 3-to-5 days per week schedule during maintenance therapy.

Hypertension
Initiate at 12.5-25 mg once daily in the morning. Dosage may be titrated up to 50 mg once daily according to response. Doses > 50 mg are often associated with significant reductions in serum potassium.

Elderly
No dosage adjustment is required.

Children
Hydrochlorothiazide should be dosed based on body weight and clinical response.

Preparations
Hydrochlorothiazide (generic); HydroDIURIL (Merck): 25, 50 mg tablets
Microzide (Watson): 12.5 mg capsules
Hydrochlorothiazide (generic): 50 mg/5 mL oral solution
Various fixed-dose combinations in conjunction with ACE inhibitors, ARBs, beta-blockers, and other antihypertensive drugs are available for the treatment of hypertension

6. Hydroflumethiazide (hydroflumethiazide, Diurid, Saluron)

Indications
Edema
Hypertension

Dosage
Adults

Edema
Initiate at 50 mg once or twice a day. The usual maintenance dose ranged from 25-200 mg/d (administer in two divided doses when dosage exceeds 100 mg/d). Electrolyte imbalance may occur less frequently by administering hydroflumethiazide every other day or on a 3-to-5 days per week schedule during maintenance therapy.

Hypertension
The usual maintenance dose is 50-100 mg/d. Do not exceed 200 mg/d.

Elderly
No dosage adjustment is required.

Children
Safety and effectiveness have not been established.

Preparations
Hydroflumethiazide (generic); Diurid (Wyeth-Ayerst); Saluron (Apothecon): 50 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension:
Salutensin Tablets:
Hydroflumethiazide 50 mg/Reserpine 0.125 mg

7. Indapamide (indapamide, Lozol)

Indications
Edema associated with heart failure
Hypertension

Dosage
Adults

Edema
Initiate at 2.5 mg once daily in the morning. Dosage may be increased to 5 mg once daily according to response. Electrolyte imbalance may occur less frequently by administering indapamide every other day or on a 3-to-5 days per week schedule during maintenance therapy.

Hypertension
Initiate at 1.25 mg once daily in the morning. Dosage may be increased gradually to 5 mg once daily according to response.

Elderly
No dosage adjustment is required.

Children
Safety and effectiveness have not been established.

Preparations
Indapamide (generic): 2.5 mg tablets
Lozol (Aventis): 1.25, 2.5 mg tablets

8. Methyclothiazide (methyclothiazide, Endurin)
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### Methyclothiazide

**Indications**
- Edema
- Hypertension

**Dosage**

<table>
<thead>
<tr>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Edema</strong></td>
</tr>
<tr>
<td>Initiate at 2.5-10 mg once daily in the morning. The usual maintenance dose is 2.5-5 mg once daily. Electrolyte imbalance may occur less frequently by administering methyclothiazide every other day or on a 3-to-5 days per week schedule during maintenance therapy.</td>
</tr>
</tbody>
</table>

**Hypertension**
- Administer 2.5-5 mg once daily in the morning.

**Elderly**
- No dosage adjustment is required.

**Children**
- Safety and effectiveness have not been established.

**Preparations**
- Methyclothiazide (generic): 2.5, 5 mg tablets
- Aquatensen (Wallace); Enduron (Abbott): 5 mg tablets

*Fixed-Dose Combinations for Treatment of Hypertension:*
- Diutensen-R Tablets (Wallace): methyclothiazide 2.5 mg/reserpine 0.1 mg

### Metolazone (Mykrox, Zaroxolyn)

**Indications**
- Edema (Zaroxolyn only)
- Hypertension (Mykrox and Zaroxolyn)

**Dosage**

<table>
<thead>
<tr>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Edema</strong></td>
</tr>
<tr>
<td>Administer Zaroxolyn at 5-10 mg/d given once daily in the morning. Dosage up to 20 mg once daily may be used in patients with renal insufficiency. The usual maintenance dose for Zaroxolyn is 2.5-10 mg given once daily in the morning. Electrolyte imbalance may occur less frequently by administering metolazone every other day or on a 3-to-5 days per week schedule during maintenance therapy.</td>
</tr>
</tbody>
</table>

**Hypertension**
- Administer 2.5-5 mg of Zaroxolyn or 0.5-1 mg of Mykrox once daily in the morning.

**Elderly**
- No dosage adjustment is required.

**Children**
- Safety and effectiveness have not been established.

**Preparations**
- Mykrox (Celltech): 0.5 mg tablets
- Zaroxolyn (Celltech): 2.5, 5, 10 mg

### Polythiazide (Renese)

**Indications**
- Edema
- Hypertension

**Dosage**

<table>
<thead>
<tr>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Edema</strong></td>
</tr>
<tr>
<td>Administer 1-4 mg once daily in the morning. Electrolyte imbalance may occur less frequently by administering polythiazide every other day or on a 3-to-5 days per week schedule during maintenance therapy.</td>
</tr>
</tbody>
</table>

**Hypertension**
- Administer 2-4 mg once daily in the morning.

**Elderly**
- No dosage adjustment is required.

**Children**
- Safety and effectiveness have not been established.

**Preparations**
- Renese (Pfizer): 1, 2, 4 mg tablets

*Fixed-Dose Combinations for Treatment of Hypertension:*
- Minizide Capsules:
  - Polythiazide 0.5 mg/prazosin 1 mg
  - Polythiazide 0.5 mg/prazosin 2 mg
  - Polythiazide 0.5 mg/prazosin 5 mg
- Renese-R Tablets:
  - Polythiazide 2 mg/reserpine 0.25 mg

### Quinethazone (Hydromox)

**Indications**
- Edema
- Hypertension

**Note:** The metolazone formulations are not bioequivalent or therapeutically equivalent at the same doses. When switching from Zaroxolyn to Mykrox, determine the dose by titration starting at 0.5 mg once daily and increasing to 1 mg once daily according to response.
Dosage

**Adults**

**Edema**
Administer 25-200 mg/d as a single dose in the morning or in two divided doses. Electrolyte imbalance may occur less frequently by administering quinethazone every other day or on a 3-to-5 days per week schedule during maintenance therapy.

**Hypertension**
Administer 25-100 mg/d as a single dose in the morning or in two divided doses.

**Elderly**
No dosage adjustment is required.

**Children**
Safety and effectiveness have not been established.

**Preparation**
Hydromox (Lederle): 50 mg tablets

### Potassium-Sparing Diuretics

1. **Amiloride (amiloride, Midamor)**

**Indications**
As adjunctive therapy with thiazide or other kaliuretic diuretics in CHF or hypertension to prevent excessive potassium loss

**Dosage**

**Adults**
This drug is intended for use with either a thiazide or a loop diuretic. Administer 5-10 mg once daily. Although dosages > 10 mg/d are usually not necessary, higher doses (up to 20 mg/d) have been used occasionally in some patients with persistent hypokalemia.

**Elderly**
No dosage adjustment is required.

**Children**
Safety and effectiveness have not been established.

**Preparations**
Amiloride (generic); Midamor (Merck): 5 mg tablets

2. **Eplerenone (Inspra)**

(This drug is usually classified as an aldosterone receptor antagonist rather than a potassium-sparing diuretic.)

**Indications**
CHF post-MI
Hypertension

**Dosage**

**Adults**

**Hypertension**
Initial dosage is 50 mg once daily. Maintenance dosage is 50 mg once or twice daily. For patients receiving weak CYP3A4 inhibitors, such as erythromycin, saquinavir, verapamil, or fluconazole, the starting dose should be reduced to 25 mg once daily.

**CHF post-MI**
Initial dosage is 25 mg once daily, titrated to a maintenance dosage of 50 mg once daily, preferably within 4 weeks if tolerated by the patient. Serum potassium should be measured at baseline, within the first week, and at 1 month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter.

*Note:* Dosage must be adjusted based on serum potassium concentrations.

**Elderly**
Use adult dose with caution.

**Children**
Safety and efficacy have not been established.

**Preparations**
Inspra (Pfizer): 25, 50 mg tablets

3. **Spironolactone (spironolactone, Aldactone)**

**Indications**
Edema associated with CHF, liver cirrhosis, or nephrotic syndrome
Hypokalemia
Hypertension (usually used in conjunction with other agents such as a thiazide diuretic)
Primary hyperaldosteronism

**Dosage**

**Adults**

**Edema**
Initiate at 100 mg/d (range, 25-200 mg/d) administered as a single dose or in divided doses. If spironolactone is used as a sole agent, the treatment should be continued for at
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least 5 days at the initial dosage. Thereafter, the dose may be adjusted based on response or a more potent diuretic may be added.

**Diuretic-induced hypokalemia**
The usual dose ranged from 25-100 mg/d.

**Hypertension**
Initiate at 50-100 mg/d in single or divided doses. The usual dose ranged from 25-100 mg/d.

**Primary hyperaldosteronism (diagnostic test)**
Long test—Spironolactone 400 mg is administered daily for 3-4 weeks. Correction of hypokalemia and hypertension provides presumptive evidence for the diagnosis. Short test—Spironolactone 400 mg is administered daily for 4 days. If serum potassium level increases during the therapy but declines after discontinuation of the drug, a presumptive diagnosis should be considered.

**Hyperaldosteronism (maintenance therapy)**
Administer 100-400 mg daily in preparation for surgery. For patients who are not suitable for surgery, long-term therapy with spironolactone may be used. Dosage should be titrated individually (maintain at the lowest possible dose).

**Elderly**
No dosage adjustment is required.

**Children**
Safety and effectiveness have not been established, although spironolactone has been used safely and effectively in this population.

**Preparations**
Spironolactone (generic): 25 mg tablets
Aldactone (Pharmacia and Upjohn): 25, 50, 100 mg tablets

**Fixed-Dose Combinations for Treatment of Hypertension:**
Aldactazide tablets and various generic products:
Spironolactone 25 mg/hydrochlorothiazide 25 mg
Spironolactone 50 mg/hydrochlorothiazide 50 mg

4. **Triamterene (triamterene, Dyrenium)**

**Indications**
Edema associated with CHF, hepatic cirrhosis, nephrotic syndrome, steroid use, or secondary hyperaldosteronism Hypertension when used in combination with other diuretics

**Dosage**

**Adults**
When used as a single agent, the usual initial dose is 100 mg twice daily after meals. Dosage should not exceed 300 mg/d. Once edema is controlled, most patients can be maintained on 100 mg/d or every other day. When used in combination with a kaliuretic diuretic for the treatment of edema, the initial dose is 50 mg once daily. The dose should be titrated based on response to a maximum of 100 mg/d. When used in combination with a kaliuretic diuretic for the treatment of hypertension, the initial dose is 25 mg once daily. The dose should be titrated based on response to a maximum of 100 mg daily (some patients may benefit from splitting the daily dosage into 2 doses).

**Elderly**
Initiate at lowest dose and titrate to response.

**Children**
Safety and effectiveness have not been established.

**Preparations**
Dyrenium (Wellspring): 50, 100 mg capsules

**Fixed-Dose Combinations for Treatment of Hypertension:**
Diazide capsules: triamterene 37.5 mg/hydrochlorothiazide 25 mg
Maxzide capsules: triamterene 37.5 mg/hydrochlorothiazide 25 mg
Maxzide capsules: triamterene 75 mg/hydrochlorothiazide 50 mg
Various generic triamterene/hydrochlorothiazide tablets and capsule

**Endothelin Receptor Antagonist**

1. **Ambrisentan (Letairis)**

**Indication**
Treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening

**Dosage**

**Adults**
Initiate with 5 mg once daily. Dosage may be increased to 10 mg once daily as tolerated.

**Elderly**
Use usual adult dose with caution.

**Children**
Safety and efficacy have not been established.
Preparations
Letairis (Gilead Sciences): 5 and 10 mg tablets

2. Bosentan (Tracleer)

Indication
Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II to IV symptoms to improve exercise capacity and decrease clinical worsening.

Dosage
Adults
Initiate at 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury. Refer to Tracleer package insert for recommendations on dosage adjustment and monitoring in patients developing aminotransferase abnormalities during therapy.

Note: Because of potential liver injury and in an effort to make the chance of fetal exposure to bosentan as small as possible, bosentan may be prescribed only through the TRACLEER Access Program.

Elderly
Clinical experience has not identified differences in responses between elderly and younger patients.

Children (and in Adults < 40 kg)
Safety and efficacy in pediatric patients have not been established. In patients with a body weight below 40 kg but who are over 12 years, the recommended initial and maintenance dose is 62.5 mg twice daily.

Preparations
Tracleer (Actelion): 62.5, 125 mg tablets

3. Sitaxsentan (Thelin) (removed from market)

Indications
Treatment of primary pulmonary arterial hypertension or pulmonary hypertension secondary to connective tissue disease in patients with WHO functional class III who have not responded to conventional therapy

Treatment of primary pulmonary arterial hypertension in patients with WHO functional class II who did not respond to conventional therapy and for whom no appropriate alternative can be identified

Dosage
Adults
The usual dose is 100 mg once daily.

Elderly
Use usual adult dose.

Children
Safety and efficacy have not been established.

Preparations
Thelin (Encysive Pharmaceuticals): 100 mg tablets

Human B-Type Natriuretic Peptide

1. Nesiritide (Natrecor)

Indication
Treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.

Dosage
Adults
The recommended dose of nesiritide is an intravenous bolus of 2 μg/kg followed by a continuous infusion of 0.01 μg/kg/min. Nesiritide should not be initiated at a dose that is above the recommended dose. The dose-limiting side effect of nesiritide is hypotension. Blood pressure should be monitored closely during administration. If hypotension occurs during the administration of nesiritide, the dose should be reduced or discontinued and other measures to support blood pressure should be started (IV fluids, changes in body position). In the vasodilation in the management of acute congestive heart failure (VMAC) trial, when symptomatic hypotension occurred, nesiritide was discontinued and subsequently could be restarted at a dose that was reduced by 30% (with no bolus administration) once the patient was stabilized.

In the VMAC trial, there was limited experience with increasing the dose of nesiritide above the recommended dose. In those patients, the infusion dose of nesiritide was increased by 0.005 μg/kg/min (preceded by a bolus of 1 μg/kg), no more frequently than every 3 hours up to a maximum dose of 0.03 μg/kg/min.

Elderly
No dosage adjustment is required.

Children
Safety and effectiveness have not been established.

Preparations
Natrecor (Scios): powder for injection, lyophilized: 1.5 mg single-use vials.
Inotropic and Vasopressor Agents

Phosphodiesterase Inhibitors

1. Inamrinone Lactate (inamrinone lactate, Inocor)

Indications
Congestive heart failure, short-term management

Dosage
Adults
Initiate with an intravenous bolus dose of 0.75 mg/kg administered slowly over 2-3 min, followed by a continuous infusion of 5-10 μg/kg/min. A second bolus of 0.75 mg/kg may be given 30 min after the initial bolus dose. The total dose should not exceed 10 mg/kg/d. Rate of administration and duration of therapy should be determined by the responsiveness of the patient.

Elderly
Dose should be adjusted based on renal function.

Children
Safety and effectiveness have not been established.

