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Chapter 16

Heart Failure

I. Overview

Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body. Its cardinal symptoms are dyspnea, fatigue, and fluid retention. HF is due to an impaired ability of the heart to adequately fill with and/or eject blood. It is often accompanied by abnormal increases in blood volume and interstitial fluid, hence the term â€œcongestiveâ€ HF because symptoms include dyspnea from pulmonary congestion in left HF, and peripheral edema in right HF. Underlying causes of HF include arteriosclerotic heart disease, myocardial infarction, hypertensive heart disease, valvular heart disease, dilated cardiomyopathy, and congenital heart disease. Left systolic dysfunction secondary to coronary artery disease is the most common cause of HF, accounting for nearly 70 percent of all cases. The number of newly diagnosed patients with HF is increasing, because more individuals now survive acute myocardial infarction.

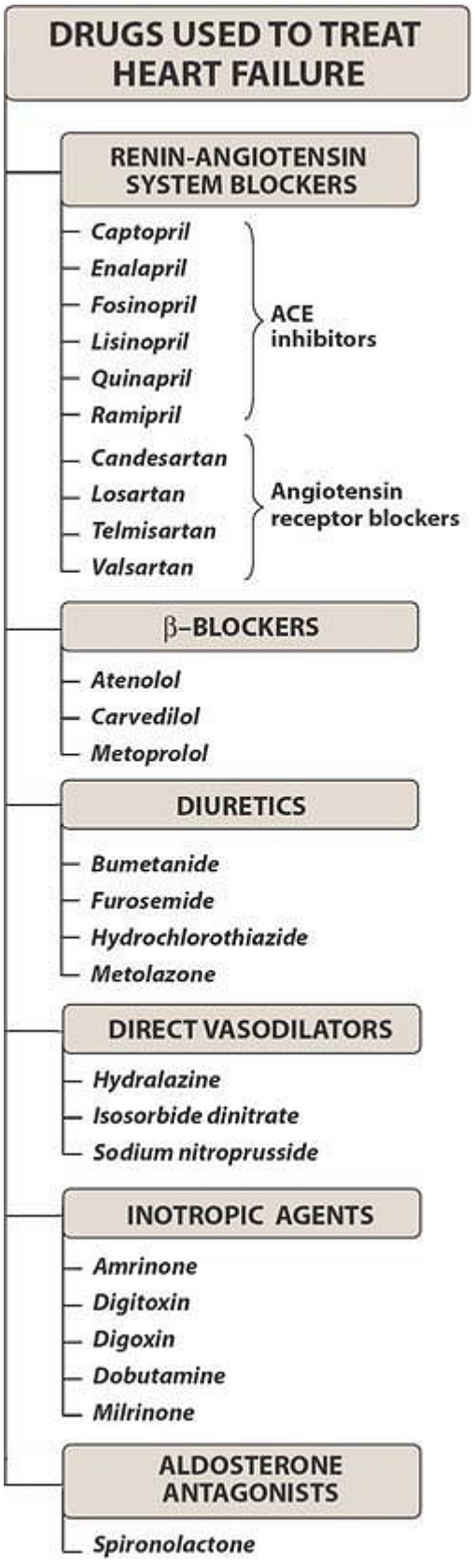

Figure 16.1 Summary of drugs used to treat heart failure. ACE = angiotensinconverting enzyme.

A. Role of physiologic compensatory mechanisms in the progression of HF

Chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis is associated with remodeling of cardiac tissue, characterized by loss of myocytes, hypertrophy, and fibrosis. The geometry of the heart becomes less elliptical and more spherical, interfering with its ability to efficiently function as a pump. This prompts additional neurohumoral activation, creating a vicious cycle that, if left untreated, leads to death.

B. Goals of pharmacologic intervention in HF

The goals are to alleviate symptoms, slow disease progression, and improve survival. Accordingly, six classes of drugs have been shown to be effective: 1) inhibitors of the renin-angiotensin system, 2) Î²-adrenoreceptor blockers, 3) diuretics, 4) inotropic agents, 5) direct vasodilators, and 6) aldosterone antagonists (Figure 16.1). Depending on the severity of cardiac failure and individual patient factors, one or more of these classes of drugs are administered. Beneficial effects of pharmacologic intervention include reduction of the load

on the myocardium, decreased extracellular fluid volume, improved cardiac contractility, and slowing of the rate of cardiac remodeling. Knowledge of the physiology of cardiac muscle contraction is essential to understanding the compensatory responses evoked by the failing heart as well as the actions of drugs used to treat HF.

II. Physiology of Muscle Contraction

The myocardium, like smooth and skeletal muscle, responds to stimulation by depolarization of the membrane, which is followed by shortening of the contractile proteins and ends with relaxation and return to the resting state. However, unlike skeletal muscle, which shows graded contractions depending on the number of muscle cells that are stimulated, the cardiac muscle cells are interconnected in groups that respond to stimuli as a unit, contracting together whenever a single cell is stimulated.

A. Action potential

Cardiac muscle cells are electrically excitable. However, unlike the cells of other muscles and nerves, the cells of cardiac muscle show a spontaneous, intrinsic rhythm generated by specialized â€œpacemakerâ€ cells located in the sinoatrial and atrioventricular nodes. The cardiac cells also have an unusually long action potential, which can be divided into five phases (0â€“4). Figure 16.2 illustrates the major ions contributing to depolarization and polarization of cardiac cells. These ions pass through channels in the sarcolemmal membrane and, thus, create a current. The channels open and close at different times during the action potential. Some respond primarily to changes in ion concentration, whereas others are sensitive to adenosine triphosphate, or to membrane voltage.

B. Cardiac contraction

The contractile machinery of the myocardial cell is essentially the same as that in striated muscle. The force of contraction of the cardiac muscle is directly related to the concentration of free (unbound) cytosolic calcium. Therefore, agents that increase these calcium levels (or that increase the sensitivity of the contractile machinery to calcium) result in an increased force of contraction (inotropic effect). [Note: The inotropic agents increase the contractility of the heart by directly or indirectly altering the mechanisms that control the concentration of intracellular calcium.]

1. **Sources of free intracellular calcium:** Calcium comes from several sources. The first is from outside the cell, where opening of voltage-sensitive calcium channels causes an immediate rise in free cytosolic calcium. Calcium may aslo enter by exchange with sodium. Calcium is also released from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium (Figure 16.3).
2. **Removal of free cytosolic calcium:** If free cytosolic calcium levels were to remain high, the cardiac muscle would be in a constant state of contraction rather than showing a periodic contraction. Mechanisms of removal include two alternatives.

a. **Sodium/calcium exchange:** Calcium is removed by a sodium/calcium exchange reaction that reversibly exchanges calcium ions for sodium ions across the cell membrane (see Figure 16.3).

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This interaction between the movement of calcium and sodium ions is significant, because changes in intracellular sodium can affect cellular levels of calcium.