Preparation
Inamrinone Lactate (Abbott Hospital): 5 mg/mL, 20 mL ampules
Inocor (Sanofi Winthrop): 5 mg/mL, 20 mL ampules

2. Milrinone Lactate (milrinone, Primacor)

Indication
Congestive heart failure, short-term management

Dosage
Adults
Initiate with an intravenous loading dose of 50 μg/kg administered slowly over 10 min, followed by a continuous infusion of 0.375 μg/kg/min. Rate of administration and duration of therapy should be determined by the responsiveness of the patient. The total dose should not exceed 1.13 mg/kg/d (or, 0.75 μg/kg/min).

The following infusion rates are recommended for patients with various renal function:

<table>
<thead>
<tr>
<th>CrCl (mL/min/1.73 m²)</th>
<th>Infusion rate (μg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 40</td>
<td>0.375</td>
</tr>
<tr>
<td>30</td>
<td>0.33</td>
</tr>
<tr>
<td>20</td>
<td>0.28</td>
</tr>
<tr>
<td>10</td>
<td>0.23</td>
</tr>
<tr>
<td>5</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Elderly
Dosage should be adjusted based on renal function.

Children
Safety and effectiveness have not been established.

Preparations
Primacor Injections (generic, Sanofi-Winthrop, Sanofi-Aventis): 1 mg/mL, 10 mL, 20 mL single-dose vials; 200 μg/mL in 100 mL of 5% dextrose injection; 200 μg/mL in 200 mL of 5% dextrose injection

Adrenergic Receptor Agonists

1. Dobutamine (dobutamine, Dobutrex)

Indication
Short-term inotropic support in patients with cardiac decompensation due to depressed contractility

Dosage
Adults
The rate of infusion required to increase cardiac output usually ranges from 2.5–15 μg/kg/min. The infusion rate and the duration of therapy should be determined based on clinical response.

Note: Consult manufacturer’s package insert for instructions on proper dilution of dobutamine injection prior to infusion.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Dobutamine (generic); Dobutrex (Lilly): 12.5 mg/mL injection, 20 mL vials

2. Dopamine (dopamine, Intropin)

Indication
Hemodynamic imbalances, after adequate fluid resuscitation

Dosage
Adults
Initially give dopamine intravenously at an infusion rate of 1-5 μg/kg/min. Adjust by increments of 1-4 μg/kg/min at intervals of 10-30 min according to clinical response. Lower initial doses are recommended for patients with
chronic heart failure (0.5-2 μg/kg/min) and for patients with occlusive vascular disease (≤ 1 μg/kg/min). Most patients respond to a dose of < 20 μg/kg/min. Severely ill patients should be given a higher initial dose of 5 μg/kg/min. Dosage may be increased gradually according to response using 5-10 μg/kg/min increments, up to a maximum rate of 20-50 μg/kg/min.

Note: Consult manufacturer’s package insert for instructions on proper dilution of dopamine injection prior to infusion.

Elderly
No dosage adjustment is required.

Children
Safety and effectiveness have not been established.

Preparations
Dopamine (generic); Intropin (Bristol-Myers Squibb): 40 mg/mL, 80 mg/mL, 160 mg/mL injections
Dopamine in 5% dextrose (Abbott): 80 mg/100 mL, 160 mg/100 mL, 320 mg/100 mL

3. Isoproterenol (isoproterenol, Isuprel)

Indications
Emergency treatment of cardiac arrhythmias
Shock
Bronchospasm

Dosage
Adults
Emergency treatment of cardiac arrhythmias
The usual initial adult intravenous bolus dose is 0.02-0.06 mg (1-3 mL of a 1:50,000 dilution); subsequent doses range from 0.01-0.2 mg (0.5-10 mL of a 1:50,000 dilution). For intravenous infusion, the initial rate of administration is 5 μg/min (1.25 mL of a 1:250,000 dilution per minute or 2.5 mL of a 1:500,000 dilution per minute); subsequent dosage is adjusted based on the patient’s response and generally ranges from 2-20 μg/min.

Shock
As an adjunct therapy for the management of shock, isoproterenol is administered by intravenous infusion. Intravenous infusion rates of 0.5-5 μg (0.25-2.5 mL of a 1:500,000 dilution) per minute have been recommended; the rate of infusion should be adjusted based on the patient’s response. Rates greater than 30 μg/min have been used in advanced stages of shock. Some clinicians have recommended that isoproterenol be administered only for a short time (≤ 1 h) to patients with septic shock.

Bronchospasm
For the control of bronchospasm occurring during anesthesia, administer 0.01-0.02 mg (0.5-1 mL of a 1:50,000 dilution) of isoproterenol intravenously. This dose may be repeated if necessary.

Elderly
No dosage adjustment is required.

Children
Safety and effectiveness have not been established. However, intravenous isoproterenol has been used in children with asthma or in postoperative cardiac patients with bradycardia.

Preparations
Isoproterenol injection (generic); Isuprel injection (Sanofi): 1:5000 solution (0.2 mg/mL)
Isuprel injection (Sanofi): 1:50,000 (0.02 mg/mL)

4. Epinephrine (epinephrine, Adrenalin, various Sources)

Indications
Cardiopulmonary resuscitation/cardiac arrest
Syncope and/or bradycardia resulting from AV block

Dosage
Adults
Cardiac arrest, ventricular fibrillation, and pulseless ventricular tachycardia; pulseless electrical activity; or asystole in advanced cardiac life support
IV: The usual dose is 0.5-1 mg (usually as 5-10 mL of a 1:10,000 injection) administered by IV push. This dose may be repeated every 3-5 minutes if needed. The initial IV administration may be followed by a continuous infusion at a rate of 1-4 μg/min.

Endotracheal: 1-3 mg diluted in 10 mL of solution before instillation

Symptomatic bradycardia
The usual initial dose is 1 μg/min (1 mg in 500 mL solution) by continuous infusion. The rate is titrated based on clinical response and usually ranges from 2-10 μg/min.

Elderly
No dosage adjustment is required.

Children
Administer with caution to infants and children. Dosage should be adjusted based on weight.

Preparations
Syringes: 1 mg/mL (1:1,000) in 0.3 mL, 1 mL, 2 mL; 0.5 mg/mL (1:2,000) in 0.3 mL; 0.1 mg/mL (1:10,000) in 10 mL
Ampules: 5 mg/mL (1:200) in 0.3 mL; 1 mg/mL (1:1000) in 1 mL.
Vials: 5 mg/mL (1:200) in 5 mL; 1 mg/mL (1:1000) in 30 mL.

5. Metaraminol (metaraminol, Aramine)

Indications
- Hypotension associated with spinal anesthesia
- Hypotension due to hemorrhage, reactions to medications, surgical complications; shock associated with brain damage due to trauma or tumor

Dosage
Adults
Prevention of hypotension
The usual intramuscular dose ranges from 2-10 mg. The lowest effective dose for the shortest possible time should be used. At least 10 min should elapse before additional doses are administered.

Note: Subcutaneous administration of metaraminol has also been used. However, this mode of administration is not recommended because of increased risk of local tissue injury. When given intravenously, metaraminol is preferably given in the large veins of the antecubital fossa or the thigh.

Severe hypotension or shock
The usual dose for a single direct intravenous injection ranges from 0.5-5 mg. If necessary, the direct intravenous injection may be followed by a continuous infusion (15-100 mg in 500 mL of compatible diluent) with the rate adjusted according to blood pressure response.

Elderly
No dosage adjustment is required.

Children
Safety and effectiveness have not been established.

Preparation
Aramine (Merck): 10 mg/mL (1% as bitartrate), 10 mL vials

6. Methoxamine (Vasoxyl)

Indications
- Hypotension associated with anesthesia
- Paroxysmal supraventricular tachycardia associated with hypotension or shock

Dosage
Adults
Hypotension
Intramuscular dose ranges from 5-20 mg. A dose of 5-10 mg may be adequate when only moderate hypotension is present. In an emergency, 3-5 mg of methoxamine may be administered slowly by direct intravenous injection. Intravenous administration may be supplemented with an intramuscular dose of 10-15 mg to provide more prolonged effects.

Prevention of hypotension during anesthesia
The usual dose is 10-15 mg (up to 20 mg may be required at high levels of anesthesia) given intramuscularly shortly before or at the time of administration of the spinal anesthetic. This dose may be repeated at intervals of at least 15 min if needed.

Paroxysmal supraventricular tachycardia
Administer 10 mg (range: 5-15 mg) intravenously over 3-5 min. Alternatively, 10-20 mg may be injected intramuscularly. Systolic blood pressure should not be raised above 160 mm Hg.

Elderly
Use with caution; no dosage adjustment is required.

Children
Safety and effectiveness have not been established.

Preparation
Vasoxyl (GlaxoSmithKline): 20 mg/mL injection

7. Norepinephrine (norepinephrine, Levophed)

Indications
- Hypotensive state
- Cardiac arrest (as an adjunct for severe hypotension)

Dosage
Adults
Norepinephrine is administered by continuous intravenous infusion (ie, 4-8 mg in 500-1000 mL solution). The dose should be initiated at a rate of 0.5-1 μg/min and titrated to maintain a desired BP response.

Elderly
Dosage should be adjusted based on clinical response.

Children
Safety and effectiveness have not been established. However, there has been experience with the use of norepinephrine in the pediatric population.

Preparation
Norepinephrine injection (generic); Levophed (Sanofi): 1 mg (as bitartrate) per mL, 4 mL ampules
8. Phenylephrine (phenylephrine, Neo-Synephrine)

Indications
Hypotensive state associated with shock, drug use, or hypersensitivity reactions
Paroxysmal supraventricular tachycardia associated with hypotension or shock
Maintenance of adequate blood pressure during spinal and inhalation anesthesia

Dosage
Adults
Mild or moderate hypotension
The usual dose is 2-5 mg (range: 1-10 mg) administered subcutaneously or intramuscularly. The initial dose should not exceed 5 mg. Additional intramuscular or subcutaneous doses may be given in 1-2 h if needed. Alternatively, phenylephrine may be administered by slow intravenous injection in a dose ranging from 0.1-0.5 mg (0.2 mg is the usual dose). The intravenous dose may be repeated after 10-15 min if necessary. For convenience in administration by intravenous injection, 1 mL of phenylephrine injection containing 10 mg/mL may be diluted with 9 mL of sterile water for injection to yield a solution containing 1 mg/mL.

Severe hypotension
A continuous intravenous infusion at a rate of 100-180 μg/min should be initiated and titrated based on clinical response. Once the blood pressure is stabilized, a maintenance infusion rate of 40-60 μg/min is usually sufficient. Infusion solutions may be prepared by adding 10 mg of phenylephrine to 500 mL of diluent.

Hypotension associated with spinal anesthesia
For the prevention of hypotension during spinal anesthesia, a dose of 2 or 3 mg should be administered intramuscularly or subcutaneously 3-4 min before administration of the anesthetic agent.

For the management of hypotensive emergencies during spinal anesthesia, an initial dose of 0.2 mg may be given intravenously. Any subsequent dose should not exceed the previous dose by 0.1-0.2 mg, and a single dose should not exceed 0.5 mg.

Paroxysmal supraventricular tachycardia
Up to 0.5 mg of phenylephrine may be given by rapid intravenous injection (over 20-30 s). Subsequent doses may be given in increments of 0.1-0.2 mg if indicated and should not exceed 1 mg in a single dose.

Elderly
Dosage should be adjusted based on clinical response.

Children
Dosage should be adjusted based on weight and clinical response.

Preparations
Phenylephrine HCl (generic): Neo-Synephrine (Sanofi): 1% (10 mg/mL) injection

Other Inotropic Agents

1. Digoxin (digoxin, Lanoxicaps, Lanoxin)

Indications
Congestive heart failure
Atrial fibrillation
Atrial flutter
Paroxysmal atrial tachycardia

Dosage
Rapid digitalization
A full digitalizing dosage of digoxin may be given if other cardiac glycosides have not been administered within the previous 2 weeks. The total dosages for rapid digitalization are listed in the table (see p. 703). Peak body digoxin stores of 8-12 μg/kg are generally required for therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Higher body digoxin stores of 10-15 μg/kg are often required for control of ventricular rate in patients with atrial flutter or fibrillation. Lower loading doses (ie, 6-10 μg/kg) should be considered in patients with severe renal impairment.

Slow digitalization or maintenance therapy
The usual maintenance dosage in adults is 100-375 μg daily. For slow digitalization in children < 10 years, 25%-35% of the total dose of digoxin for rapid digitalization is administered daily. Slow digitalization is the preferred regimen in patients with heart failure and the dose should be administered orally whenever possible. Dosage requirement for each individual should be adjusted based on clinical response and renal function. It may take 1-3 weeks for a patient to reach steady-state serum digoxin concentrations depending on the renal function. In patients with severe renal impairment, a maintenance dose given every 2-3 days may be adequate to maintain desired serum digoxin concentrations.

Elderly
Dosage should be adjusted based on renal function, clinical response, and serum concentration.

Children
Dosage should be adjusted based on age, weight, renal...
Usual Digitalizing Dosages Based on Lean Body Weight in Patients with Normal Renal Function

<table>
<thead>
<tr>
<th>Age</th>
<th>Capsules*</th>
<th>Elixir†</th>
<th>Injection*</th>
<th>Tablets†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature neonates</td>
<td>—</td>
<td>20-30 μg/kg</td>
<td>15-25 μg/kg</td>
<td>20-30 μg/kg</td>
</tr>
<tr>
<td>Full-term neonates</td>
<td>—</td>
<td>25-35 μg/kg</td>
<td>20-30 μg/kg</td>
<td>25-35 μg/kg</td>
</tr>
<tr>
<td>1-24 months</td>
<td>—</td>
<td>35-60 μg/kg</td>
<td>30-50 μg/kg</td>
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</tr>
<tr>
<td>2-5 years old</td>
<td>25-35 μg/kg</td>
<td>30-40 μg/kg</td>
<td>25-35 μg/kg</td>
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<tr>
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<tr>
<td>&gt; 10 years old</td>
<td>8-12 μg/kg</td>
<td>10-15 μg/kg</td>
<td>8-12 μg/kg</td>
<td>10-15 μg/kg</td>
</tr>
</tbody>
</table>

*This loading dose is usually given in three divided doses, with 50% of the total dose given as the first dose and two additional doses (25% each) given at 4- to 8-h intervals after assessing clinical response. For intravenous administration, digoxin injection is given either undiluted over a period of at least 5 min or diluted with a fourfold or greater volume of sterile water for injection, 5% dextrose injection, or 0.9% sodium chloride injection and given over a period of at least 5 min.
†This loading dose is usually given in three divided doses, with 50% of the total dose given as the first dose and two additional doses (25% each) given at 6- to 8-h intervals after assessing clinical response.

function, clinical response, and serum concentration.

Preparations
Digoxin (generic): 0.125, 0.25 mg tablets
Lanoxin (GlaxoSmithKline): 0.125, 0.25 mg tablets
Digitek (Bertek): 0.125 mg, 0.25 mg tablets
Lanoxicaps (GlaxoSmithKline) 0.05, 0.1, 0.2 mg capsules
Digoxin elixir (generic); Lanoxin (GlaxoSmithKline): 50 μg/mL
Digoxin injection (generic): 250 μg/mL
Lanoxin injection (GlaxoSmithKline): 100 μg/mL, 250 μg/mL.

Lipid-Lowering Agents

Bile-Acid Sequestrants

1. Cholestyramine (cholestyramine, Questran, Questran Light, Prevalite)

Indications
As adjunctive therapy to diet in patients with elevated LDL cholesterol (type II hyperlipidemia)
Relief of pruritus associated with partial biliary obstruction

Dosage
Adults
Initiate at 4 g (anhydrous cholestyramine resin) one to two times daily at mealtime. The contents of 1 powder packet or 1 level scoop must be mixed with 60-180 mL water or noncarbonated beverage before administration. Maintenance dose is up to 4 g (anhydrous cholestyramine resin) 6 times daily at mealtime and at bedtime. The maximum recommended daily dose is 24 g (anhydrous cholestyramine resin).

Note: The administration time for cholestyramine should be modified to avoid interference with the absorption of other medications. Because cholestyramine may worsen constipation, patients who are constipated should be started on dosages of one packet or scoop once daily for 5-7 days, increasing by one dose per day every month up to a maximum of 6 doses per day.

Elderly
Dosage adjustment is not necessary.

Children
Optimal dosing has not been established; long-term effects are not known in this population.

Preparations
Cholestyramine (generic); Questran (Apothecon): 4 g anhydrous cholestyramine resin/9 g powder
Cholestyramine Light (generic): 4 g anhydrous cholestyramine resin/dose
Questran Light (Apothecon): 4 g (as anhydrous cholestyramine resin)/5 g powder
Prevalite (Upsher Smith): 4 g (as anhydrous cholesterylamine resin)/5.5 g powder

2. Colestipol (Colestid)

Indications
As adjunctive therapy to diet in patients with elevated LDL cholesterol (type II hyperlipidemia)

Dosage
Adults
Granules: Initiate at 5 g once or twice daily; dosage may be increased by 5 g daily at 1-2 month intervals. The usual daily dose is 5-30 g given once or in divided doses. The prescribed amount of granules must be mixed with a glassful of liquid before administration; do not take dry. Tablets: Initiate at 2 g once or twice daily; dosage may be increased by 2 g once or twice daily at 1-2 month intervals. The usual daily dose is 2-16 g given once or in divided doses. Tablets should be swallowed whole, one at a time, with plenty of water or other appropriate fluids.

Note: The administration time for colestipol should be modified to avoid interference with the absorption of other medications. Because colestipol may worsen constipation, patients who are constipated should be started on a once-daily dose for 5-7 days, increasing by one dose per day every month up to a maximum of 6 doses per day.

Elderly
Dosage adjustment is not necessary.

Children
Safety and effectiveness have not been established.

Preparations
Colestid Granules (Pharmacia and Upjohn): 5 g colestipol HCL/dose, 5 g colestipol HCl/7.5 g powder
Colestid Tablets (Pharmacia and Upjohn): 1 g

3. Colesevelam (Welchol)

Indications
As adjunctive therapy to diet and exercise used alone or in combination with an HMG-CoA reductase inhibitor as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, and apo B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia
As adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia
In combination with atorvastatin or simvastatin for the reduction of elevated total cholesterol and LDL cholesterol levels in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis), or if such treatments are unavailable.

Dosage
Adults
The recommended dose is 3 tablets taken twice daily or 6 tablets once daily. Colesevelam should be taken with a meal and liquid.

Elderly
Dosage adjustment is not necessary.

Children
Safety and effectiveness have not been established.

Preparations
Welchol (Daiichi Sankyo): 625 mg tablets

Cholesterol Absorption Inhibitor

1. Ezetimibe (Zetia)

Indications
As monotherapy or in combination with an HMG-CoA reductase inhibitor as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, and apo B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia
As adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia
In combination with atorvastatin or simvastatin for the reduction of elevated total cholesterol and LDL cholesterol levels in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis), or if such treatments are unavailable

Dosage
Adults
The usual dose is 10 mg once daily with or without food. Ezetimibe may be administered with an HMG-CoA reductase inhibitor for incremental effect. If a bile acid sequestrant (BAS) is being used concurrently, dosing of ezetimibe should occur at least 2 h before or at least 4 h after administration of the BAS.

Elderly
Use usual adult dose

Children
Treatment with ezetimibe in children < 10 years is not recommended.

Preparations
Zetia (Merck): 10 mg tablets
Fixed combination formulations:
Vytorin-ezetimibe/simvastatin: 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg
Fibric Acid Derivatives

1. Fenofibrate (Tricor, Lofibra)

Indications
As adjunctive therapy to diet for the reduction of LDL cholesterol, total cholesterol, triglycerides, and apolipoprotein B, and to increase HDL cholesterol in patients with primary hypercholesterolemia or mixed dyslipidemia (types IIa and IIb hyperlipidemias)

As adjunctive therapy to diet for the reduction of elevated triglyceride concentrations (types IV and V hyperlipidemias)

Dosage
Adults
Primary hypercholesterolemia/Mixed hyperlipidemia
The initial dose is 160 mg/d.

Hypertriglyceridemia
The initial dose ranges from 54-160 mg/d. Dosage should be individualized according to patient response and adjusted if necessary following repeat lipid determinations at 4-8 week intervals. The maximum dose is 160 mg/d.

Note: The 160 mg tablet is equivalent to the 200 mg capsule (micromized); the 54 mg tablet is equivalent to the 67 mg capsule (micronized).

Elderly
Initiate with a dose of 54 mg/d.

Children
Safety and effectiveness have not been established.

Preparations
Tablets (generic, TriCor): 48, 54, 145, 160 mg
Tablets (Triglide): 50, 160 mg
Tablets (Fenoglide): 40, 120 mg
Capsules, micronized (generic, Lofibra): 67, 134, 200 mg

2. Fenofibric Acid (Trilipix)

Indication
In combination with a statin to reduce TG and increase HDL cholesterol in patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD-risk equivalent who are on optimal statin therapy to achieve their LDL cholesterol goal

As monotherapy to reduce TG in patients with severe hypertriglyceridemia

Dosage
Adults
Co-administration therapy with statins for the treatment of mixed dyslipidemia
Fenofibric acid at 135 mg may be co-administered with a statin in patients with mixed dyslipidemia. For convenience, the daily dose of fenofibric acid may be taken at the same time as a statin, according to the dosing recommendations for each medication. Co-administration with the maximum dose of a statin has not been evaluated in clinical trials and should be avoided unless the benefits are expected to outweigh the risks.

Severe Hypertriglyceridemia
The initial dose of fenofibric acid is 45-135 mg once daily. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4-8 week intervals. The maximum dose is 135 mg once daily.

Primary Hyperlipidemia or mixed dyslipidemia
The dose of fenofibric acid is 135 mg once daily.

Elderly
Dose selection should be based on renal function

Children
Safety and efficacy have not been established.

Preparations
Trilipix (Abbott): 45, 135 mg delayed release capsules

3. Gemfibrozil (gemfibrozil, Lopid)

Indications
As adjunctive therapy to diet in patients with elevated triglyceride concentrations (types IV and V hyperlipidemias) who are at risk for pancreatitis

Reducing the risk of developing CHD in patients with type IIb hypercholesterolemia with low HDL cholesterol in addition to elevated LDL cholesterol and triglycerides and no history or symptoms of CHD after other treatments have failed

Dosage
Adults
The usual dosage is 600 mg twice daily 30 min before the morning and evening meal.

Note: Gemfibrozil may worsen renal impairment in patients with serum creatinine concentrations > 2.0 mg/dL and should therefore be used cautiously in this group.
Elderly
Dosage adjustment is not required.

Children
Safety and effectiveness have not been established.

Preparations
Gemfibrozil (generic); Lopid (Parke-Davis): 600 mg tablets

Nicotinic Acid

1. Nicotinic Acid (nicotinic acid extended-release, Niacor, Niaspan, Slo-Niacin)

Indications
As adjunctive therapy to diet for reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B, and triglyceride concentrations, and to increase HDL cholesterol in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (types IIa and IIb)

As adjunctive therapy in the management of elevated triglyceride concentrations (types IV and V hyperlipidemias) who are at risk for pancreatitis

As adjunctive therapy to diet to reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hypercholesterolemia (extended-release niacin, Niaspan)

As combination therapy with a bile acid sequestrant to slow the progression or promote regression of atherosclerosis in patients with clinical evidence of coronary heart disease who have elevated cholesterol concentrations (extended-release niacin, Niaspan)

Dosage

Adults
Immediate-release preparations
The usual dose of immediate-release niacin (Niacor) is 1-2 g two to three times daily with meals. Initiate with 250 mg as a single daily dose after the evening meal and increase the frequency of dosing and total daily dose at 4- to 7-day intervals until the desired LDL or triglyceride level is reached or the first-level therapeutic dose of 1.5-2 g/d is reached. If hyperlipidemia is not adequately controlled after 2 months at this level; dosage may be further increased at 2- to 4-week intervals to 3 g/d (1 g three times per day). The maximum dose is 6 g/d.

Extended-release preparations
The usual initial dosage of extended-release niacin preparation (Niaspan) is 500 mg daily at bedtime. Dosage may be increased by no more than 500 mg daily at 4-week intervals as needed until the desired response is achieved. The maximum daily dose is 2 g.

Note: Immediate and extended-release preparations are not interchangeable. For patients switching from immediate-release to extended-release preparations, therapy should be instituted with the recommended initial dose and gradually titrated upward.

Elderly
Dosage adjustment is not necessary.

Children
Safety and effectiveness have not been established.

Preparations
Tablets, immediate-release (generic): 50, 100, 250, 500 mg Niacor (Upsher-Smith): 500 mg tablets (scored)
Niaspan (Kos Pharmaceuticals): 500, 750, 1000 mg extended-release tablets
Niacin SR (generic): 125 mg, 250 mg extended-release tablets
Slo-Niacin (Upsher-Smith): 250 mg, 500 mg, 750 mg extended-release tablets

Fixed-Dose Combinations for the Treatment of Primary Hypercholesterolemia and Mixed Dyslipidemia:
Advicor (Kos Pharmaceuticals): niacin extended-release/lovastatin combination tablets: 500 mg/20 mg; 750 mg/20 mg; 1000 mg/20 mg

HMG-CoA Reductase Inhibitors

1. Atorvastatin (atorvastatin, Lipitor)

Indications
As an adjunct therapy to diet to:
- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD but with multiple risk factors
- Reduce the risk of MI and stroke in patients with type 2 diabetes mellitus without CHD but with multiple risk factors
- Reduce the risk of nonfatal MI, fatal and nonfatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD
- Reduce elevated total cholesterol, LDL cholesterol, apo B, and triglyceride levels and increase HDL cholesterol in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
- Reduce elevated triglyceride in patients with hypertriglyceridemia and primary dysbetalipoproteinemia
• Reduce total cholesterol and LDL cholesterol in patients with homozygous familial hypercholesterolemia
• Reduce elevated total cholesterol, LDL cholesterol, and apo B levels in boys and postmenarchal girls, 10-17 years, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy

Dosage

Adults
The usual initial dosage is 10 mg once daily. Dosage may be titrated every 2-4 weeks up to 80 mg once daily. Patients who require large LDL cholesterol reduction (>45%) may start at 40 mg once daily.

Elderly
Dosage adjustment is not necessary.

Children
Initiate with 10 mg once daily. The maximum recommended dose is 20 mg once daily. Doses greater than 20 mg have not been studied in this patient population

Preparations
Lipitor (Pfizer): 10, 20, 40, 80 mg tablets
Fixed-dose combinations for the treatment of hypertension and hyperlipidemia
Caduet: amlodipine/atorvastatin: 2.5 mg/10 mg, 2.5 mg/20 mg, 2.5 mg/40 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg

2. Fluvastatin (Lescol, LescolXL)

Indications
As adjunctive therapy to diet to reduce elevated total and LDL cholesterol concentrations, apo B, and triglyceride concentrations and to increase HDL cholesterol concentrations in patients with primary hypercholesterolemia and mixed dyslipidemia (types IIA and IIB hyperlipidemia)
To reduce the risk of undergoing coronary revascularization procedures in patients with CHD
To slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy to lower total and LDL cholesterol to target levels

Dosage

Adults
Patients requiring LDL cholesterol reduction to a goal of ≥25%
The recommended initial dose is 40 mg as 1 capsule, 80 mg as 1 tablet administered as a single dose in the evening, or 80 mg in divided doses of the 40 mg capsule given twice daily.

Patients requiring LDL cholesterol reduction to a goal of <25%
An initial dose of 20 mg may be used. The recommended dosing range is 20-80 mg/day. Dosage adjustments may be made at intervals of ≥4 weeks.

Concomitant lipid-lowering therapy
Lipid-lowering effects on total cholesterol and LDL cholesterol are additive when immediate release (IR) fluvastatin is combined with a bile acid-binding resin or niacin. When administering a bile acid resin (eg, cholestyramine) and fluvastatin, administer fluvastatin at bedtime, at least 2 h following the resin to avoid a significant interaction because of drug binding to resin.

Elderly
Dosage adjustment is not necessary.

Children
Safety and effectiveness have not been established.

Preparations
Lescol (Novartis/Reliant): 20, 40 mg capsules
Lescol XL (Novartis/Reliant): 80 mg extended-release tablets

3. Lovastatin (lovastatin, Altocor, Mevacor)

Indications
As adjunctive therapy to diet for reduction of elevated total cholesterol, LDL cholesterol in patients with primary hypercholesterolemia (types IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and to other nonpharmacological measures alone has not been adequate—Immediate release only
To slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy to lower total and LDL cholesterol to target levels
Primary prevention of CHD in individuals without symptomatic cardiovascular disease who have average to moderately elevated total cholesterol and LDL cholesterol, and below-average HDL cholesterol
As adjunctive therapy to diet to reduce total and LDL cholesterol and apo B concentrations in adolescent boys and girls who are at least 1 y post menarche, 10-17 year, with heterozygous familial hypercholesterolemia if after an adequate trial of diet remains >160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular disease risk factors are present in the adolescent patient—Immediate release only
As adjunctive therapy to diet for the reduction of elevated total and LDL cholesterol, apo B, and triglycerides and to increase HDL cholesterol in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (types IIa and IIb hyperlipidemia)—Extended release only

Dosage

**Adults**

**Immediate release**

The usual initial dosage is 20 mg once daily for patients requiring ≥ 20% reductions in LDL cholesterol and 10 mg once daily for patients requiring LDL cholesterol reductions of < 20%, administered with the evening meal. Dosage may be titrated every 4 weeks or more up to 80 mg once daily or in 2 divided doses.

**Extended release**

The usual recommended initial dose is 20, 40, or 60 mg once daily given in the evening at bedtime. The recommended dosing range is 10-60 mg/d in single doses. An initial dose of 10 mg/d may be considered for patients requiring smaller reductions of LDL cholesterol. Adjust dosage at intervals of ≥ 4 weeks.

**Adolescents 10-17 years with heterozygous familial hypercholesterolemia (Immediate release only)**

The usual initial dosage is 20 mg once daily for patients requiring ≥ 20% reductions in LDL cholesterol and 10 mg once daily for patients requiring LDL cholesterol reductions of < 20%. The recommended dosing range is 10-40 mg/day. Adjust dosage at intervals of ≥ 4 weeks.

**Concomitant lipid-lowering therapy**

If used in combination with fibrates or niacin, the dose of lovastatin should not exceed 20 mg/d.

**Concomitant cyclosporine**

InitiateLovastatin at 10 mg/d. The maximum dose is 20 mg/d as the risk of myopathy increases at higher doses.

**Concomitant amiodarone or verapamil (immediate release only)**

In patients taking amiodarone or verapamil concurrently withLovastatin, the dose ofLovastatin should not exceed 40 mg/d.