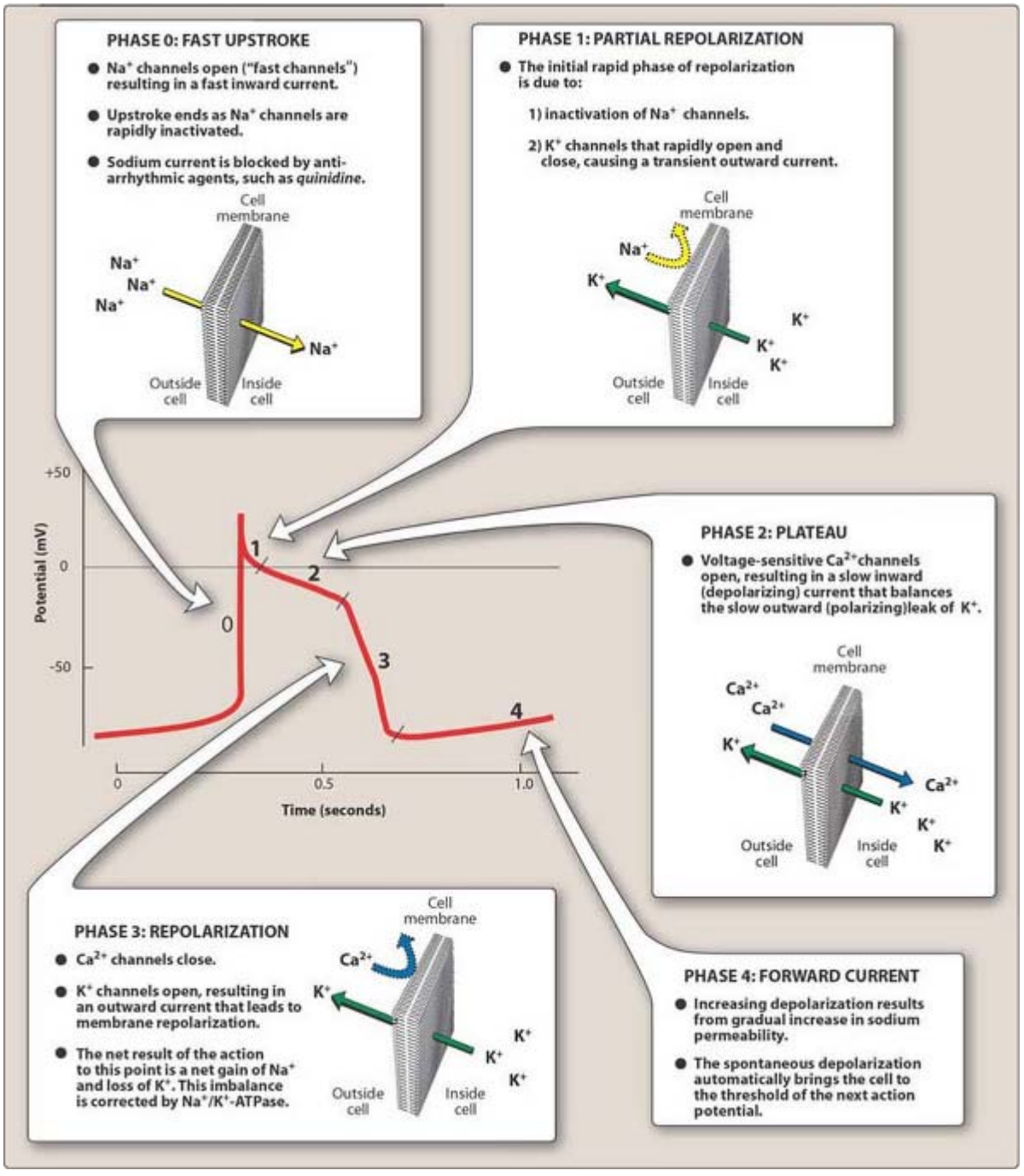

Figure 16.2 Action potential of a Purkinje fiber. ATPase = adenosine triphosphatase.

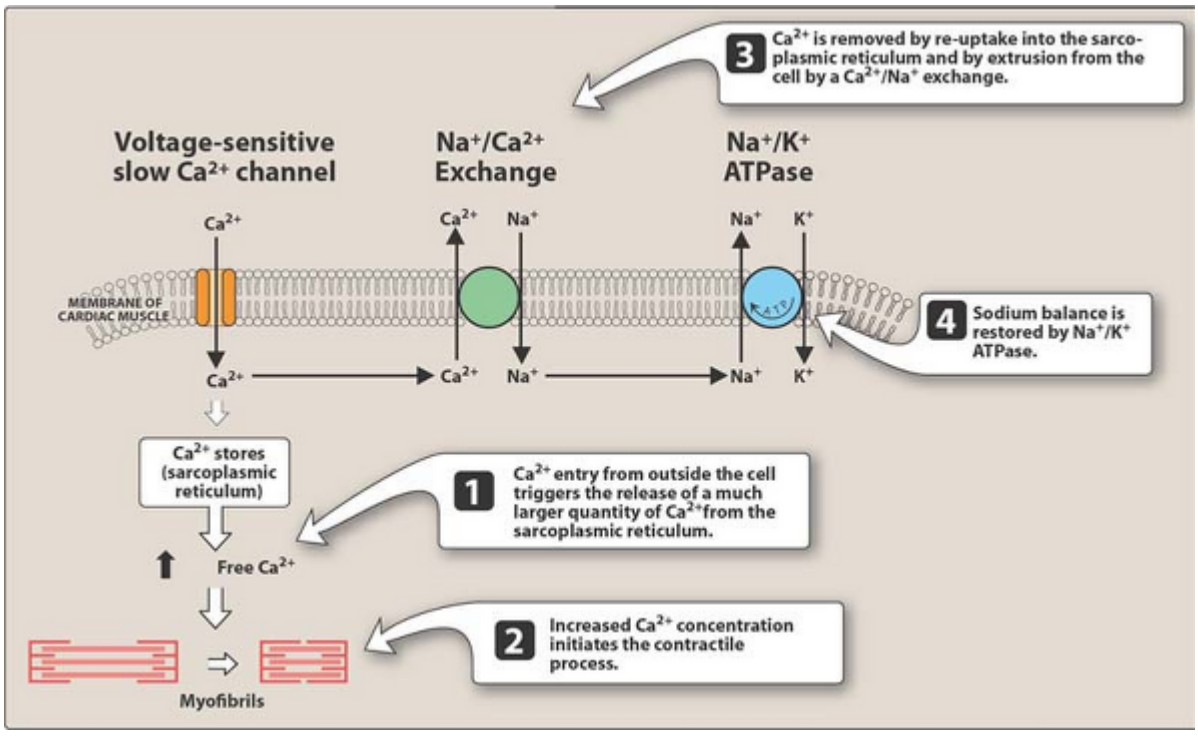

Figure 16.3 Ion movements during the contraction of cardiac muscle. ATPase = adenosine triphosphatase.

b. **Uptake of calcium by the sarcoplasmic reticulum and mitochondria:** Calcium is also recaptured by the sarcoplasmic reticulum and the mitochondria. More than 99 percent of the intracellular calcium is located in these organelles, and even a modest shift between these stores and free calcium can lead to large changes in the concentration of free cytosolic calcium.

C. Compensatory physiological responses in HF

The failing heart evokes three major compensatory mechanisms to enhance cardiac output (Figure 16.4). Although initially beneficial, these alterations ultimately result in further deterioration of cardiac function.

1. **Increased sympathetic activity:** Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system, which stimulates Î²-adrenergic receptors in the heart. This results in an increased heart rate and a greater force of contraction of the heart muscle (see Figure 16.4). In addition, vasoconstriction ($Î±_1$-mediated) enhances venous return and increases cardiac preload. These compensatory responses increase the work of the heart and, therefore, can contribute to further decline in cardiac function.

2. **Activation of the renin-angiotensin system:** A fall in cardiac output decreases blood flow to the kidney, prompting the release of renin, with a resulting increase in the formation of angiotensin II and release of aldosterone. This results in increased peripheral resistance and retention of sodium and water. Blood volume increases, and more blood is returned to the heart. If the heart is unable to pump this extra volume, venous pressure increases and peripheral edema and pulmonary edema occur (see Figure 16.4). These compensatory responses increase the work of the heart and, therefore, can contribute to further decline in cardiac function.
3. **Myocardial hypertrophy:** The heart increases in size, and the chambers dilate and become more globular. Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive

elongation of the fibers results in weaker contractions, and the geometry diminishes the ability to eject blood. This type of failure is termed systolic failure and is the result of a ventricle being unable to pump effectively. Less commonly, patients with HF may have diastolic dysfunctionâ€"a term applied when the ability of the ventricles to relax and accept blood is impaired by structural changes, such as hypertrophy. The thickening of the ventricular wall and subsequent decrease in ventricular volume decrease the ability of heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed diastolic HFâ€"a particularly common feature of HF in elderly women. Diastolic dysfunction in its pure form is characterized by signs and symptoms of HF in the presence of a normal function of the left ventricle. However, both systolic and diastolic dysfunction commonly coexist in HF.

D. Decompensated HF

If the mechanisms listed above adequately restore cardiac output, the HF is said to be compensated. However, these compensations increase the work of the heart and contribute to further decline in cardiac performance. If the adaptive mechanisms fail to maintain cardiac output, the HF is termed decompensated.

E. Therapeutic strategies in HF

Chronic HF is typically managed by a reduction in physical activity, low dietary intake of sodium (<1500 mg/day), treatment of comorbid conditions, and judicious use of diuretics, inhibitors of the renin-angiotensin system, and inotropic agents. Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs, alcohol, calcium-channel blockers, and some antiarrhythmic drugs, should be avoided if possible. Patients with HF complain of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and dependent edema.

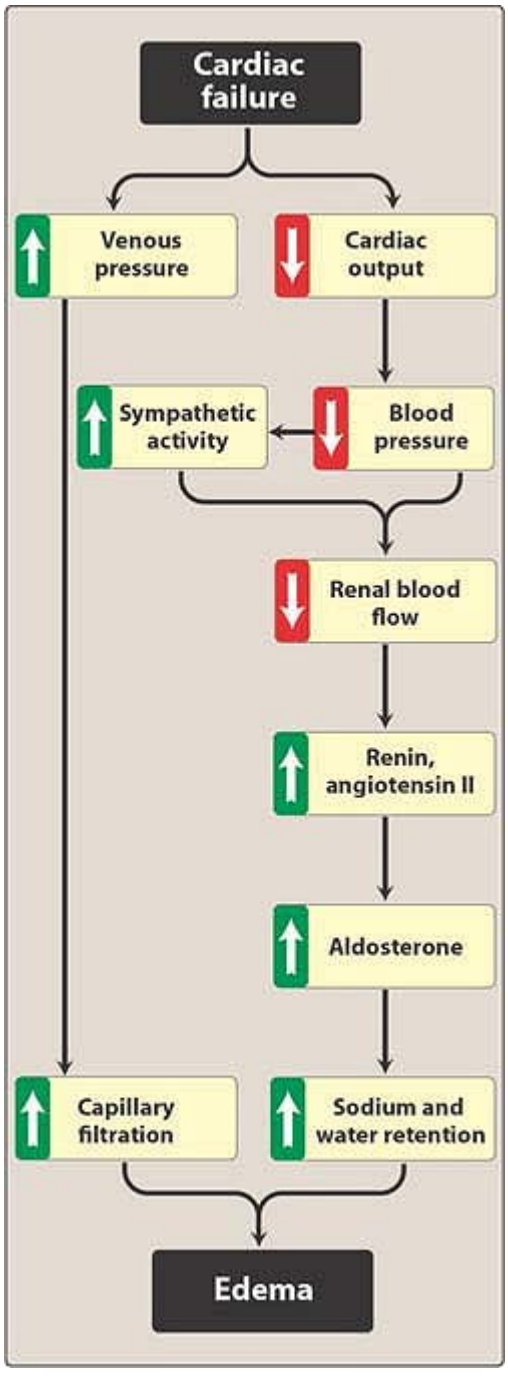

Figure 16.4 Cardiovascular consequences of heart failure.

III. Inhibitors of the Renin-Angiotensin System

HF leads to activation of the renin-angiotensin system via two mechanisms: 1) Increased renin release by juxtaglomerular cells in renal afferent arterioles occurs in response to the diminished renal perfusion pressure produced by the failing heart, and 2) renin release by the juxtaglomerular cells is promoted by sympathetic stimulation. The production of angiotensin IIâ€"a potent vasoconstrictorâ€"and the subsequent stimulation of aldosterone release that causes salt and water retention lead to the increases in

both preload and afterload that are characteristic of the failing heart. In addition, high levels of angiotensin II and of aldosterone have direct detrimental effects on the cardiac muscle, favoring remodeling, fibrosis, and inflammatory changes.

A. Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are the agents of choice in HF. These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II (Figure 16.5). These agents also diminish the rate of bradykinin inactivation. [Note: Vasodilation occurs as a result of the combined effects of lower vasoconstriction caused by diminished levels of angiotensin II and the potent vasodilating effect of increased bradykinin.] By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

1. **Actions on the heart:** ACE inhibitors decrease vascular resistance, venous tone, and blood pressure, resulting in an increased cardiac output (see Figure 16.5). ACE inhibitors also blunt the usual angiotensin IIâ€“mediated increase in epinephrine and aldosterone seen in HF. ACE inhibitors improve clinical signs and symptoms in patients also receiving thiazide or loop diuretics and/or *digoxin*. The use of ACE inhibitors in the treatment of HF has significantly decreased both morbidity and mortality. For example, Figure 16.6 shows that the ACE inhibitor *enalapril* [e-NAL-a-pril] decreases the cumulative mortality in patients with congestive HF. [Note: Reduction in mortality is due primarily to a decrease in deaths caused by progressive HF.] Treatment with *enalapril* also reduces arrhythmic death, myocardial infarction, and strokes. Similar data have been obtained with other ACE inhibitors.

2. **Indications:** ACE inhibitors may be considered for single-agent therapy in patients who present with mild dyspnea on exertion and do not show signs or symptoms of volume overload. ACE inhibitors are useful in decreasing HF in asymptomatic patients with an ejection fraction of less than 35 percent (left ventricular dysfunction). Patients who have had a recent myocardial infarction also benefit from long-term ACE inhibitor therapy. Patients with the lowest ejection

fraction show the greatest benefit. Early use of ACE inhibitors is indicated in patients with all stages of left ventricular failure, with and without symptoms, and therapy should be initiated immediately after myocardial infarction. (See p. 221 for the use of ACE inhibitors in the treatment of hypertension.)

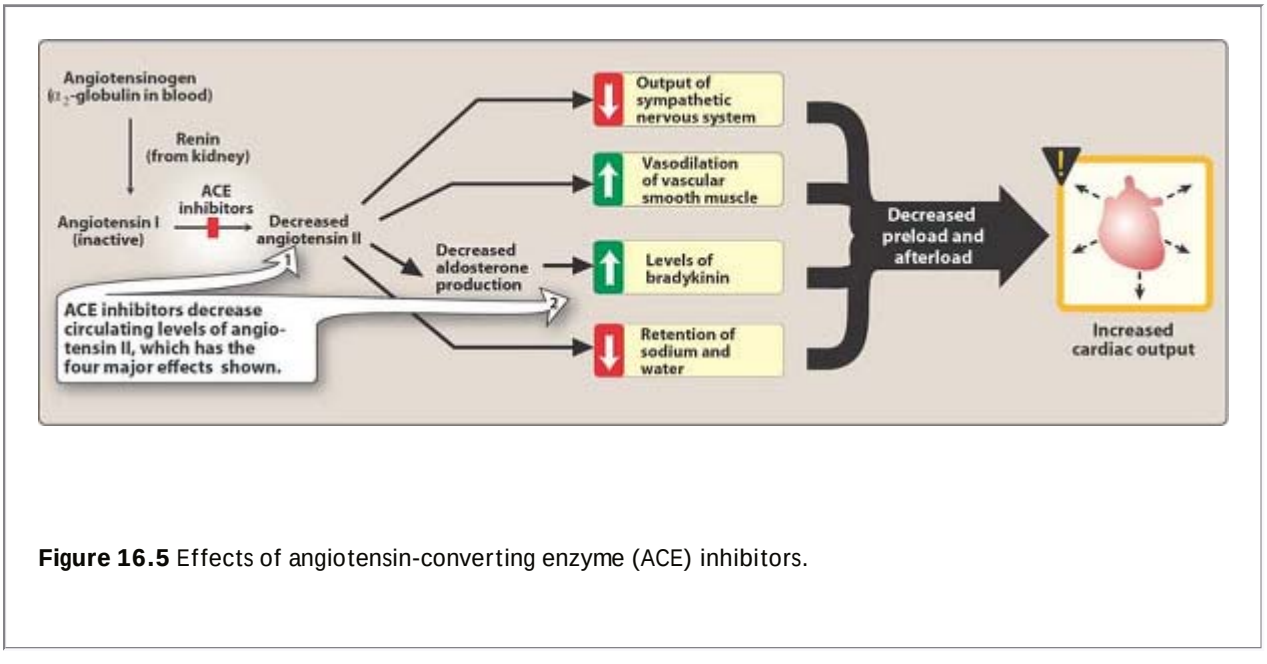

Figure 16.5 Effects of angiotensin-converting enzyme (ACE) inhibitors.

3. **Pharmacokinetics:** All ACE inhibitors are adequately but incompletely absorbed following oral administration.

The presence of food may decrease absorption, so they should be taken on an empty stomach. Except for *captopril* [CAP-toe-pril], ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes. Renal elimination of the active moiety is important for most ACE inhibitors, an exception being *fosinopril* [foe-SIH-no-pril]. Plasma half-lives of active compounds vary from 2 to 12 hours, although the inhibition of ACE may be much longer. The newer compounds such as *ramipril* [RA-mi-pril] and *fosinopril* require only once-a-day dosing.

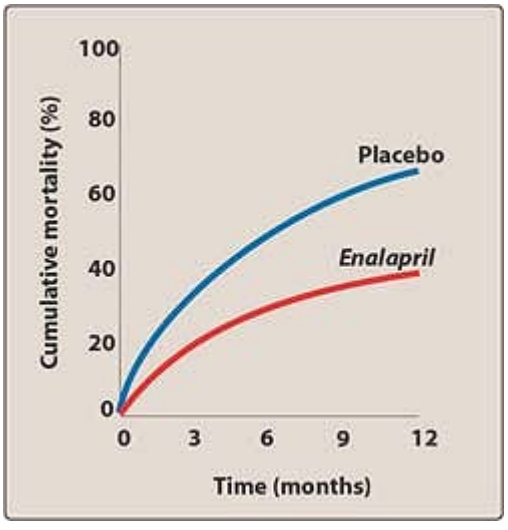

Figure 16.6 Effect of *enalapril* on the mortality of patients with congestive heart failure.

4. **Adverse effects:** These include postural hypotension, renal insufficiency, hyperkalemia, angioedema, and a persistent dry cough. The potential for symptomatic hypotension with ACE inhibitor therapy requires careful monitoring. ACE inhibitors should not be used in pregnant women, because they are fetotoxic.

B. Angiotensin-receptor blockers

Angiotensin-receptor blockers (ARBs) are nonpeptide, orally active compounds that are extremely potent competitive antagonists of the angiotensin type 1 receptor. *Losartan* [loe-SAR-tan] is the prototype drug. ARBs have the advantage of more complete blockade of angiotensin action, because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II. Further, the ARBs do not affect bradykinin levels. Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical. Even so, ARBs are a substitute for ACE inhibitors in those patients who cannot tolerate the latter.