**Elderly**

Dosage adjustment is not necessary.

**Children**

Safety and effectiveness have not been established.

**Preparations**

Lovastatin (generic); Mevacor (Merck): 10, 20, 40 mg tablets

Altocor (Andrx Pharmaceuticals) 10, 20, 40, 60 mg extended-release tablets

**Fixed-Dose Combinations for the Treatment of Primary Hypercholesterolemia and Mixed Dyslipidemia:**

Advicor (Kos Pharmaceuticals and Abbott Laboratories)—niacin extended-release/ lovastatin combination tablets: 500 mg/20 mg; 750 mg/20 mg; 1000 mg/20 mg, 1000 mg/40 mg.

4. **Pravastatin (pravastatin, Pravachol)**

**Indications**

**Primary prevention of coronary events:** In hypercholesterolemic patients without clinically evident CHD, to reduce the risk of MI; to reduce the risk of undergoing myocardial revascularization procedures; to reduce the risk of cardiovascular mortality with no increase in death from noncardiovascular causes.

**Secondary prevention of cardiovascular events:** In patients with clinically evident CHD, to reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke, and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis.

As adjunctive therapy to diet for the reduction of elevated total and LDL cholesterol, apo B, and triglyceride concentrations and to increase HDL cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia (types IIa and IIb hyperlipidemia)

As adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride concentrations (type IV hyperlipidemia)

For the treatment of patients with primary dysbeta-lipoproteinemia (type III hyperlipidemia) who do not respond adequately to diet.

As adjunctive therapy to diet and lifestyle modification for treatment of heterozygous familial hypercholesterolemia in children and adolescents ≥ 8 years if after an adequate trial of diet, the following findings are present: (1) LDL cholesterol remains ≥ 190 mg/dL or (2) LDL cholesterol remains ≥ 160 mg/dL and (3) there is a positive family history of premature cardiovascular disease or (4) two or more other cardiovascular disease risk factors are present in the patient.

**Dosage**

**Adults**

The recommended initial dose is 40 mg once daily. If a daily dose of 40 mg does not achieve desired cholesterol concentrations, 80 mg once daily may be given. Dosage should be titrated based on response at 4-week intervals. A lower initial dose of 10 mg is recommended for patients with significant renal or hepatic impairment. If used in
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combination with cyclosporine, therapy should begin with 10 mg pravastatin once daily at bedtime and generally should not exceed 20 mg/d. Dosage must be titrated with caution.

**Elderly**
Dosage adjustment is not necessary.

**Children**
For children 8-13 years, the recommended dose is 20 mg once daily. Doses > 20 mg have not been studied in this patient population.

**Preparations**
Pravachol (Bristol-Myers Squibb): 10, 20, 30, 40, 80 mg tablets
Pravastatin (generic): 10, 20, 30, 40, 80 mg tablets

5. Rosuvastatin (Crestor)

**Indications**
As adjunctive therapy to diet to reduce elevated total cholesterol, LDL cholesterol, apo B, non-HDL cholesterol, and triglyceride levels and to increase HDL cholesterol in patients with primary hypercholesterolemia or mixed dyslipidemia
As adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels
As adjunctive therapy to diet for the treatment of patients with primary dysbetalipoproteinemia
As adjunctive therapy to other lipid-lowering treatments (eg, LDL apheresis) or alone if such treatments are unavailable to reduce LDL cholesterol, total cholesterol, and ApoB in patients with homozygous familial hypercholesterolemia
As adjunctive therapy to diet to slow the progression of atherosclerosis in patients as part of a treatment strategy to lower total cholesterol and LDL cholesterol to target levels

**Dosage**

**Adults**
*Hyperlipidemia, mixed dyslipidemia, hypertriglycerideremia, primary dysbetalipoproteinemia and slowing of the progression of atherosclerosis*
The usual initial dose is 10 mg once daily. For patients with marked hypercholesterolemia (LDL > 190 mg/dL) and aggressive lipid targets, a 20 mg starting dose may be considered.

*Homozygous familial hypercholesterolemia*
The recommended initial dose is 20 mg once daily. Response to therapy should be estimated from pre-apheresis LDL cholesterol levels

*Note: A lower initial dose of 5 mg once daily should be considered for Asian patients. In patients taking cyclosporine, dose of rosuvastatin should be limited to 5 mg once daily. In patients taking a combination of lopinavir and ritonavir, the dose of rosuvastatin should be limited to 10 mg once daily. If rosuvastatin is used in combination with gemfibrozil, the dose of rosuvastatin should be limited to 10 mg once daily.*

**Elderly**
No initial dosage adjustment is needed

**Children**
Safety and efficacy have not been established

**Preparations**
Crestor (AstraZeneca): 5, 10, 20, and 40 mg tablets

6. Simvastatin (simvastatin, Zocor)

**Indications**
As an adjunctive therapy to diet to:
Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of nonfatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events
Reduce elevated total-cholesterol, LDL cholesterol, Apo B, triglyceride and increase HDL cholesterol in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
Reduce elevated triglyceride in patients with hypertriglycerideremia and reduce triglyceride and VLDL cholesterol in patients with primary dysbetalipoproteinemia
Reduce total cholesterol and LDL cholesterol in adult patients with homozygous familial hypercholesterolemia
Reduce elevated total cholesterol, LDL cholesterol, and Apo B in boys and postmenarchal girls, 10-17 years with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy

**Dosage**

**Adults**
The usual dose range is 5-80 mg/day. The recommended usual starting dose is 20-40 mg once a day in the evening.
The recommended starting dose for patients at high risk of CHD is 40 mg/day.

*Concomitant lipid-lowering therapy*
If simvastatin is used in combination with gemfibrozil, the dose of simvastatin should not exceed 10 mg/d.

*Concomitant cyclosporine*
In patients taking cyclosporine concomitantly with simvastatin, therapy should begin with 5 mg/d and should not exceed 10 mg/d.
Concomitant amiodarone or verapamil
In patients taking amiodarone or verapamil concomitantly with simvastatin, the dose should not exceed 20 mg/d.

Elderly
Dosages of ≤ 20 mg daily are generally sufficient for maximum LDL reduction in the elderly.

Children
For adolescents 10-17 years with HeFH, the starting dose is 10 mg/day. The maximum recommended dose is 40 mg/day.

Preparations
Zocor (Merck); simvastatin (generic): 5, 10, 20, 40, 80 mg tablets
Combination formulations:
Vytorin—ezetimibe/simvastatin combination tablets: 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg
Simcor—niacin/simvastatin combination tablets: 500 mg/20 mg, 750 mg/20 mg, 1000 mg/20 mg

Omega-3 Fatty Acids

1. Omega-3-acid ethyl esters (Lovaza)

Indication
As adjunctive therapy to diet to reduce triglyceride levels in patients with very high (≥ 500 mg/dL) triglyceride levels

Dosage
Adults
The recommended daily dose of Lovaza is 4 g per day. The daily dose may be taken as a single 4 g dose (4 capsules) or as two 2 g doses (2 capsules twice daily).

Elderly
Use usual adult dose.

Children
Safety and efficacy have not been established.

Preparations
Lovaza (GlaxoSmithKline): 1 g capsules (transparent soft-gelatin capsules filled with light-yellow oil)

2. Omega-3-acid ethyl esters (Omacor)

Indications
As adjunctive therapy in secondary prevention after myocardial infarction
As adjunctive therapy to diet to reduce triglyceride levels

Dosage
Adults
Post myocardial infarction
One capsule daily

Hypertriglyceridemia
Initiate with 2 capsules daily. Dosage may be increased to 4 capsules daily if needed.

Elderly
Use usual adult dose. There is no or limited information of use in elderly.

Children
Safety and efficacy have not been established

Preparations
Omacor (Solvay): 1 g capsules

Neuronal and Ganglionic Blockers

1. Guanadrel (Hylorel)

Indications
Hypertension

Dosage
Adults
Initiate at 5 mg twice daily. Dosage may be adjusted at weekly or monthly intervals until blood pressure is controlled. The usual maintenance dose is 20-75 mg/d in 2-4 divided doses. For patients with CrCl of 30-60 mL/min, initiate therapy with 5 mg q 24 h. For patients with CrCl of < 30 mL/min, increase dosage interval to 48 h. Dosage increments should be made cautiously at intervals ≥ 7 days for patients with moderate renal insufficiency and ≥ 14 days for patients with severe renal insufficiency.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Hylorel (Medeva Pharmaceuticals): 10, 25 mg tablets

2. Guanethidine (guanethidine, Ismelin)

Indications
Moderate to severe hypertension
Renal hypertension
Dosage

Adults
Initiate at 10 or 12.5 mg/d. Dosage may be increased gradually according to response (10-12.5 mg increments at weekly intervals). The usual maintenance dose is 25-50 mg/d. Dosage may be increased more rapidly and with larger increments under careful hospital supervision.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Guanethidine (generic); Ismelin (Novartis): 10, 25 mg tablets (both are scored)

3. Mecamylamine (Inversine)

Indication
Severe hypertension

Dosage

Adults
Initiate at 2.5 mg twice daily. Dosage may be adjusted in increments of 2.5 mg at intervals of at least every 2 days according to response. The smallest dose should be taken in the mornings to limit the orthostatic adverse effects of the drug. The usual maintenance dose is 25 mg/d in three divided doses.

Note: It is recommended that mecamylamine be administered at consistent times in relation to meals because hypotension may occur after a meal. Ingestion of mecamylamine with meals may slow the drug’s absorption and thereby produce desired gradual correction of severe hypertension. Therapy with mecamylamine should not be discontinued abruptly.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Inversine (Merck): 2.5 mg, 10 mg tablets

4. Reserpine (reserpine)

Indications
Hypertension
Psychotic disorders

Dosage

Adults
The usual maintenance dose for hypertension is 0.1-0.25 mg/d, taken with meals to avoid gastric irritation.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Reserpine (generic): 0.1, 0.25 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension:
Diupres—Reserpine/chlorthiazide combination tablets: 0.125 mg/250 mg; 0.125 mg/500 mg
Regroton—Reserpine/chlorthalidone combination tablets: 0.25 mg/50 mg
Demi-Regroton—Reserpine/chlorthalidone combination tablets: 0.125 mg/25 mg
Hydropres—Reserpine/hydrochlorothiazide combination tablets: 0.125 mg/25 mg; 0.125 mg/50 mg
Salutensin—Reserpine/hydroflumethiazide combination tablets: 0.125 mg/50 mg
Diutensen-R (Wallace)—Reserpine/methyclothiazide combination tablets: 0.1 mg/2.5 mg
Metatensin—Reserpine/trichlormethiazide combination tablets: 0.1 mg/2 mg; 0.1 mg/4 mg
Renese-R—Reserpine/trichlormethiazide combination tablets: 0.25 mg/2 mg
Hydrap-ES; Marpres; Ser-Ap-Es; Tri-Hydroserpine—Reserpine/hydrochlorothiazide/hydralazine HCl combination tablets: 0.1 mg/15 mg/25 mg

5. Trimethaphan (Arfonad)

Indications
Production of controlled hypotension during surgery
Short-term acute control of blood pressure in hypertensive emergencies
Emergency treatment of pulmonary edema in patients with pulmonary hypertension associated with systemic hypertension

Dosage

Adults
For controlled hypotension during surgery, initiate therapy as an intravenous infusion at 3-4 mg/min. Infusion rate should be adjusted according to response to a maintenance dose ranging from 0.2-6 mg/min. Trimethaphan should be administered after the patient is anesthetized, and this drug should be discontinued prior to wound
Appendix 2

closure to allow blood pressure to return toward normal. For hypertensive emergency, initiate trimethaphan at 0.5-1 mg/min and adjust the infusion rate according to response. The usual maintenance infusion rate is 1-5 mg/min.

Note: Trimethaphan should be diluted in the proper amount of compatible fluid prior to intravenous infusion (500 mg, 10 mL, of trimethaphan may be diluted in 500 mL of 5% dextrose injection to yield to final solution containing 1 mg/mL of trimethaphan).

Elderly
Initiate at lowest dose and titrate to response.

Children
Dosage is based on body weight; use with caution.

Preparation
Arfonad (Roche): 50 mg/mL injection

Phosphodiesterase 5 inhibitor

1. Sildenafil (Revatio)

Indication
Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening

Dosage
Adults
The recommended dose is 20 mg three times a day. Sildenafil should be taken approximately 4-6 hours apart.

Elderly
Use normal adult dose with caution.

Children
Safety and effectiveness have not been established

Preparations
Revatio (Pfizer): 20 mg tablets

2. Tadalafil (Adcirca)

Indication
Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability

Dosage
Adults
The usual recommended dose is 40 mg (two 20 mg tablets) taken once daily.

Elderly
No dose adjustment is needed in patients > 65 years old without renal or hepatic impairment.

Children
Safety and efficacy have not been established.

Preparations
Adcirca (Eli Lilly): 20 mg tablets

Renin Inhibitor

1. Aliskiren (Tekturna)

Indication
Hypertension

Dosage
Adults
The usual initial dose is 150 mg once daily. Dosage may be increased to 300 mg daily based on response.

Elderly
No initial dosage adjustment is required in elderly patients.

Children
Safety and efficacy have not been established.

Preparations
Tekturna (Novartis): 150 and 300 mg tablets

Fixed-Dose Combinations for Treatment of Hypertension: Tekturna HCT—aliskiren/hydrochlorothiazide oral tablet: 150 mg/12.5 mg; 150 mg/25 mg; 300 mg/12.5 mg; 300 mg/25 mg
Valturna—aliskiren/valsartan tablet: 150 mg/160 mg, 300 mg/320 mg
Tekamlo—aliskiren/amlodipine tablet: 150 mg/10 mg, 300 mg/5 mg; 300 mg/10 mg
Amburnide—aliskiren/HCTZ/amlodipine tablet

Vasodilators

1. Cilostazol (Pletal)

Please refer to the section on Antiplatelet Agents (starting page 674) for the summary of this agent.
2. Diazoxide (diazoxide, Hyperstat IV, Proglycem)

Indications
Hypertensive emergencies (intravenous formulation)
Hypoglycemia (oral formulation)

Dosage
Adults
Hypertensive emergencies
Administer 1-3 mg/kg (up to 150 mg in a single injection) by rapid intravenous injection every 5-15 min as needed to obtain the desired blood pressure response. Further doses may be given every 4-24 h as needed to maintain desired blood pressure until oral antihypertensive medication can be instituted. Continued treatment for > 4-5 days is usually not necessary; do not use for > 10 days.

Note: Intravenous injection should be administered only into a peripheral vein. Treatment is most effective when intravenous administration is completed in 30 s. The solution’s alkalinity is irritating to tissue; avoid extravasation. Patient should remain recumbent during and for 15-30 min after medication administration.

Hypoglycemia
Initiate therapy with the oral formulation at 1 mg/kg q 8 h; adjust dosage according to clinical response. The usual maintenance dose is 3-8 mg/kg/d given in 2-3 divided doses.

Elderly
Initiate at lowest dose and titrate to response.

Children
Dosing is based on weight. Drug-induced edema may occur in infants given the oral formulation of diazoxide.