1. **Actions on the cardiovascular system:** All the ARBs are approved for treatment of hypertension based on their clinical efficacy in lowering blood pressure and reducing the morbidity and mortality associated with hypertension. As indicated above, their use in HF is as a substitute for ACE inhibitors in those patients with severe cough or angioedema.

2. **Pharmacokinetics:** All the drugs are orally active and require only once-a-day dosing. *Losartan*, the first approved member of the class, differs from the others in that it undergoes extensive first-pass hepatic metabolism, including conversion to its active metabolite. The other drugs have inactive metabolites. Elimination of metabolites and parent compounds occurs in the urine and feces; the proportion is dependent on the individual drug. All are highly plasma proteinâ€“bound (greater than 90 percent) and, except for *candesartan* [kan-des-AR-tan], have large volumes of distribution.

3. **Adverse effects:** ARBs have an adverse effect profile similar to that of ACE inhibitors. However, ARBs do not

produce cough. ARBs are contraindicated in pregnancy.

IV. Î²-Blockers

Although it may seem counterintuitive to administer drugs with negative inotropic activity to a patient with HF, several clinical studies have clearly demonstrated improved systolic functioning and reverse cardiac remodeling in patients receiving Î²-blockers. These benefits arise in spite of occasional initial exacerbation of symptoms. The benefit of Î²-blockers is attributed, in part, to their ability to prevent the changes that occur because of the chronic activation of the sympathetic nervous system, including decreasing the heart rate and inhibiting the release of renin. In addition, Î²-blockers also prevent the direct deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy and cell death. Two Î²-blockers have been approved for use in HF: *carvedilol* [KAR-ve-dil-ol], and long-acting *metoprolol* [me-TOE-proe-lol]. *Carvedilol* is a nonselective Î²-adrenoreceptor antagonist that also blocks Î±-adrenoreceptors, whereas *metoprolol* is a $\hat{I}^2_1$-selective antagonist. [Note: The pharmacology of Î²-blockers is described in detail in Chapter 7.] Î²-Blockade is recommended for all patients with heart disease except those who are at high risk but have no symptoms or those who are in acute HF. *Carvedilol* and *metoprolol* reduce morbidity and mortality associated with HF. Treatment should be started at low doses and gradually titrated to effective doses based on patient tolerance. Obviously, the patient who also is hypertensive will obtain additional benefit from the Î²-blocker. Figure 16.7 shows the beneficial effect of *metoprolol* treatment in patients with HF.

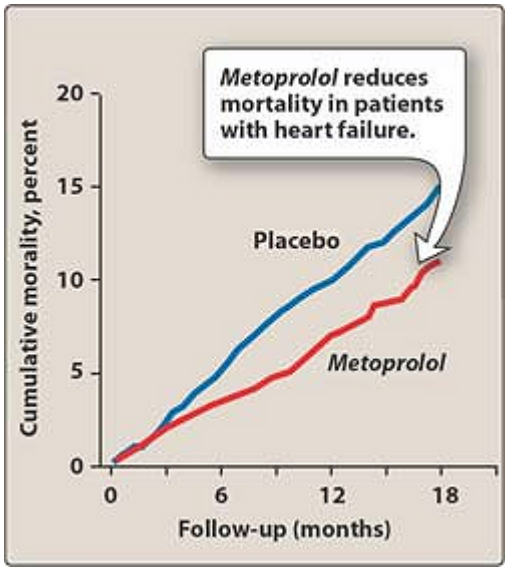

Figure 16.7 Cumulative mortality in patients with heart failure treated using placebo or *metoprolol*.

V. Diuretics

Diuretics relieve pulmonary congestion and peripheral edema. These agents are also useful in reducing the symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea. Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases the cardiac workload and the oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thus decreasing blood pressure. Thiazide diuretics are relatively mild diuretics and lose efficacy if patient creatinine clearance is less than 50 mL/min. Loop diuretics are used for patients who require extensive diuresis and those with renal insufficiency. [Note: Overdoses of loop diuretics can lead to profound hypovolemia.]

VI. Direct Vasodilators

Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing the venous capacitance; arterial dilators reduce systemic arteriolar resistance and decrease afterload. Nitrates are commonly employed venous dilators for patients with congestive HF. If the patient is intolerant of ACE inhibitors or Î²-blockers, the combination of *hydralazine* and *isosorbide dinitrate* is most commonly used. [Note: Calcium-channel blockers should be avoided in patients with HF.]

VII. Inotropic Drugs

Positive inotropic agents enhance cardiac muscle contractility and, thus, increase cardiac output. Although these drugs act by different mechanisms, in each case the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.

A. Digitalis

The cardiac glycosides are often called *digitalis* or digitalis glycosides, because most of the drugs come from the digitalis (foxglove) plant. They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are widely used in treating HF. Like the antiarrhythmic drugs described in Chapter 17, the cardiac glycosides influence the sodium and calcium ion flows in the cardiac muscle, thereby increasing contraction of the atrial and ventricular myocardium (positive inotropic action). The digitalis glycosides show only a small difference between a therapeutically effective dose and doses that are toxic or even fatal. Therefore, the drugs have a low therapeutic index. The most widely used agent is *digoxin* [di-JOX-in].

1. **Mechanism of action:**

   a. **Regulation of cytosolic calcium concentration:** Free cytosolic calcium concentrations at the end of contraction must be lowered for cardiac muscle to relax. The Na^+/Ca^{2+}-exchanger plays an important role in this process by extruding Ca^{2+} from the myocyte in exchange for Na^+ (Figure 16.8). The concentration gradient for both ions is a major determinant of the net movement of ions. By inhibiting the ability of the myocyte to actively pump Na^+ from the cell, cardiac glycosides decrease the Na^+ concentration gradient and, consequently, the ability of the Na^+/Ca^{2+}-exchanger to move calcium out of the cell. Further, the higher cellular Na^+ is exchanged by extracellular Ca^{2+} by the Na^+/Ca^{2+}-exchanger increasing intracellular Ca^{2+}. Because more Ca^{2+} is retained intracellularly, a small but physiologically important increase occurs in the free Ca^{2+} that is available at the next contraction cycle of the cardiac muscle. It follows that if the Na^+/K^+â€“adenosine triphosphatase is extensively inhibited, the ionic gradient becomes so disturbed that dysrhythmias can occur.

   b. **Increased contractility of the cardiac muscle:** Administration of digitalis glycosides increases the force of cardiac contraction, causing the cardiac output to more closely resemble that of the

   normal heart (Figure 16.9). Increased myocardial contraction leads to a decrease in end-diastolic volume, thus increasing the efficiency of contraction (increased ejection fraction). The resulting improved circulation leads to reduced sympathetic activity, which then reduces peripheral resistance. Together, these effects cause a reduction in heart rate. Vagal tone is also enhanced, so the heart rate decreases and myocardial oxygen demand diminishes. [Note: In the normal heart, the positive inotropic effect of *digitalis* is counteracted by compensatory autonomic reflexes.]

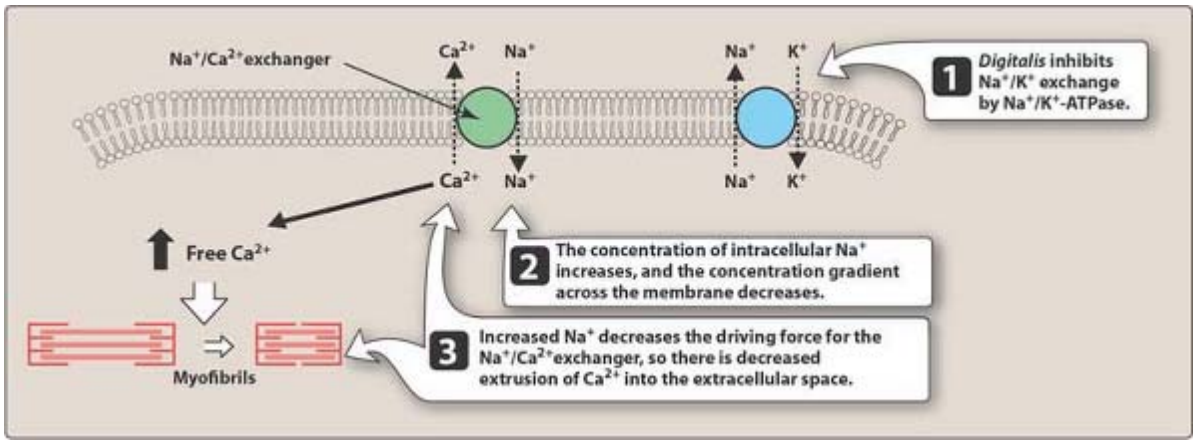

Figure 16.8 Mechanism of action of cardiac glycosides, or *digitalis*. ATPase = adenosine triphosphatase.

2. **Therapeutic uses:** *Digoxin* therapy is indicated in patients with severe left ventricular systolic dysfunction after initiation of ACE inhibitor and diuretic therapy. *Digoxin* is not indicated in patients with diastolic or right-sided HF. *Digoxin's* major indication is HF with atrial fibrillation. *Dobutamine* [doe-BYOO-ta-meen], another inotropic agent, can be given intravenously in the hospital, but at present, no effective oral inotropic agents exist other than *digoxin.* Patients with mild to moderate HF will often respond to treatment with ACE inhibitors and diuretics, and they do not require *digoxin*.

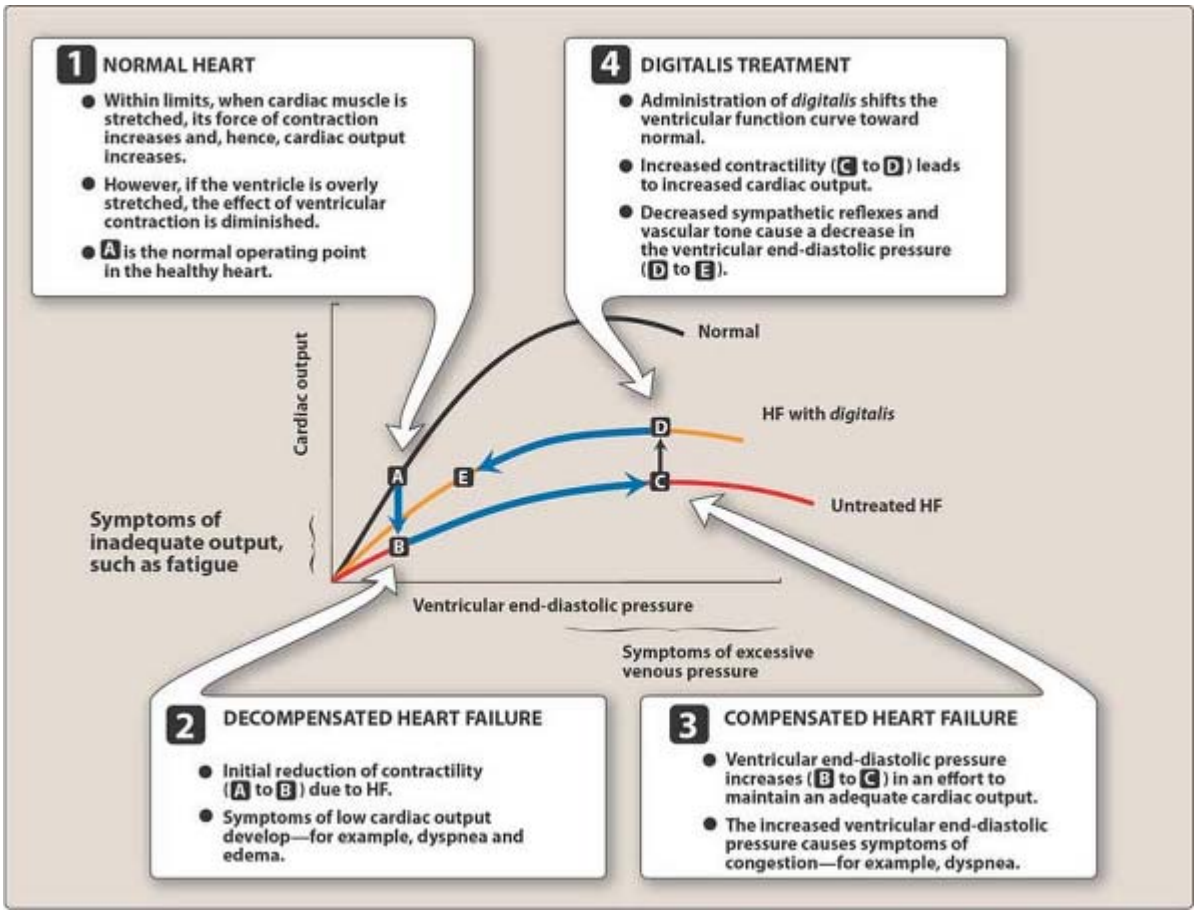

Figure 16.9 Ventricular function curves in the normal heart, in heart failure (HF), and in HF treated with *digitalis*.

3. **Pharmacokinetics:** All digitalis glycosides possess the same pharmacologic actions, but they vary in potency and pharmacokinetics (Figure 16.10). *Digoxin* is the only digitalis available in the United States. *Digoxin* is very potent, with a narrow margin of safety and long half-life of around 36 hours. *Digoxin* is mainly eliminated intact by the kidney, requiring dose adjustment based on creatinine clearance. *Digoxin* has a large volume of distribution, because it accumulates in muscle. A loading dose regimen is employed when acute digitalization is needed. *Digitoxin* [DIJ-i-tox-in] has a much longer half-life and is extensively metabolized by the liver before excretion in the feces, and patients with hepatic disease may require decreased doses.

4. **Adverse effects:** *Digitalis* toxicity is one of the most commonly encountered adverse drug reactions. Side effects often can be managed by discontinuing cardiac glycoside therapy, determining serum potassium levels (decreased K^+ enhances potential for cardiotoxicity), and if indicated, giving potassium supplements. In general, decreased serum levels of potassium predispose a patient to *digoxin* toxicity. *Digoxin* levels must be closely monitored in the presence of renal insufficiency, and dosage adjustment may be necessary. Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to *digoxin* (digoxin immune Fab), which bind and inactivate the drug. Types of adverse effects include:

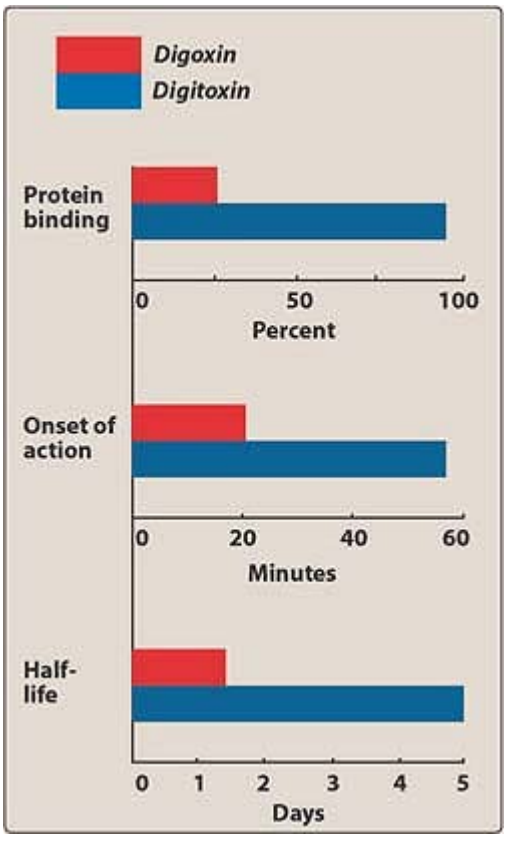

Figure 16.10 A comparison of the properties of *digoxin* and *digitoxin*.

a. **Cardiac effects:** The common cardiac side effect is arrhythmia, characterized by slowing of atrioventricular conduction associated with atrial arrhythmias. A decrease in intracellular potassium is the primary predisposing factor in these effects.

b. **Gastrointestinal effects:** Anorexia, nausea, and vomiting are commonly encountered adverse effects.

c. **Central nervous system effects:** These include headache, fatigue, confusion, blurred vision, alteration of color perception, and halos on dark objects.

5. **Factors predisposing to digitalis toxicity:**

a. **Electrolytic disturbances:** Hypokalemia can precipitate serious arrhythmia. Reduction of serum potassium levels is most frequently observed in patients receiving thiazide or loop diuretics, and this usually can be prevented by use of a potassium-sparing diuretic or supplementation with potassium chloride. Hypercalcemia and hypomagnesemia also predispose to *digitalis* toxicity.

b. **Drugs:** *Quinidine, verapamil*, and *amiodarone*, to name a few, can cause *digoxin* intoxication, both by displacing *digoxin* from tissue protein-binding sites and by competing with *digoxin* for renal excretion. As a consequence, *digoxin* plasma levels may increase by 70 to 100 percent, requiring dosage reduction. Potassium-depleting diuretics, corticosteroids, and a variety of other drugs can also increase *digoxin* toxicity (Figure 16.11). Hypothyroidism, hypoxia, renal failure, and myocarditis are also predisposing factors to *digoxin* toxicity.