Preparations
Hyperstat IV (Schering), Diazoxide IV (generic): 15 mg/mL injection, 20 mL ampules
Proglycem (Baker Norton): 50 mg/mL oral suspension

3. Epoprostenol (epoprostenol, Flolan)

Indication
Primary pulmonary hypertension (epoprostenol is indicated for the long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and Class IV patients)

Dosage
Adults
Acute dose-ranging
The infusion rate is initiated at 2 ng/kg/min and adjusted in increments of 2 ng/kg/min every 15 min or longer until dose-limiting pharmacologic effects occur. The most common dose-limiting pharmacologic effects are nausea, vomiting, headache, hypotension, and flushing. During acute dose-ranging in clinical trials, the mean maximum dose that did not result in dose-limiting pharmacologic effects was 8.6 ± 0.3 ng/kg/min.

Note: Epoprostenol must be reconstituted only with sterile diluent for epoprostenol. Reconstituted solutions of epoprostenol must not be diluted or administered with other parenteral solutions or medications.

Continuous chronic infusion
Chronic infusions of epoprostenol should be initiated at 4 ng/kg/min less than the maximum-tolerated infusion rate determined during acute dose-ranging. If the maximum-tolerated infusion rate is < 5 ng/kg/min, the chronic infusion should be initiated at one-half the maximum-tolerated infusion rate. During clinical trials, the mean initial chronic infusion rate was 5 ng/kg/min.

Note: Chronic continuous infusion of epoprostenol should be administered through a central venous catheter. Temporary peripheral intravenous infusions may be used until central access is established.

Dosage adjustments
Adjustments in the chronic infusion rate should be based on persistence, recurrence, or worsening of the patient’s symptoms of primary pulmonary hypertension and the occurrence of adverse events due to excessive doses of epoprostenol. In general, increases in dose from the initial chronic dose should be expected. Increments in dose should be considered if symptoms of primary pulmonary hypertension persist or recur after improving. The infusion should be adjusted by 1-2 ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 min. In contrast, reduced dosage of epoprostenol should be considered when dose-related pharmacologic events occur. Dosage reductions should be made gradually in decrements of 2 ng/kg/min every 15 min or longer until the dose-limiting adverse effects resolve.

Note: Abrupt withdrawal of epoprostenol or sudden large reductions in infusion rates should be avoided with the exception of life-threatening situations such as unconsciousness or collapse. Consult manufacturer’s package insert for detailed information on administration and reconstitution of epoprostenol.

Elderly
Use usual dose with caution.

Children
Safety and effectiveness have not been established.
Preparations
Flolan (GlaxoSmithKline): 0.5 mg, 1.5 mg powder for re-
constitution and 50 mL vials of sterile diluent for Flolan
Epoprostenol (generic): 0.5 mg, 1.5 mg powder for recon-
stitution for intravenous use

4. Fenoldopam (Corlopam)

Indications
Short-term management of severe hypertension
Malignant hypertension associated with deteriorating
end-organ function

Dosage
Adults
The initial dose of fenoldopam is chosen according to the
desired magnitude and rate of blood pressure reduction
in a given clinical situation. In general, there is a greater
and more rapid blood pressure reduction as the initial
dose is increased. Lower initial doses (0.03-0.1 \( \mu g/\) kg/\) min) titrated slowly have been associated with less re-
flex tachycardia than have higher initial doses ( 0.3 \( \mu g/\) kg/min). The recommended increments for titration are
0.05-0.1 \( \mu g/\) kg/min at intervals of 15 min. Doses of < 0.1
\( \mu g/\) kg/min have very modest effects and appear only mar-
ginally useful in patients with severe hypertension. Doses
from 0.01-1.6 \( \mu g/\) kg/min have been studied in clinical tri-
als. Most of the effect of a given infusion rate is attained
within 15 min. Fenoldopam infusion can be abruptly
discontinued or gradually tapered prior to discontinua-
tion. Oral antihypertensive agents can be added during
fenoldopam infusion (after blood pressure is stable) or
following its discontinuation.

Note: Fenoldopam should be administered by continu-
ous intravenous infusion only. A bolus dose should not be
used. The fenoldopam injection ampule concentrate must
be diluted with the appropriate amount of compatible
fluid prior to infusion. Consult manufacturer's package
insert for instructions on proper dilution of fenoldopam.

Elderly
Dosage adjustment is not necessary.

Children
Safety and effectiveness have not been established.

Preparation
Corlopam (Abbott): 10 mg/mL injection, concentrate

5. Hydralazine (hydralazine, Apresoline)

Indications
Essential hypertension (oral formulation)

Severe essential hypertension when the drug cannot be
given orally or when the need to lower blood pressure is
urgent (parenteral formulation)

Dosage
Adults
Oral formulation
Initiate therapy at 10 mg four times per day for the first
2-4 days; increase to 25 mg four times per day for the rest
of the first week. Thereafter, the dosage may be increased
to 50 mg four times per day during the second and subse-
quent weeks. Dosage should be maintained at the lowest
effective level. The maximum dose is 300 mg/d. Higher
doses have been used in the treatment of CHF.

Parenteral administration
The usual dose is 10-20 mg administered intravenously
or 10-50 mg administered intramuscularly; low doses in
these ranges should be used initially. Parenteral doses may
be repeated as necessary and may be increased within the
above ranges based on blood pressure response.

Note: Because hydralazine interacts with stainless steel
resulting in a pink discoloration, the injections should
be used as quickly as possible after being drawn through
a needle or syringe; stainless steel filters should also be
avoided. In addition, hydralazine should not be diluted
with solutions containing dextrose or other sugars.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established; how-
ever, there is experience with the use of hydralazine in
children.

Preparations
Hydralazine (generic), Apresoline (Novartis): 10, 25, 50,
100 mg tablets
Hydralazine (generic): 20 mg/mL injection, 1 mL vials

Fixed-Dose Combinations for Treatment of Hypertension:
Hydra-Zide—Hydralazine hydrochloride/hydrochloro-
thiazide combination capsules: 25 mg/25 mg; 50 mg/50
mg; 100 mg/ 50 mg
Hydrap-ES; Marpres; Ser-Ap-Es; Tri-Hydroserpine—Re-
serpine/hydrochlorothiazide/hydralazine HCl combina-
tion tablets: 0.1 mg/15 mg/25 mg

6. Iloprost (Ventavis)

Indication
Treatment of pulmonary arterial hypertension (WHO
Group I) in patients with NYHA Class III or IV symptoms
Dosage

Adults

Iloprost should be inhaled using either of two pulmonary drug delivery devices: the I-neb AAD system or the Pro-dose AAD system. The first inhaled dose is 2.5 mcg (as delivered at the mouthpiece). If the initial dose is well tolerated; dosage should be increased to 5 mcg and maintained at that dose. Otherwise, maintain the dose at 2.5 mcg. Iloprost should be taken 6-9 times per day (no more than once every 2 hours) during waking hours based on individual need and tolerability. The maximum daily dose is 45 mcg (5 mcg 9 times per day).

Elderly

Use usual adult dose with caution.

Children

Safety and efficacy have not been established.

Preparations

Ventavis inhalation solution (Actelion Pharmaceuticals): 1 mL and 2 mL ampules (10 mcg iloprost/1 mL)

7. Isosorbide dinitrate (isosorbide dinitrate, Isordil, Isordil Titradose, Isordil Tembids, Sorbitrate, Dilatrate-SR)

Indications

Angina (treatment and prevention)

Dosage

Adults

Short-acting oral tablets (isosorbide dinitrate, Isordil Titradose, Sorbitrate)

Administer 5-20 mg three times daily; dosage may be adjusted as needed and tolerated. The usual dose ranges from 10-40 mg three times daily. Use with caution in patients with hepatic or renal impairment.

Note: A daily nitrate-free interval of at least 14 h has been recommended to minimize tolerance. The optimal nitrate-free interval may vary among different patients, doses, and regimens.

Sustained-release oral tablets and capsules (isosorbide dinitrate, Isordil Tembids, Dilatrate-SR) Administer sustained-release preparations once daily or twice daily in doses given 6 h apart (ie, 8 AM and 2 PM). Do not exceed 160 mg/d.

Sublingual and chewable tablets (isosorbide dinitrate, Isordil, Sorbitrate): The usual initial dose is 2.5-5 mg for sublingual tablets and 5 mg for chewable tablets. Dosage may be titrated upward until angina is relieved or until dose-related adverse effects occur. For acute prophylaxis, 5-10 mg of sublingual or chewable tablets may be admin-
istered q 2-3 h or 15 minutes before expected activity. The use of sublingual or chewable isosorbide dinitrate for the termination of acute anginal attacks should be reserved for patients who are intolerant of or unresponsive to sublingual nitroglycerin.

Elderly

Initiate at lowest dose and titrate to response.

Children

Safety and effectiveness have not been established.

Preparations

Tablets, short-acting (isosorbide dinitrate): 5, 10, 20, 30 mg
Tablets, short-acting (Isordil Titradose, Sorbitrate): 5, 10, 20, 30, 40 mg
Tablets, sublingual (isosorbide dinitrate, Isordil): 2.5, 5, 10 mg
Tablets, sublingual (Sorbitrate): 2.5, 5 mg
Tablets, chewable (Sorbitrate): 5, 10 mg
Tablets, sustained-release (isosorbide dinitrate, Isordil Tembids): 40 mg
Capsules, sustained-release (Dilatrate-SR, Isordil Tembids): 40 mg

8. Isosorbide mononitrate (isosorbide mononitrate, ISMO, Monoket, Imdur)

Indication

Angina (prevention)

Dosage

Adults

Tablets (isosorbide mononitrate, Monoket, ISMO) Administer 20 mg twice daily with doses given 7 h apart. An initial dose of 5 mg twice daily may be appropriate for persons of small stature; dosage should be increased to at least 10 mg by the second or third day of therapy.

Extended-release tablets (isosorbide mononitrate, Imdur) Initiate at 30 or 60 mg once daily. Dosage may be increased to 120 mg once daily after several days if necessary.

Elderly

Dosage adjustment is not necessary.

Children

Safety and effectiveness have not been established.

Preparations

Tablets (isosorbide mononitrate, ISMO): 20 mg
Tablets (Monoket): 10, 20 mg
Tablets, extended-release (isosorbide mononitrate): 60 mg
Appendix 2

Tablets, extended-release (Imdur): 30, 60, 120 mg

9. Minoxidil (minoxidil, Loniten)

Indications
Severe hypertension (oral formulation)
Male pattern baldness of the vertex of the scalp (topical formulation)

Dosage
Adults

Oral formulation
Initiate therapy at 5 mg once daily; dosage may be increased by 10 mg at intervals of 3 days as needed. The usual maintenance dose is 10-40 mg/d in one to two divided doses. The maximum dose is 100 mg/d.

Topical formulation
Apply 1 mL to affected areas of the scalp twice daily (morning and night). Wash hands after applying.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established; however, there is experience with the use of minoxidil in children for the treatment of severe hypertension.

Preparations
Minoxidil (generic); Loniten (Pharmacia and Upjohn): 2.5, 10 mg tablets
Rogaine topical solution (Pharmacia and Upjohn): 2% per 60 mL, 5% per 60 mL

10. Nitroglycerin (Various sources)

Indications
Prevention of angina (oral sustained-release tablets and capsules, transdermal system)
Prevention and treatment of angina (sublingual tablets, translingual spray, topical ointment)
Control of blood pressure in perioperative hypertension (intravenous formulation)
Congestive heart failure associated with acute myocardial infarction (intravenous formulation)
Angina unresponsive to recommended doses of organic nitrates or beta-blockers (intravenous formulation)
Controlled hypotension during surgical procedures (intravenous formulation)

Dosage
Adults

Sublingual tablets (Nitrostat)
Dissolve one tablet under the tongue or in the buccal pouch at first sign of an acute anginal attack. Repeat approximately every 5 min until relief is obtained. No more than 3 tablets should be taken in 15 min. If pain persists, patient should notify physician or get to the emergency department immediately. Sublingual tablets may also be used prophylactically 5-10 min prior to activities that might trigger an acute attack.

Note: Although the traditional recommendation is for patients to take 1 nitroglycerin dose sublingually, 5 minutes apart, for up to 3 doses before calling for emergency evaluation, this recommendation has been modified to encourage earlier contacting of emergency medical services (EMS) by patients with symptoms suggestive of ST-elevation myocardial infarction. According to the American College of Cardiology/American Heart Association guidelines for the management of patients with ST-elevation myocardial infarction, health care providers should instruct patients for whom nitroglycerin has been prescribed previously take ONE nitroglycerin dose sublingually in response to chest discomfort/pain. If chest discomfort/pain is unimproved or worsening 5 minutes after 1 sublingual nitroglycerin dose has been taken, it is recommended that the patient or family member/friend call 911 immediately to access EMS.

Translingual spray (Nitrolingual PumpSpray)
At the onset of an attack, spray one to two metered doses onto or under the tongue. No more than 3 metered doses should be administered within 15 min. If chest pain continues, seek immediate medical attention. Translingual spray may also be used prophylactically 5-10 min prior to activities that might trigger an acute attack. Do not inhale spray.

Sustained-release capsules (nitroglycerin, Nitro-Time)
Initiate therapy at 2.5 mg three times daily. Dosage may be titrated upward to an effective dose or until dose-related adverse effects occur. Tolerance may develop when nitroglycerin is administered without a nitrate-free interval. Consider administering on a reduced schedule (one or twice daily).

Sustained-release tablets (Nitrong)
Initiate therapy at 2.6 mg three times daily. Dosage may be titrated upward to an effective dose or until dose-related adverse effects occur. Tolerance may develop when nitroglycerin is administered without a nitrate-free interval. Consider administering on a reduced schedule (once or twice daily).

Topical ointment (nitroglycerin, Nitro-Bid)
Initiate therapy at 7.5 mg (one-half inch) q 8 h; dosage may be increased by one-half inch per application q 6 h to a maximum of 75 mg (5 inches) per application q 4 h.

Note: Any regimen of nitroglycerin ointment administration should include a daily nitrate-free interval of
about 10–12 h to avoid tolerance. To apply the ointment using the dose-measuring paper applicator, place the applicator on a flat surface, printed side down. Squeeze the necessary amount of ointment from the tube onto the applicator, place the applicator (ointment side down) on the desired area of skin (usually on nonhairy skin of chest or back), and tape the applicator into place. Do not rub in.

Transdermal Systems (Nitroglycerin Transdermal, Minitrans, Nitro-Dur)
Initiate therapy with a 0.1 or 0.2 mg/h patch. Apply patch for 12–14 h; remove for 10–12 h before applying a new patch. Patch should be applied on to clean, dry, hairless skin of chest, inner upper arm, or shoulder. Avoid placing below knee or elbow. Vary site of placement to decrease skin irritation. Apply a new patch if the first patch loosens or falls off.

Intravenous formulations (nitroglycerin IV, Tridil IV, Nitro-Bid IV, nitroglycerin in 5% dextrose)
Initiate intravenous infusion at 5 μg/min; increase by increments of 5 μg/min at 3- to 5-minute intervals until desired effect is obtained or to 20 μg/min. Dosage may be increased beyond 20 μg/min by 10 μg/min increments at 3- to 5-minute intervals, then by 20 μg/min increments until desired effect is achieved. Reduce dosage increments and frequency of dosage increments as partial effects are noted. There is no fixed optimum dose. Continuously monitor physiologic parameters such as blood pressure and heart rate and other measurements, such as pulmonary capillary wedge pressure, to achieve accurate dose. Maintain adequate blood and coronary perfusion pressures.

Note: Intravenous infusion must be given through a special nonpolyvinylchloride (nonPVC) intravenous infusion set or infusion pump. Consult manufacturer’s package insert for instructions on dilution and administration of intravenous nitroglycerin.

11. Papaverine (papaverine, Para-Time SR)
Indications
Relief of cerebral and peripheral ischemia associated with arterial spasm and myocardial ischemia complicated by arrhythmias

Dosage
Adults
Oral formulation
Administer 150 mg in an extended-release formulation q 8 to 12 h or 300 mg q 12 h.

Note: It is uncertain if effective plasma concentrations are maintained for 12 h with extended-release preparations. In the past, the Food and Drug Administration has recommended that papaverine products be withdrawn from the market.

Parenteral administration
Papaverine may be administered intramuscularly or by slow intravenous injection over a period of 1-2 min. The intravenous route is preferred when an immediate effect is desired. The usual parenteral dose is 30 mg; however, a dosage of 30–120 mg may be repeated q 3 h as needed.

Elderly
Initiate at lowest dose and titrate to response.

Children
Safety and effectiveness have not been established.

Preparations
Papaverine HCl (generic, Para-Time SR); 150 mg extended-release capsules
Papaverine HCl (generic): 30 mg/mL injection

12. Pentoxifylline (pentoxifylline, Pentoxil, Trental)
Indications
Intermittent claudication
Dosage

Adults
Initiate therapy at 400 mg three times daily with meals; dosage may be reduced to 400 mg twice daily if GI or CNS adverse effects occur. Although therapeutic effects may be observed within 2–4 weeks, continue treatment for ≥ 8 weeks.

Elderly
Use usual dose with caution.

Children
Safety and effectiveness have not been established.

Preparations
Pentoxifylline (generic): 400 mg extended-release tablets
Pentoxil (Upsher-Smith): 400 mg extended-release tablets
Trental (Aventis): 400 mg extended-release tablets

13. Nitroprusside (sodium nitroprusside, Nitropress)

Indications
Hypertensive crises
Production of controlled hypotension in order to reduce bleeding during surgery
Acute congestive heart failure

Dosage

Adults
The usual initial dose is 0.3 μg/kg/min (range, 0.1–0.5 μg/kg/min) as an intravenous infusion. Dosage may be adjusted slowly in increments of 0.5 μg/kg/min according to response. The usual infusion rate is 3 μg/kg/min. The maximum recommended infusion rate is 10 μg/kg/min; infusion at the maximum dose rate should never last for > 10 min. To keep the steady-state thiocyanate concentration below 1 mmol/L, the rate of a prolonged infusion should not exceed 3 μg/kg/min (1 μg/kg/min in anuric patients). When > 500 μg/kg of nitroprusside is administered faster than 2 μg/kg/min, cyanide is generated faster than the unaided patient can eliminate.

Note: After reconstitution with the appropriate diluent, sodium nitroprusside injection is not suitable for direct injection. The reconstituted solution must be further diluted in the appropriate amount of sterile 5% dextrose injection before infusion. The diluted solution should be protected from light by promptly wrapping the medication container with the supplied opaque sleeve. Sodium nitroprusside should be administered through an infusion pump, preferably a volumetric pump. Consult manufacturer’s package insert for complete prescribing information.

Elderly
Use usual dose with caution.

Children
Appropriate studies have not been performed; however, pediatrics-specific problems that would limit the usefulness of this agent in children are not expected.

Preparations
Sodium nitroprusside (generic); Nitropress (Abbott): 50 mg per vial, powder for injection

14. Treprostinil (Remodulin)

Indications
For the treatment of pulmonary arterial hypertension (PAH) in patients with NYHA class II-IV symptoms, to diminish symptoms associated with exercise
For patients who require transition from epoprostenol (Flolan), to reduce the rate of clinical deterioration

Dosage

Adults
PAH patients with NYHA Class II-IV symptoms
The infusion rate is initiated at 1.25 ng/kg/min SQ continuous infusion for patients new to prostacyclin infusion therapy. The infusion rate is reduced to 0.625 ng/kg/min if not tolerated. The dose can then be titrated by no more than 1.25 ng/kg/min per week for the first 4 weeks, then no more than 2.5 ng/kg/min per week thereafter, depending on the clinical response. There is limited experience with doses > 40 ng/kg/min. Abrupt cessation of infusion should be avoided.

Transition from epoprostenol
The recommended initial treprostinil dose is 10% of the current epoprostenol dose. Increase individualized dosage as epoprostenol dose is decreased, based on constant observation of response. See manufacturer’s package insert for details.

Elderly
Use usual dose with caution.

Children
Safety and effectiveness have not been established.

Preparations
Remodulin (United Therapeutics): injection 1 mg/mL, 2.5 mg/mL, 5 mg/mL, 10 mg/mL (20 mL).
**Vasopressin**

1. **Vasopressin (vasopressin, Pitressin)**

   **Indication**
   - Prevention and treatment of postoperative abdominal distention
   - Used in abdominal roentgenography to dispel interfering gas shadows
   - Diabetes insipidus
   - Septic shock (not FDA-approved but used clinically)
   - Cardiac arrest (in ACLS; not FDA-approved)

   **Dosage**
   **Adults**
   - **Abdominal distention**
     5 units IM initially; increase to 10 units IM at subsequent injections (at 3-4 h interval) if necessary
   - **Abdominal roentgenography**
     Two IM or SC injections of 10 units, given 2 h and 0.5 h, respectively, before films are exposed.
   - **Diabetes insipidus**
     If administered by IM or SC, 5-10 units repeated 2 or 3 times daily as needed. If administered intranasally by spray or on pledgets, the dosage and interval between treatments must be determined for each patient.
   - **Septic shock**
     0.01-0.04 unit/min IV infusion; in combination with 1-2 additional catecholamines
   - **Cardiac arrest**
     40 units IV/intraosseous to replace first or second dose of epinephrine (American Heart Association, 2005)

   **Elderly**
   Use normal adult dose with caution.

   **Children**
   Safety and efficacy have not been established.

   **Preparations**
   - Pitressin (Parke-Davis); vasopressin (generic): 20 units/mL (1 mL vial)

**Vasopressin Receptor Antagonists**

1. **Conivaptan (Vaprisol)**

   **Indication**
   Treatment of euvoletic and hypervolemic hyponatremia in hospitalized patients

   **Dosage**
   **Adults**
   Initiate with a loading dose of 20 mg IV administered over 30 minutes. The loading dose should be followed by 20 mg of conivaptan administered in a continuous intravenous infusion over 24 hours. Following the initial day of treatment, conivaptan is to be administered for an additional 1-3 days in a continuous infusion of 20 mg/day. If serum sodium is not rising at the desired rate, conivaptan may be titrated upward to a dose of 40 mg daily, again administered in a continuous intravenous infusion. The total duration of infusion of conivaptan (after the loading dose) should not exceed 4 days. The maximum daily dose of conivaptan (after the loading dose) is 40 mg/day.

   **Elderly**
   Use usual dose with caution.

   **Children**
   Safety and efficacy have not been established.

   **Preparations**
   - Vaprisol (Astellas Tokai): 20 mg/4 mL ampule, 20 mg in 100 mL premixed solution

2. **Tolvaptan (Samsca)**

   **Indication**
   Treatment of clinically significant hypervolemic and euvoletic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

   **Dosage**
   **Adults**
   The recommended initial dose is 15 mg once daily. Dosage may be increased at intervals ≥ 24 h-30 mg once daily, and to a maximum of 60 mg once daily as needed to raise serum sodium. Monitor serum sodium and volume status.

   **Elderly**
   Use normal adult dose.

   **Children**
   Safety and efficacy have not been established.

   **Preparations**
   - Samsca (Ostsuka): 15 and 30 mg tablets
## Appendix 3

**Guide to Cardiovascular Drug Use in Pregnancy and with Nursing**

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<td>Doxazosin</td>
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*Table continued on p. 724.*
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<td>Breastfeeding not recommended; drug excreted in breast milk</td>
<td>C</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td>Isosorbide Dinitrate</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td>Isosorbide Mononitrate</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td>Isoxsuprine</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; drug excreted in breast milk</td>
<td>C</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td>Papaverine</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; drug excreted in breast milk</td>
<td>C</td>
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<tr>
<td>Tolazoline</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td><strong>Vasopressor</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vasopressin</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td><strong>Vasopressin Receptor Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conivaptan</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Weigh benefits vs risk</td>
<td>Breastfeeding not recommended; excretion in milk unknown</td>
<td>C</td>
</tr>
</tbody>
</table>

Pregnancy Categories/US Food and Drug Administration Pregnancy Risk Classification:
B = Either animal reproduction studies have not demonstrated fetal risk or else they have not shown an adverse effect (other than a decrease in fertility). However, there are no controlled studies of pregnant women in the first trimester to confirm these findings and no evidence of risk in the later trimesters.
C = Either animal studies have revealed adverse effects (teratogenic or embryocidal), but there are no confirmatory studies in women, or studies in both animals and women are not available. Because of the potential risk to the fetus, drugs should be given only if justified by potentially greater benefits.
D = Evidence of human fetal risk is available. Despite the risk, benefits from use in pregnant women may be justifiable in select circumstances (e.g., if the drug is needed in a life-threatening situation and/or no other safer acceptable drugs are effective). An appropriate "warning" statement will appear on the labeling.
X = Studies in animals and humans have demonstrated fetal abnormalities and/or evidence of fetal risk based on human experience. Thus, the risk of drug use and consequent fetal harm outweighs any potential benefit, and the drug is contra-
indicated in pregnant women. An appropriate “contraindicated” statement will appear on the labeling.  
*Only diltiazem and verapamil are indicated for arrhythmias.  
†The pregnancy category of methyclothiazide has ranged from B to D.  
§This drug is usually classified as an aldosterone receptor antagonist rather than a potassium-sparing diuretic.  
ACE = angiotensin converting enzyme; BAS = bile acid sequestrants; FADS = fibric acid derivatives; HMG-CoA = hydroxymethylglutaryl coenzyme A.

## Appendix 4

### Dosing Recommendations of Cardiovascular Drugs in Patients with Hepatic Disease and/or Congestive Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cirrhosis</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-Adrenergic Antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Phenoxylbenzamine</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>α₂-Adrenergic Agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Guanabenz</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Captopril</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Moexipril</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Angiotensin-II-Receptor Antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Losartan</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Dose reduction may be necessary; consider alternative treatment</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
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</table>

*(Table continued on p. 730.)*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Cirrhosis</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antianginal Agent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Contraindicated in patients with clinically significant hepatic impairment</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Antiarrhythmics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Atropine</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Bretylium</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Initiate with lower dose</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Contraindicated in severe hepatic impairment</td>
<td>Contraindicated in patients with NYHA Class IV heart failure or NYHA Class II to III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>Use lower dose or alternative treatment</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Initiate with lower dose</td>
<td>Initiate with lower dose</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>Initiate with lower dose</td>
<td>Initiate with lower dose</td>
</tr>
<tr>
<td>Moricizine</td>
<td>Use lower dose or alternative treatment</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Dose reduction may be necessary</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Initiate with lower dose</td>
<td>Contraindicated in uncontrolled CHF</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Reduce maintenance dose and monitor serum concentration*</td>
<td>Contraindicated in uncontrolled CHF</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Usual dose with frequent monitoring</td>
<td>Contraindicated in uncontrolled CHF</td>
</tr>
<tr>
<td>Tocainide</td>
<td>Avoid loading dose; limit dose to 1200 mg/d</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td><strong>Antithrombotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
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<tr>
<td>Enoxaparin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
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<tr>
<td>Fondaparinux</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Heparin</td>
<td>Dose reduction may be necessary; titrate dose based on coagulation test results</td>
<td></td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Initiate at lower dose</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td><strong>Antiplaquelets</strong></td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Reduce dose with biliary obstruction</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Abciximab</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Contraindicated in severe hepatic impairment</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Initiate at lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
</tbody>
</table>
### Dosing Recommendations of Drugs in Patients with Hepatic Disease and/or Congestive Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cirrhosis</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombolytics</strong></td>
<td></td>
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<tr>
<td>Alteplase</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Anistreplase</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Reteplase</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>Use usual dose with caution; risk of bleeding may increase</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>ß-Adrenergic Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Timolol</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>ß-Selective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>Use with caution in patients with moderate hepatic impairment; contraindicated in severe hepatic impairment</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>With ISA: Nonselective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carteolol</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>With ISA: ß-Selective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Dual-Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Initiate with lower dose</td>
<td>Initiate at lower dose; contraindicated in severely decompensated CHF</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Calcium-Channel Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Dose reduction may be necessary</td>
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<tr>
<td>Felodipine</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Initiate with lower dose</td>
<td>Avoid in patients with severe left ventricular dysfunction</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
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<td></td>
</tr>
<tr>
<td>Loop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide, Ethacrynic Acid, Furosemide</td>
<td>May precipitate hepatic coma. Dose reduction is probably not necessary; titrate dosage based on clinical response</td>
<td>Usual dose with frequent monitoring</td>
</tr>
</tbody>
</table>

(Table continued on p. 732.)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Cirrhosis</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop (continued)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torsemide, Thiazide, Bendroflumethiazide, Benzthiazide, Chlorothiazide, Hydrochlorothiazide, Hydroflumethiazide, Methylclothiazide, Polythiazide, Quinethazone</td>
<td>May precipitate hepatic coma. Dose reduction is probably not necessary; titrate dosage based on clinical response</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Metolazone</td>
<td>May precipitate hepatic coma; diuretic effect is preserved in patients with renal insufficiency. Dosage adjustment is probably not required in hepatic impairment</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Potassium-Sparing</strong></td>
<td></td>
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</tr>
<tr>
<td>Amiloride</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
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<tr>
<td>Spironolactone</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
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<td>Triamterene</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Endothelin Receptor Antagonist</strong></td>
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<tr>
<td>Ambrisentan</td>
<td>Use with caution in patients with mild pre-existing impaired liver function (reduced dose may be required); not recommended in patients with moderate or severe hepatic impairment.</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Caution should be exercised during the use of bosentan in patients with mildly impaired liver function. Bosentan should generally be avoided in patients with moderate or severe liver impairment.</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Sitaxsentan</td>
<td>Contraindicated with elevated liver aminotransferases (&gt; 3 x ULN) prior to initiation of therapy.</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Human B-Type Natriuretic Peptide</strong></td>
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</tr>
<tr>
<td>Nesiritide</td>
<td>Cirrhotic patients with ascites and avid sodium retention were shown to have blunted natriuretic response to low-dose brain natriuretic peptide</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Inotropic Agents and Vasopressors</strong></td>
<td></td>
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</tr>
<tr>
<td>Amrinone (inamrinone)</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Digoxin, dobutamine</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Dopamine, milrinone</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring; initiate dopamine at lower dose in patients with chronic heart failure</td>
</tr>
<tr>
<td>Norepinephrine, epinephrine,</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Isoproterenol, metaraminol</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Methoxamine, phenylephrine</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Lipid-Lowering</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BAS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Contraindicated in total biliary obstruction</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Drug</td>
<td>Cirrhosis</td>
<td>CHF</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Contraindicated in total biliary obstruction</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Contraindicated in total biliary obstruction</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Cholesterol Absorption Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Contraindicated in patients with active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>FAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Contraindicated in clinically significant hepatic dysfunction, including primary biliary cirrhosis and in patients with unexplained persistent transaminase elevation.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Fenofibric acid</td>
<td>Contraindicated in patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Contraindicated in clinically significant hepatic dysfunction, including primary biliary cirrhosis</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>HMG-CoA Reductase Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin, Fluvastatin, lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin</td>
<td>Start at lowest dose and titrate cautiously; contraindicated in patients with active liver disease or unexplained persistent transaminase elevation</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Use with caution; contraindicated in patients with active liver disease or unexplained persistent transaminase elevation</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Omega-3 Fatty Acids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3-acid ethyl esters</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Neuronal and Ganglionic Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanadrel</td>
<td>Usual dose with frequent monitoring</td>
<td>Contraindicated in frank CHF</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>Dose reduction may be necessary</td>
<td>Contraindicated in frank CHF</td>
</tr>
<tr>
<td>Mecamylamine</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Trimethaphan</td>
<td>Dose reduction may be necessary</td>
<td>Contraindicated in severe cardiac disease</td>
</tr>
<tr>
<td><strong>Phosphodiesterase 5 Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Consider a starting dose of 20 mg once daily in patients with mild to moderate hepatic cirrhosis. Avoid use in severe hepatic cirrhosis.</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Renin Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprostadil</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Usual dose with frequent monitoring</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