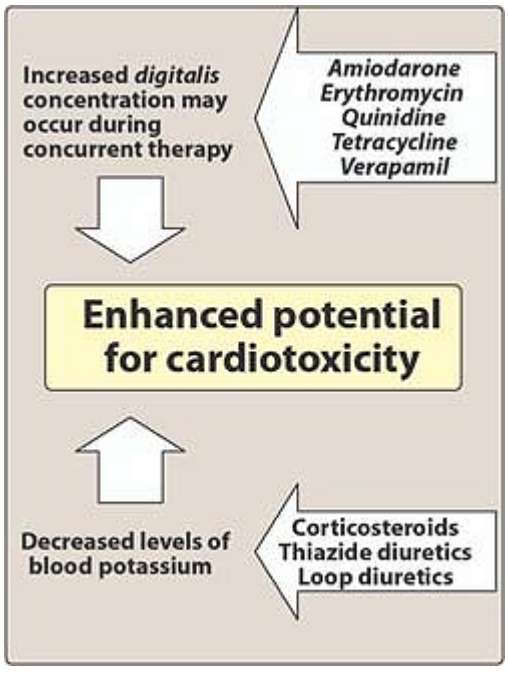

Figure 16.11 Drugs interacting with *digoxin* and other digitalis glycosides.

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B. Î²-Adrenergic agonists

Î²-Adrenergic stimulation improves cardiac performance by causing positive inotropic effects and vasodilation. *Dobutamine* is the most commonly used inotropic agent other than *digitalis*. *Dobutamine* leads to an increase in intracellular cyclic adenosine monophosphate (cAMP), which results in the activation of protein kinase. Slow calcium channels are one important site of phosphorylation by protein kinase. When phosphorylated, the entry of calcium ion into the myocardial cells increases, thus enhancing contraction (Figure 16.12). *Dobutamine* must be given by intravenous infusion and is primarily used in the treatment of acute HF in a hospital setting.

C. Phosphodiesterase inhibitors

Amrinone [AM-ri-none] and *milrinone* [MIL-ri-none] are phosphodiesterase inhibitors that increase the intracellular concentration of cAMP (see Figure 16.12). This results in an increase of intracellular calcium and, therefore, cardiac contractility, as discussed above for the Î²-adrenergic agonists. Long-term *amrinone* or *milrinone* therapy may be associated with a substantial increase in the risk of mortality. However, short-term use of intravenous *milrinone* is not associated with increased mortality, and some symptomatic benefit may be obtained when it is used in patients with refractory HF.

VIII. Spironolactone

Patients with advanced heart disease have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone.

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Spironolactone is a direct antagonist of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia. *Spironolactone* therapy should be reserved for the most advanced cases of HF. Because *spironolactone* promotes potassium retention, patients should not be taking potassium supplements. Adverse

effects include gastric disturbances, such as gastritis and peptic ulcer; central nervous system effects, such as lethargy and confusion; and endocrine abnormalities, such as gynecomastia, decreased libido, and menstrual irregularities.

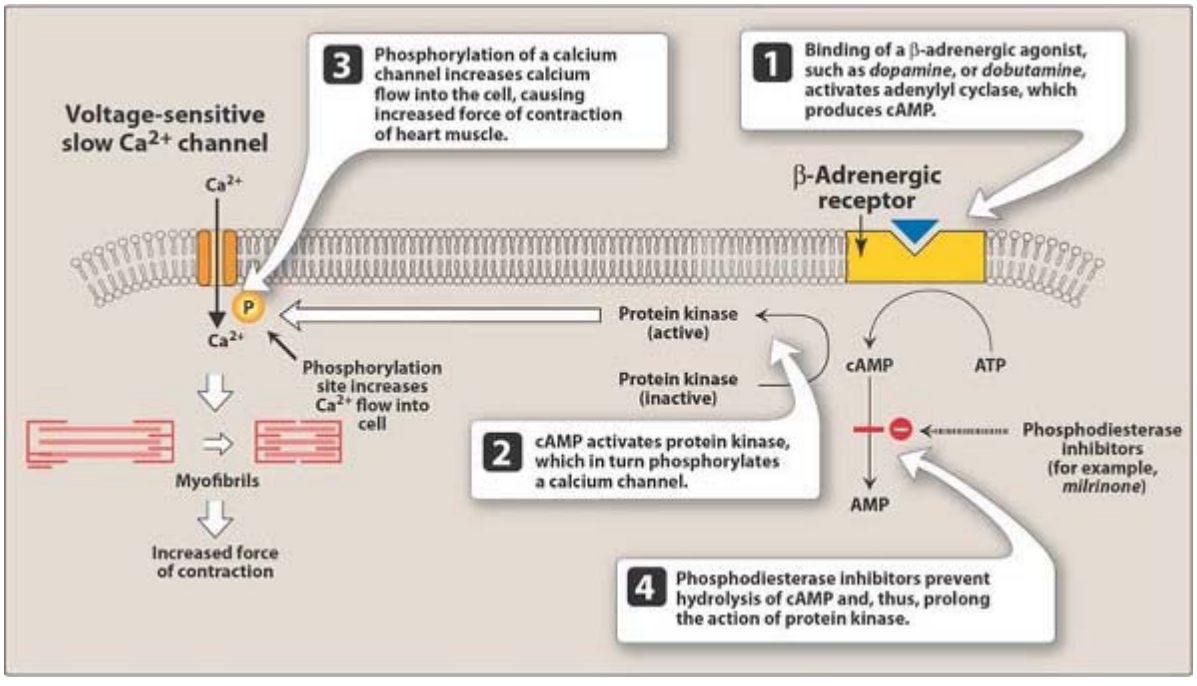


Figure 16.12 Sites of action by Î²-adrenergic agonists on heart muscle. AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; P = phosphate.

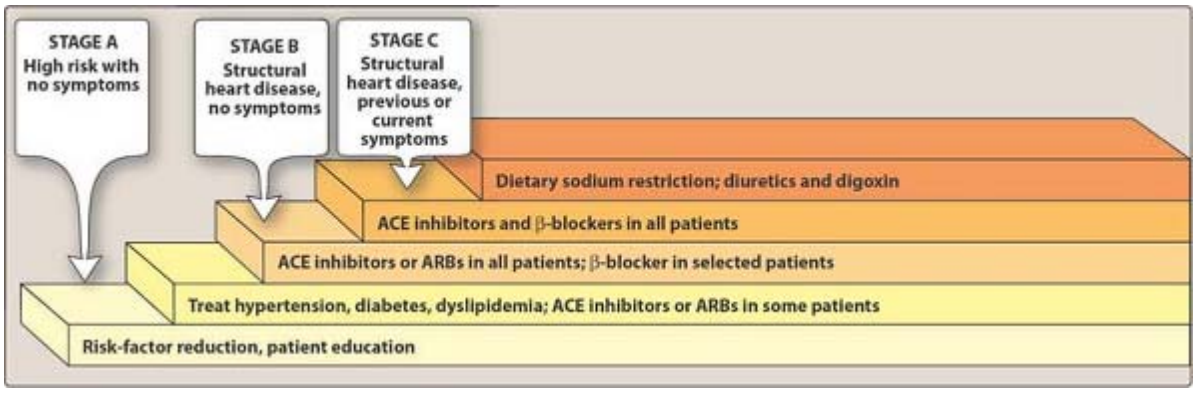


Figure 16.13 Treatment options for various stages of heart failure. ACE = Angiotensin-converting enzyme; ARB = angiotensinreceptor blockers. Stage D (refractory symptoms requiring special interventions) is not shown.

IX. Order of Therapy

Experts have classified HF into four stages, from least severe to most severe. Figure 16.13 shows a treatment strategy using this classification and the drugs described in this chapter. Note that as the disease progresses, polytherapy is initiated.

In patients with overt heart failure, loop diuretics are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema. ACE inhibitors, or if not tolerated, ARBs are added after the optimization of diuretic therapy. Gradually titrate the dosage to that which is maximally tolerated and/or produces optimal cardiac output. b Blockers are initiated after the patient is stable on ACE inhibitors, again beginning at low doses with titration to optimal levels. *Digoxin* is initiated in patients who continue to have symptoms of heart failure despite the multiple drug therapy. For example, Figure 16.14 shows that treatment with *digoxin* plus a diuretic plus an ACE inhibitor in patients with HF is superior to treatment with diuretics alone or a diuretic plus either *digoxin* or an ACE inhibitor.

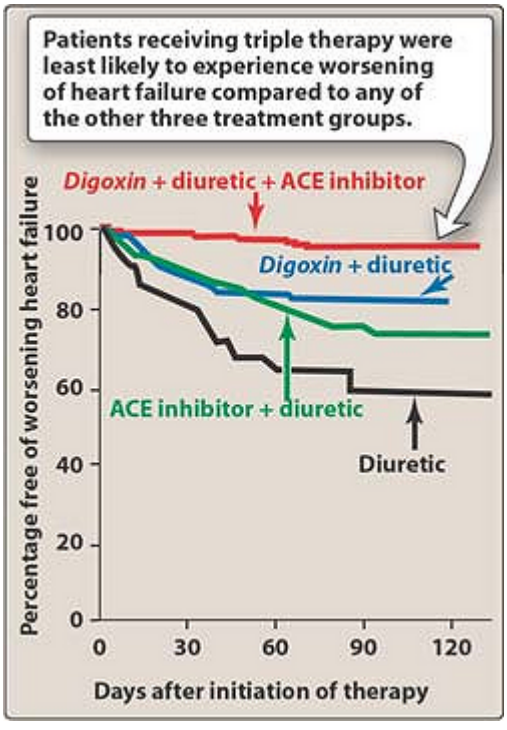


Figure 16.14 Use of multiple drugs in the treatment of heart failure. ACE = angiotensin-converting enzyme.

Study Questions

Choose the ONE best answer.

16.1 Digitalis has a profound effect on myocyte intracellular concentrations of Na^+, K^+, and Ca^{2+}. These effects are caused by digitalis inhibiting:

A. Ca^{2+}â€“adenosine triphosphatose (ATPase) of the sarcoplasmic reticulum.

B. Na^+/K^+-ATPase of the myocyte membrane.

C. Cardiac phosphodiesterase.

D. Cardiac Î²$_1$ receptors.

E. Juxtaglomerular renin release.

View Answer

16.2 Compensatory increases in heart rate and renin release that occur in heart failure may be alleviated by which of the following drugs?

A. Milrinone.

B. Digoxin.

C. Dobutamine.

D. Enalapril.

E. Metoprolol.

View Answer

16.3 A 58-year-old man is admitted to the hospital with acute heart failure and pulmonary edema. Which one of the following drugs would be most useful in treating the pulmonary edema?

A. Digoxin.

B. Dobutamine.

C. Furosemide.

D. Minoxidil.

E. Spironolactone.

View Answer

16.4 A 46-year-old man is admitted to the emergency department. He has taken more than 90 digoxin tablets (0.25 mg each), ingesting them about 3 hours before admission. His pulse is 50 to 60 beats per minute, and the electrocardiogram shows third-degree heart block. Which one of the following is the most important therapy to initiate in this patient?

A. Digoxin immune Fab.

B. Potassium salts.

C. Lidocaine.

D. Phenytoin.

E. DC cardioversion.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 17

Antiarrhythmics

I. Overview

In contrast to skeletal muscle, which contracts only when it receives a stimulus, the heart contains specialized cells that exhibit automaticity; that is, they can intrinsically generate rhythmic action potentials in the absence of external stimuli. These â€œpacemakerâ€ cells differ from other myocardial cells in showing a slow, spontaneous depolarization during diastole (Phase 4), caused by an inward positive current carried by sodium- and calcium-ion flows. This depolarization is fastest in the sinoatrial (SA) node (the normal initiation site of the action potential), and it decreases throughout the normal conduction pathway through the atrioventricular (AV) node to the bundle of His and the Purkinje system. Dysfunction of impulse generation or conduction at any of a number of sites in the heart can cause an abnormality in cardiac rhythm. Figure 17.1 summarizes the drugs used to treat cardiac arrhythmias.

II. Introduction to the Arrhythmias

The arrhythmias are conceptually simpleâ€”dysfunctions cause abnormalities in impulse formation and conduction in the myocardium. However, in the clinic, arrhythmias present as a complex family of disorders that show a variety of symptoms. For example, cardiac arrhythmias may cause the heart to beat too slowly (bradycardia) or to beat too rapidly (tachycardia), and to beat regularly (sinus tachycardia or sinus bradycardia) or irregularly (atrial fibrillation). The heart cavity from which the arrhythmia originates gives the name to the arrhythmiaâ€”atrial tachycardia for a rapid arrhythmia originating in the atria. Impulses originating from sites other than the SA node, or impulses traveling along accessory (extra) pathways that lead to deviant depolarizations (AV reentry, Wolff-Parkinson-White syndrome), may also trigger arrhythmias. To make sense of this large group of disorders, it is useful to organize the arrhythmias into groups according to the anatomic site of the abnormalityâ€”the atria, the AV node, or the ventricles. Figure 17.2 summarizes several commonly occurring atrial, AV junction, or ventricular arrhythmias. Although not shown here, each of these abnormalities can be further divided into subgroups depending on the electrocardiogram findings.

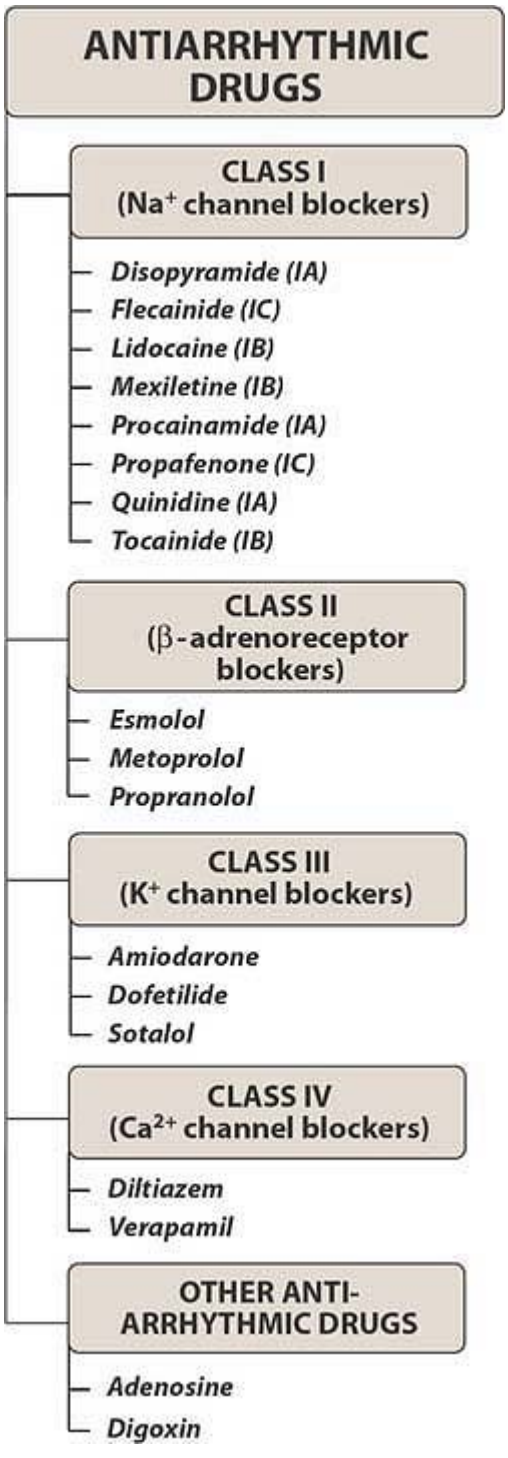


Figure 17.1 Summary of antiarrhythmic drugs.

A. Causes of arrhythmias

Most arrhythmias arise either from aberrations in impulse generation (abnormal automaticity) or from a defect in impulse conduction.