(Table continued on p. 734.)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Cirrhosis</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasodilators (continued)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Usual dose with frequent monitoring</td>
<td>Contraindicated in severe left ventricular systolic dysfunction</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Dose reduction may be necessary</td>
<td>Higher doses have been used</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Not studied. Use usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Use lower dose; avoid in severe hepatic impairment</td>
<td>Used in combination with hydralazine</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Caution in severe hepatic impairment</td>
<td>Avoid in acute CHF</td>
</tr>
<tr>
<td>Isosuprine</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Dose reduction may be necessary; avoid in severe hepatic impairment</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Initiate with lower dose</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Papaverine</td>
<td>Dose reduction may be necessary</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Usual dose with frequent monitoring</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tolazoline</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Vasopressor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conivaptan</td>
<td>Use usual dose with caution</td>
<td>Use usual dose with caution</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Usual dose with frequent monitoring</td>
<td>Usual dose with frequent monitoring</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; BAS = bile acid sequestrants; CHF = congestive heart failure; FADS = fibric acid derivatives; HMG-CoA = hydroxymethylglutaryl coenzyme A; ISA = intrinsic sympathomimetic activity; NYHA = New York Heart Association; ULN = upper limits of normal.

*Due to an increased volume of distribution, a larger loading dose of quinidine may be indicated.

**This drug is usually classified as an aldosterone receptor antagonist rather than a potassium-sparing diuretic.

# Appendix 5

## Dose Adjustment in Patients with Renal Insufficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-Adrenergic Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Phenoxycobenzamine</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td><strong>α₂-Adrenergic Agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Guanabenz</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Angiotensin-Converting Enzyme Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Captopril</td>
<td>Start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response.</td>
<td>Yes</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>Yes</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>Yes</td>
</tr>
<tr>
<td>Moexipril</td>
<td>For patients with CrCl ≤ 40 mL/min, start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Start with low dose and titrate based on response.</td>
<td>The use of this drug is not recommended because of significant perindoprilat accumulation.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(Table continued on p. 736.)
<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinapril</td>
<td>Start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Ramipril</td>
<td>For patients with CrCl &lt; 40 mL/min, start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response; up to a max of 5 mg/d.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>Yes (trandolaprilat)</td>
</tr>
<tr>
<td><strong>Angiotensin-II-Receptor Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Losartan</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response; maximum dose should not exceed 20 mg.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td><strong>Antianginal Agent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Antiarrhythmic Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Atropine</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td><strong>Class IA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>↓ loading dose by 25% to 50%; ↓ maintenance dose by 25% or give 100 mg (nonsustained release) q 6 to 8 h</td>
<td>↓ loading dose by 50% to 75%; ↓ maintenance dose by 50% to 75% or give 100 mg (nonsustained release) q 12 to 24 h</td>
<td>No’</td>
</tr>
<tr>
<td>Procainamide</td>
<td>↓ dosing interval to q 4 to 6 h</td>
<td>↓ dosing interval to q 8 to 24 h</td>
<td>Yes (give maintenance dose after dialysis or supplement with 250 mg post hemodialysis).</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution; ↓ maintenance dose by 25% if CrCl &lt; 10 mL/min.</td>
<td>Yes (give maintenance dose after dialysis or supplement with 200 mg post hemodialysis).</td>
</tr>
<tr>
<td><strong>Class IB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>Use usual dose.</td>
<td>Reduce dose if CrCl &lt;10 mL/min.</td>
<td>No</td>
</tr>
<tr>
<td>Tocainide</td>
<td>Use usual dose.</td>
<td>↓ 25% to 50% or ↓ dosing interval to q 24 h</td>
<td>Yes (give maintenance dose after dialysis or supplement with 25% of maintenance dose post hemodialysis).</td>
</tr>
<tr>
<td><strong>Class IC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>Use usual dose.</td>
<td>Initiate with 100 mg q 24 h or 50 mg q 12 h; titrate based on response.</td>
<td>No</td>
</tr>
</tbody>
</table>
## Dose Adjustment in Patients with Renal Insufficiency

### Class IC (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moricizine</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
</tbody>
</table>

### Class II (β-Adrenergic Antagonists)

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>↓ 50%</td>
<td>↓ 75%</td>
<td>Yes—both acebutolol and diacetolol</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Use usual dose with caution.</td>
<td>Up to a max of 50 mg q 24 to 48 h</td>
<td>No</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>Use usual dose with caution.</td>
<td>Up to a max of 20 mg q 24 h</td>
<td>No</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Use usual dose with caution.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Carteolol</td>
<td>↑ dosing interval to q 48 h</td>
<td>↑ dosing interval to q 48 to 72 h</td>
<td>Unknown</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Use usual dose with caution.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Use usual dose with caution.</td>
<td>↑ dosing interval to q 48 to 72 h</td>
<td>Yes</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>Use usual dose.</td>
<td>Initiate with lower dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Timolol</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
</tbody>
</table>

### Class III

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Bretylium</td>
<td>↓ 50%</td>
<td>↓ 50% to 75%.</td>
<td>No</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Start with lower dose and titrate based on response</td>
<td>Start with lower dose and titrate based on response; doetilide is contraindicated in patients with CrCl of &lt;20 mL/min.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>↑ dosing interval to q 24 h</td>
<td>↑ dosing interval to q 36–48 h; individualize dosing for patients with CrCl of &lt;10 mL/min.</td>
<td>Yes (give maintenance dose after dialysis or supplement with 80–mg post hemodialysis).</td>
</tr>
</tbody>
</table>

### Class IV (Calcium Antagonists)

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Use usual dose.</td>
<td>Use usual dose; titrate dose carefully.</td>
<td>No</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
</tbody>
</table>

(Table continued on p. 738.)
<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antithrombotic Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abciximab</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Yes</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Use usual dose.</td>
<td>Reduce usual dose.</td>
<td>Yes</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Use lower dose if SCr &gt;2 mg/dL.</td>
<td>Contraindicated if SCr &gt;4 mg/dL.</td>
<td>Yes</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Use usual dose.</td>
<td>Use with caution; dose reduction may be required.</td>
<td>No</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Use usual dose with caution.</td>
<td>50%.</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Reduce infusion dose by $=20%$.</td>
<td>Reduce infusion dose by $=60%$ to $90%$.</td>
<td>Yes ($=25%$ removed)</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution; specific recommendations on dosage adjustments are not available.</td>
<td>No</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Use usual dose.</td>
<td>Use with caution; dose reduction may be required, ($=20%$ to $30%$).</td>
<td>No</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Use usual dose with caution.</td>
<td>Contraindicated</td>
<td>Yes</td>
</tr>
<tr>
<td>Heparin</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Bolus dose: $0.2 \text{ mg/kg}$; Infusion rate: $30%$ to $50%$ of usual dose</td>
<td>Bolus dose: $0.2 \text{ mg/kg}$; Infusion rate: $15%$ of usual dose; contraindicated if SCr $&gt;6 \text{ mg/dL}$.</td>
<td>Yes</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution; specific recommendations on dosage adjustments are not available.</td>
<td>No</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td><strong>Thrombolytic Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alteplase</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Anistreplase</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Retepase</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td><strong>Diuretics (Contraindicated in anuric patients)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Ethacrynic Acid</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Torsemide</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td><strong>Thiazide Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Use usual dose with caution.</td>
<td>Ineffective</td>
<td>No</td>
</tr>
<tr>
<td>Hydrochlorothiazide and similar agents</td>
<td>Use usual dose with caution.</td>
<td>Ineffective</td>
<td>No</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Use usual dose with caution.</td>
<td>Ineffective if CrCl $&lt;15 \text{ mL/min}$</td>
<td>No</td>
</tr>
<tr>
<td>Metolazone</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
</tbody>
</table>
### Dose Adjustment in Patients with Renal Insufficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potassium-Sparing Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>Use usual dose with caution.</td>
<td>Contraindicated</td>
<td>Unknown</td>
</tr>
<tr>
<td>Eplerenone§</td>
<td>Use usual dose with caution.</td>
<td>Contraindicated</td>
<td>No</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Use usual dose with caution.</td>
<td>Contraindicated</td>
<td>No</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Use usual dose with caution.</td>
<td>Contraindicated</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Endothelin Receptor Antagonist</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td><strong>Human B-Type Natriuretic Peptide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nesiritide</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td><strong>Inotropic Agents and Vasopressors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amrinone (Inamrinone)</td>
<td>Start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Use usual dose and titrate based on response.</td>
<td>Start with low dose, many patients only need a dose q 48 to 72 h; if loading dose is indicated, ↓ 25%.</td>
<td>No</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Use usual dose and titrate based on response.</td>
<td>Use usual dose and titrate based on response.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Use usual dose and titrate based on response.</td>
<td>Use usual dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>Start with low dose and titrate to response.</td>
<td>Start with low dose and titrate to response.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Milrinone</td>
<td>↓ 25% to 50%;Start with low dose and titrate based on response.</td>
<td>↓ 50% to 75%;Start with low dose and titrate based on response.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenytoine</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Lipid-Lowering Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
</tr>
<tr>
<td>Colestipol</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
<td>The possibility of hyperchloremic acidosis is increased in patients with renal insufficiency; use usual dose with caution.</td>
</tr>
<tr>
<td><strong>Cholesterol Absorption Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td>FADS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Fenofibric Acid</td>
<td>Start with low dose and titrate based on response.</td>
<td>Avoid use.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
</tbody>
</table>

*(Table continued on p. 740.)*
<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG-CoA Reductase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>No</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Use usual dose.</td>
<td>Start with 5 mg once daily and not exceed 10 mg once daily in patients not on hemodialysis.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>Start with low dose and titrate based on response; use with caution.</td>
<td>Start with low dose and titrate based on response; use with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Omega-3 Fatty Acids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3-acid ethyl esters</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Neuronal and Ganglionic Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanadrel</td>
<td>1× dosing interval to q 24 h; dosage increments should be made cautiously at intervals ≥ 7 days.</td>
<td>1× dosing interval to q 48 h; dosage increments should be made cautiously at intervals ≥ 14 days.</td>
<td>Unknown (probably no)</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>Start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response; use with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mecamylamine</td>
<td>Start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response; use with caution, if at all.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution; avoid use if CrCl is &lt;10 mL/min.</td>
<td>No</td>
</tr>
<tr>
<td>Trimethaphan</td>
<td>Start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response; use with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Phosphodiesterase 5 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Use usual dose.</td>
<td>Use usual dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Start with lower dose and titrate based on response.</td>
<td>Avoid use.</td>
<td>No</td>
</tr>
<tr>
<td><strong>Renin Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprostadil</td>
<td>Individualize dose.</td>
<td>Individualize dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution. Patients on hemodialysis have not been studied.</td>
<td>No</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Individualize dose.</td>
<td>Individualize dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Individualize dose.</td>
<td>Individualize dose.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>1× dosing interval to q 6 to 8 h</td>
<td>1× dosing interval to q 8 to 24 h</td>
<td>No</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
### Dose Adjustment in Patients with Renal Insufficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl: 30 to 60 mL/min</th>
<th>CrCl &lt; 30 mL/min</th>
<th>Dialyzability (Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide dinitrate</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response; use with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Isoxsuprine</td>
<td>Start with low dose and titrate based on response.</td>
<td>Start with low dose and titrate based on response; use with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Use usual dose.</td>
<td>Start with low dose and titrate based on response.</td>
<td>No</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>No</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Start with low dose and titrate based on response; use with caution.</td>
<td>Start with low dose and titrate based on response; use with caution.</td>
<td>Yes</td>
</tr>
<tr>
<td>Papaverine</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tolazoline</td>
<td>Start with low dose and titrate based on response; use with caution. Specific dosing guidelines are lacking.</td>
<td>Start with low dose and titrate based on response; use with caution. Specific dosing guidelines are lacking.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Use usual dose.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Conivaptan</td>
<td>Use usual dose with caution.</td>
<td>Use usual dose with caution.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Use usual dose.</td>
<td>Use usual dose in patients with CrCl ≥ 10 mL/min. Contraindicated in anuric patients</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**BAS = bile acid sequestrants; CrCl = creatinine clearance; FAD = fibric acid derivatives; HMG-CoA = hydroxymethylglutaryl coenzyme A; SCr = serum creatinine.**

*Hemodialysis does not remove appreciable amounts of this drug. However, dialysis may be considered in overdosed patients with severe renal impairment.

†Only diltiazem and verapamil are indicated for arrhythmias.

§This drug is usually classified as an aldosterone receptor antagonist rather than a potassium-sparing diuretic.
Appendix 6

Selected Cardiovascular Medications and Gender Issues

<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence for Efficacy in Women</th>
<th>Considerations When Treating Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelet Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Primary Prevention: US Nurses’ Cohort shows decreased MI*. Secondary CAD Prevention: Decreases reinfarction†</td>
<td>Women have higher rate of hemorrhagic stroke than men; Physician’s Health Study showed an increased risk of bleeding when on aspirin; increased risk of bleeding at term in pregnancy; present in breast milk.</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa antagonists</td>
<td>Effective in women undergoing PTCA</td>
<td>Women have higher risk than men with PTCA but benefit as much from treatment.</td>
</tr>
<tr>
<td><strong>Agents that Affect Blood Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>Post-MI: decreased mortality†</td>
<td>Cough is two to three times greater in women; increased fetal abnormalities possible; present in breast milk.</td>
</tr>
<tr>
<td>Angiotensin-II-Receptor Blockers</td>
<td></td>
<td>Increased fetal abnormalities possible</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>Antihypertension: effective in preventing MI, CVA, and death in women† Post-MI: decreases mortality†</td>
<td>Present in breast milk; blood levels of propranolol may be higher in men.</td>
</tr>
<tr>
<td>Calcium Blockers</td>
<td>Increased risk of MI in women† Increased effect of amlodipine in women in reducing blood pressure†</td>
<td>Edema may be more common in women; verapamil clearance may be greater in women than in men; present in breast milk.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>No data about efficacy in women</td>
<td>Inability to achieve orgasm; possible decreased craving for tobacco more common in women†</td>
</tr>
<tr>
<td>Thiazide Diuretics</td>
<td>Decreased CVA, MI, death†</td>
<td>Decreased urinary calcium excretion; women have greater increase in risk of gout; acute pulmonary edema and allergic interstitial pneumonitis is more common in women; excreted in breast milk.</td>
</tr>
<tr>
<td>Guanethidinide</td>
<td></td>
<td>Orthostatic is hypotension more common in women.</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Effective in hypertension in pregnancy and peripartum</td>
<td>SLE more common in women than men; present in breast milk.</td>
</tr>
</tbody>
</table>

(Table continued on p. 744.)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence for Efficacy in Women</th>
<th>Considerations When Treating Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agents that Affect Blood Pressure</strong> (continued)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Often preferred in pregnancy for treating hypertension</td>
<td>Painful breast enlargement; decreased libido</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Decreased mortality after MI†</td>
<td>Potential for difference in metabolism in women</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiarrhythmic Agents</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disopyramide</td>
<td>No data looking at efficacy in women</td>
<td>Complication of torsade de pointes more frequent in women†</td>
</tr>
<tr>
<td>Procainamide</td>
<td>No gender-specific data available</td>
<td>Drug-induced SLE more common in women</td>
</tr>
<tr>
<td>Quinidine</td>
<td>No gender-specific data available</td>
<td>Torsade de pointes more common in women; clearance may be faster in women; present in breast milk.</td>
</tr>
<tr>
<td>Conjugated Estrogens</td>
<td>Increased HDL-cholesterol decreases total cholesterol and lipoprotein* Primary prevention: ineffective</td>
<td>Need for progestin in women with intact uterus to prevent endometrial abnormalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypolipidemic Agents</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Colestipol</td>
<td>No effect on primary prevention†</td>
<td></td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Effective in secondary prevention in women†</td>
<td></td>
</tr>
<tr>
<td>HMG-CoA Reductase</td>
<td>Primary and secondary prevention: Possible efficacy in women†</td>
<td>Gastrointestinal side effects more common in women</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Decreases cholesterol and slows plaque progression without respect to gender</td>
<td></td>
</tr>
<tr>
<td>Nicotine Preparations</td>
<td>Gum equally effective in women† Patch effective in women†</td>
<td>Gum may suppress weight gain; not recommended in pregnancy</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CVA = cerebrovascular accident; HDL = high-density lipoprotein; HMG-CoA = hydroxymethylglutaryl coenzyme A; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SLE = systemic lupus erythematosus; US = United States.

†Studies of efficacy in both men and women, with analysis by gender.

### Appendix 7

Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly

<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_1/2$</th>
<th>$V_d$</th>
<th>Cl</th>
<th>Primary Route(s) of Elimination</th>
<th>Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$\alpha$-Adrenergic Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxazosin</td>
<td>↑</td>
<td>↑</td>
<td>↑'</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Prazosin</td>
<td>↑</td>
<td></td>
<td></td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Terazosin</td>
<td>↑</td>
<td></td>
<td></td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td><strong>$\alpha_2$-Adrenergic Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Guanabenz</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>↑</td>
<td>—</td>
<td>↓</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td><strong>Angiotensin-Converting Enzyme Inhibitors</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>↑</td>
<td></td>
<td></td>
<td>Renal</td>
<td>No initial dosage adjustment is needed.</td>
</tr>
<tr>
<td>Captopril</td>
<td>NS</td>
<td>—</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Enalapril</td>
<td>—</td>
<td>—</td>
<td></td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
<td>No initial dosage adjustment is needed.</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>↑</td>
<td>NS</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Moexipril</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Perindopril</td>
<td>—</td>
<td>—</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Quinapril</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Ramipril</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td><strong>Angiotensin-II-Receptor Blockers</strong></td>
<td></td>
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<tr>
<td>Candesartan</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
<td>No initial dosage adjustment is needed.</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/biliary/renal</td>
<td>No initial dosage adjustment is needed.</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>NS</td>
<td>—</td>
<td></td>
<td>Hepatic</td>
<td>No initial dosage adjustment is needed.</td>
</tr>
<tr>
<td>Losartan</td>
<td>—</td>
<td>—</td>
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<td>Hepatic</td>
<td>No initial dosage adjustment is needed.</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal/biliary</td>
<td>No initial dosage adjustment is needed.</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
<td>No initial dosage adjustment is needed.</td>
</tr>
<tr>
<td>Valsartan</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>No initial dosage adjustment is needed.</td>
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</table>

(Table continued on p. 746.)


745
<table>
<thead>
<tr>
<th>Drug</th>
<th>T½</th>
<th>Vₐ</th>
<th>Cl</th>
<th>Primary Route(s) of Elimination</th>
<th>Dosage Adjustment</th>
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<tbody>
<tr>
<td><strong>Antiarrhythmic Agents</strong></td>
<td></td>
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<tr>
<td><strong>Class I</strong></td>
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<tr>
<td>Disopyramide</td>
<td>↑</td>
<td>—</td>
<td>↓</td>
<td>Renal/renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Flecainide</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>↑</td>
<td>↑</td>
<td>NS</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Moricizine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Procainamide</td>
<td>—</td>
<td>—</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Propafenone</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Quinidine</td>
<td>↑</td>
<td>NS</td>
<td>↓</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Tocainide</td>
<td>↑</td>
<td>—</td>
<td>↓</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td><strong>Class II (see Beta-Blockers)</strong></td>
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<tr>
<td><strong>Class III</strong></td>
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<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/biliary</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Bretylium</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>—</td>
<td>—</td>
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<td>Renal</td>
<td>Adjust dose based on renal function.</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Sotalol</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal</td>
<td>Adjust dose based on renal function.</td>
</tr>
<tr>
<td><strong>Class IV (see Calcium Channel Blockers)</strong></td>
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<tr>
<td><strong>Other Antiarrhythmics</strong></td>
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<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Erythrocytes/vascular</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Atropine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td><strong>Antithrombotics</strong></td>
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<td><strong>Anticoagulants</strong></td>
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<td>Argatroban</td>
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<td>Hepatic/biliary</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal/proteolytic cleavage</td>
<td>Adjust dose based on renal function.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal/hepatic</td>
<td>No adjustment necessary.</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>↑</td>
<td>—</td>
<td>↓</td>
<td>Renal</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Heparin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/reticuloendothelial system</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>↓</td>
<td>—</td>
<td>↓</td>
<td>Renal</td>
<td>Adjust dose based on renal function.</td>
</tr>
<tr>
<td><strong>Antiplatelets</strong></td>
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<td>Abciximab</td>
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<td>—</td>
<td>◀</td>
<td>Unknown</td>
<td>Use usual dose with caution.</td>
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<tr>
<td>Aspirin</td>
<td>—</td>
<td>—</td>
<td>◀</td>
<td>Hepatic/renal</td>
<td>Use usual dose with caution.</td>
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<tr>
<td>Clopidogrel</td>
<td>NS</td>
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<td>Hepatic</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/biliary</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Renal/plasma</td>
<td>Use usual dose with caution.</td>
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<tr>
<td>Prasugrel</td>
<td>—</td>
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<td>—</td>
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<td>Use usual dose with caution.</td>
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<tr>
<td>Ticlopidine</td>
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<td>◀</td>
<td>Hepatic</td>
<td>Use usual dose with caution.</td>
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<tr>
<td>Tirofiban</td>
<td>↑</td>
<td>—</td>
<td>◀</td>
<td>Hepatic</td>
<td>Use usual dose with caution.</td>
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<tr>
<td><strong>Thrombolytics</strong></td>
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<tr>
<td>Alteplase</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Anistreplase</td>
<td>—</td>
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<td>Unknown</td>
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<tr>
<td>Reteplase</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Circulating antibodies/reticuloendothelial system</td>
<td>Use usual dose with caution.</td>
</tr>
</tbody>
</table>
Selected Cardiovascular Drugs in the Elderly

<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_{1/2}$</th>
<th>$V_d$</th>
<th>Cl</th>
<th>Primary Route(s) of Elimination</th>
<th>Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Adrenergic Blockers</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nonselective Without ISA</td>
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</tr>
<tr>
<td>Nadolol</td>
<td>NS</td>
<td>—</td>
<td>—</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Propranolol</td>
<td>↑ NS ↓</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td><strong>β₁-Selective Without ISA</strong></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Atenolol</td>
<td>↑ NS ↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
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<tr>
<td>Bisoprolol</td>
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<td>Erythrocytes</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
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<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>Metoprolol</td>
<td>NS NS</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
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</tr>
<tr>
<td>Nebivolol</td>
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<td>—</td>
<td>Hepatic/renal</td>
<td>No adjustment necessary</td>
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<tr>
<td><strong>Nonselective with ISA</strong></td>
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<td>Carteolol</td>
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<td>—</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response.</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic</td>
<td>Use usual dose with caution.</td>
</tr>
<tr>
<td>Pindolol</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatic/renal</td>
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<tr>
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<tr>
<td><strong>Dual-Acting</strong></td>
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<tr>
<td>Amlodipine</td>
<td>↑</td>
<td>—</td>
<td>↓</td>
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<tr>
<td>Clevidipine</td>
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<td>—</td>
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<td>Use usual dose with caution.</td>
</tr>
<tr>
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<td>↑ NS ↓</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response.</td>
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<tr>
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<td>—</td>
<td>—</td>
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<td>Initiate at lowest dose; titrate to response.</td>
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<td>Bumetanide</td>
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(Table continued on p. 748.)
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<th>Drug</th>
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<th>CI</th>
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<th>Dosage Adjustment</th>
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<td>NS</td>
<td>NS</td>
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<td>Nesiritide</td>
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<tr>
<td>Norepinephrine</td>
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<td>No adjustment necessary</td>
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<tr>
<td>Colestipol</td>
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<td>Not absorbed from GI tract</td>
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</tr>
<tr>
<td>Colesevelam</td>
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<td><strong>FADS</strong></td>
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<td>$V_{\text{d}}$</td>
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*Increase in Cl is small when compared to increase in $V_{\text{d}}$.
*This drug is usually classified as an aldosterone receptor antagonist rather than a potassium-sparing diuretic.

$T_{\text{hal}} =$ half-life; $V_{\text{d}} =$ volume of distribution; Cl = clearance; ↑ = increase; ↓ = decrease; — = no information or not relevant; BAS = bile acid sequestrants; FADS = fibric acid derivatives; GI = gastrointestinal; HMG-CoA = hydroxymethylglutaryl coenzyme A; ISA = intrinsic sympathomimetic activity; ISDN = isosorbide dinitrate; ISMN = isosorbide mononitrate; LMWH = low-molecular-weight heparin; NS = no significant change.
## Appendix 8

### Selected Cardiovascular Medications and Ethnic Issues

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<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Evidence of Efficacy in Various Ethnic Groups</th>
<th>Consideration in Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-Adrenergic Antagonists</strong></td>
<td>Prazosin is less effective in blacks.</td>
<td>Blacks may need higher doses, generally a second-line agent.</td>
</tr>
<tr>
<td><strong>Beta-Blockers</strong></td>
<td>No difference in plasma concentrations of propranolol between Malays, Indians, and Chinese. Compared to white patients, black patients have lower plasma concentration of propranolol when this drug is taken orally. S-isomer clears more slowly than R-isomer. All metabolic pathways have higher metabolic rates in blacks as compared to whites. Chinese have lower plasma concentrations and higher clearance of propranolol, mainly secondary to increased ring oxidation and conjugation.</td>
<td>Blacks may need higher doses of propranolol to achieve same effects as whites.</td>
</tr>
<tr>
<td><strong>Propranolol</strong></td>
<td>No differences in metabolism of metoprolol between whites and blacks in the United States; Chinese have a higher incidence of slow metabolizers (with one or two copies of CYP2D6*10) and have significantly higher plasma concentrations of R- and S-metoprolol. The S-isomer (which confers beta-blocking activity) reaches higher concentrations than the R-isomer. In poor metabolizers, there is a lasting effect after 24 hours, which correlates with reduced clearance of the S-isomer.</td>
<td>Lower doses of metoprolol are required in Chinese.</td>
</tr>
<tr>
<td><strong>Metoprolol</strong></td>
<td>Response of blacks to other beta-blockers is similar to the response of whites. Labetalol and nebivolol seem to be effective in blacks. Carvedilol was effective in CHF treatment in all subgroups. In blacks, bucindolol was worse than placebo in advanced heart failure. Unusually high plasma concentrations of alprenolol and timolol have been found in subjects with CYP2D6-poor metabolizer phenotype. The plasma concentrations and the degree of beta-blockade were greater in subjects with the CYP2D6-PM-phenotype taking timolol.</td>
<td>Carvedilol can be used in blacks for heart failure. Bucindolol should be avoided in blacks with advanced heart failure.</td>
</tr>
</tbody>
</table>

(Table continued on p. 752.)
<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Calcium-Channel Blockers</td>
<td><strong>Nifedipine</strong> clearance is faster in whites than in blacks. South Asians, Mexicans, and Nigerians have higher drug exposure and longer half-life when compared to whites. Diltiazem is less effective in younger white men when compared to blacks.</td>
<td>Nifedipine might be a good initial treatment for hypertension in Asians, Hispanics, and blacks. Diltiazem may not be a good choice in young white patients.</td>
</tr>
<tr>
<td>Diuretics</td>
<td><strong>Blacks</strong> respond better to thiazide diuretics than do whites.</td>
<td>Good initial choice for antihypertensive therapy in blacks.</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td><strong>Propafenone</strong> concentrations elevated in poor metabolizers of dextromethorphan in a Chinese population, and CNS side effects were more frequent. Poor metabolizers of propafenone have a higher incidence of side effects. Poor metabolizers of flecainide have higher drug exposure and longer half-lives.</td>
<td>Close observation of side effects may be warranted in CYP2D6-intermediate metabolizers, such as many Asians, and in CYP2D6-poor metabolizers.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Mean maintenance dose of warfarin in Chinese subjects is around 3.1 mg vs 6.1 mg in whites.</td>
<td>Use lower warfarin doses in Chinese.</td>
</tr>
<tr>
<td>Aspirin</td>
<td>In Nigerians, overall excretion (particularly the glucuronide conjugate) is higher in males than in females.</td>
<td>Some populations may have increased side effects or decreased effectiveness.</td>
</tr>
<tr>
<td>ACE-Inhibitors, Angiotensin-Receptor Blockers (ARB), and Direct Renin Inhibitors</td>
<td><strong>Fosinoprilat</strong> has lower clearance and distribution volume in Chinese as compared to whites. Less antihypertensive effect in blacks at lower doses. However, the antihypertensive effect of ACE inhibitors, ARBs, and renin inhibitors are increased when a diuretic is given concurrently. ACE-inhibitors may not be as effective in blacks as in whites for heart failure, which might partially explain worse outcome of left ventricular dysfunction in blacks.</td>
<td>Chinese may need lower doses. Blacks may need additional drug (such as a diuretic) to achieve blood pressure control. Alternative or additional therapy in blacks with left ventricular dysfunction may be needed.</td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitors</td>
<td>Pharmacokinetic studies have shown an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with white controls.</td>
<td>Initiation of rosuvastatin at a lower dose (5 mg once daily) should be considered for Asian patients.</td>
</tr>
<tr>
<td>Nitrates</td>
<td>In combination with hydralazine, more effective in black patients (isosorbide dinitrate) for heart failure.</td>
<td></td>
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