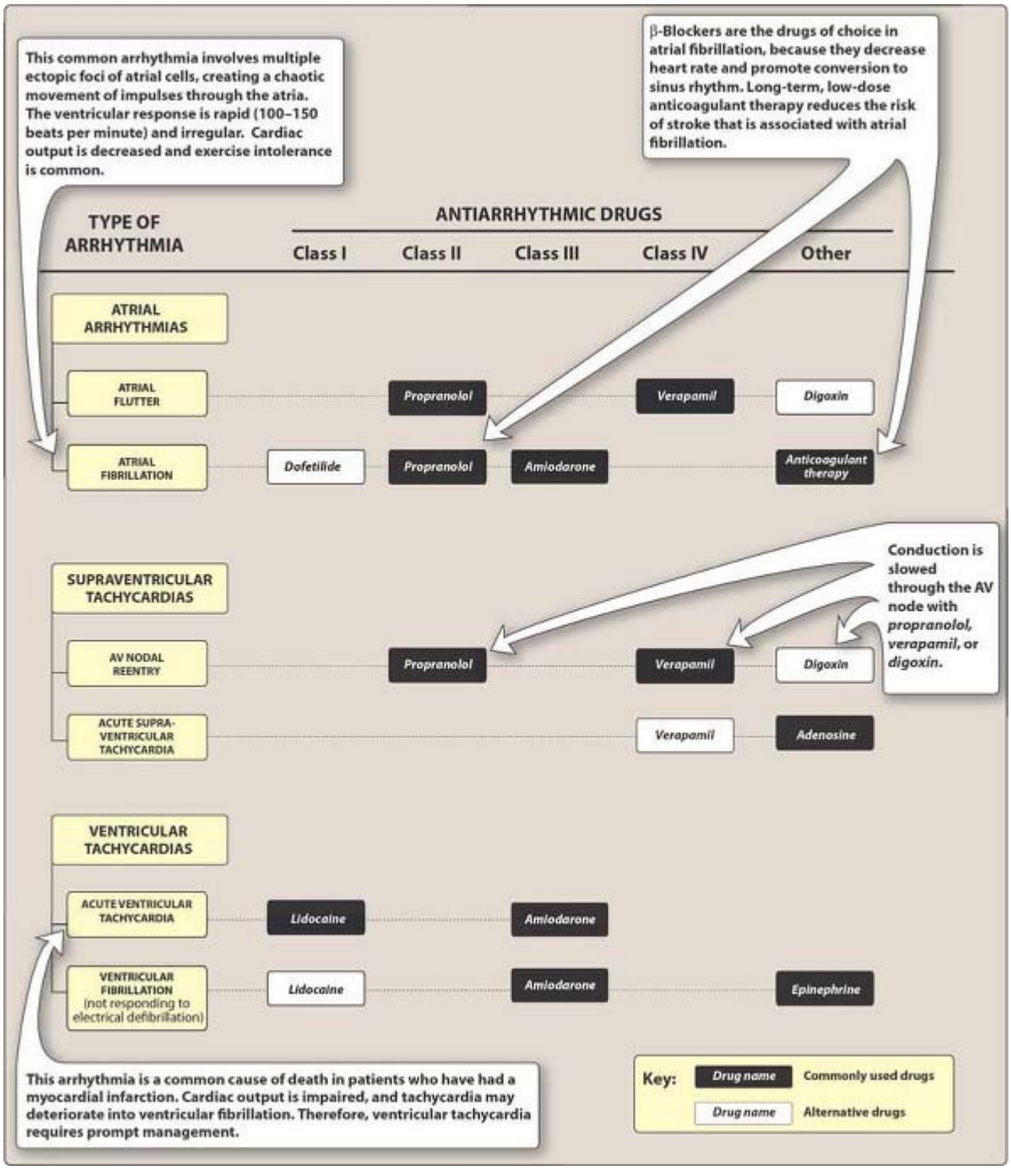


Figure 17.2 Therapeutic indications for some commonly encountered arrhythmias. AV = atrioventricular.

P.198

P.199

1. **Abnormal automaticity:** The SA node shows the fastest rate of Phase 4 depolarization and, therefore, exhibits a higher rate of discharge than that occurring in other pacemaker cells exhibiting automaticity. Thus, the SA node normally sets the pace of contraction for the myocardium, and latent pacemakers are depolarized by impulses coming from the SA node. However, if cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise. Abnormal automaticity may also occur if the

myocardial cells are damaged (for example, by hypoxia or potassium imbalance). These cells may remain partially depolarized during diastole and, therefore, can reach the firing threshold earlier than normal cells. Abnormal automatic discharges may thus be induced.

2. **Effect of drugs on automaticity:** Most of the antiarrhythmic agents suppress automaticity by blocking either Na^+ or Ca^{2+} channels to reduce the ratio of these ions to K^+. This decreases the slope of Phase 4 (diastolic) depolarization and/or raises the threshold of discharge to a less negative voltage. Such drugs cause the frequency of discharge to decreaseâ€"an effect that is more pronounced in cells with ectopic pacemaker activity than in normal cells.

3. **Abnormalities in impulse conduction:** Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire ventricular surface (Figure 17.3). A phenomenon called reentry can occur if a unidirectional block caused by myocardial injury or a prolonged refractory period results in an abnormal conduction pathway. Reentry is the most common cause of arrhythmias, and it can occur at any level of the cardiac conduction system. For example, consider a single Purkinje fiber with two conduction pathways to ventricular muscle. An impulse normally travels down both limbs of the conduction path. However, if myocardial injury results in a unidirectional block, the impulse may only be conducted down Pathway 1 (see Figure 17.3). If the block in Pathway 2 is in the forward direction only, the impulse may travel in a retrograde fashion through Pathway 2 and reenter the point of bifurcation. This short-circuit pathway results in reexcitation of the ventricular muscle, causing premature contraction or sustained ventricular arrhythmia.

4. **Effects of drugs on conduction abnormalities:** Antiarrhythmic agents prevent reentry by slowing conduction and/or increasing the refractory period, thereby converting a unidirectional block into a bidirectional block.

B. Antiarrhythmic drugs

As noted above, the antiarrhythmic drugs can modify impulse generation and conduction. More than a dozen such drugs that are potentially useful in treating arrhythmias are currently available. However, only a limited number of these agents are clinically beneficial in the treatment of selected arrhythmias. For example, the acute termination of ventricular tachycardia by *lidocaine* or of supraventricular tachycardia by *adenosine* or *verapamil* are examples in which antiarrhythmic therapy results in decreased morbidity. In contrast, many of the antiarrhythmic agents are now known to have dangerous proarrhythmic actionsâ€"that is, to cause

arrhythmias. The efficacy of many antiarrhythmic agents remains unproven in placebo-controlled, random trials. [Note: Implantable cardioverter defibrillators are becoming more widely used to manage this condition.]

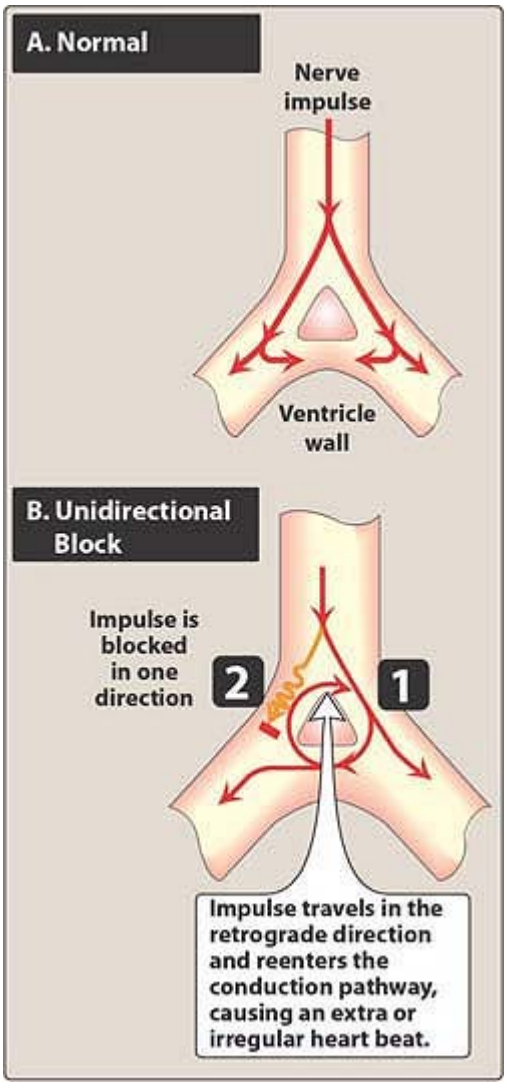


Figure 17.3 Schematic representation of reentry.

III. Class I Antiarrhythmic Drugs

The antiarrhythmic drugs can be classified according to their predominant effects on the action potential (Figure 17.4). Although this classification is convenient, it is not entirely clear-cut, because many of the drugs have actions relating to more than one class or may have active metabolites with a different class of action. Class I antiarrhythmic drugs act by blocking voltage-sensitive sodium channels via the same mechanism as local anesthetics. The decreased rate of entry of sodium slows the rate of rise of Phase 0 of the action potential. [Note: At therapeutic doses, these drugs have little effect on the resting, fully polarized membrane because of their higher affinity for the active and inactive channels rather than for the resting channel.] Class I antiarrhythmic drugs, therefore, generally cause a decrease in excitability and conduction velocity. The use of sodium channel blockers has been declining continuously due to their possible proarrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease.

A. Use-dependence

Class I drugs bind more rapidly to open or inactivated sodium channels than to channels that are fully repolarized

following recovery from the previous depolarization cycle. Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing (for example, during tachycardia, when the sodium channels open often). This property is called use-dependence (or state-dependence), and it enables these drugs to block cells that are discharging at an abnormally high frequency without interfering with the normal, low-frequency beating of the heart. The Class I drugs have been subdivided into three groups according to their effect on the duration of the action potential. Class IA agents slow the rate of rise of the action potential (thus slowing conduction), prolong the action potential, and increase the ventricular effective refractory period. They have an intermediate speed of association

with activated/inactivated sodium-channels and an intermediate rate of dissociation from resting channels. Prolongation of duration of the action potential and increased ventricular effective period are due to concomitant Class III activity. Class IB drugs have little effect on the rate of depolarization; rather, they decrease the duration of the action potential by shortening repolarization. They rapidly interact with sodium channels. Class IC agents markedly depress the rate of rise of the membrane action potential. Therefore, they cause marked slowing of conduction but have little effect on the duration of the membrane action potential or the ventricular effective refractory period. They bind slowly to sodium channels.

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

Figure 17.4 Actions of antiarrhythmic drugs.

B. Arrhythmias

Inhibition of potassium channels (Class III activity) widens the action potential, leading to a prolonged QT interval on the electrocardiogram. Such an effect is associated with increased risk of developing life-threatening ventricular tachyarrhythmias (torsades de pointes). The most common cause of QT prolongation is drug-induced, although it may also be genetic. QT prolongation is not only seen with Class III antiarrhythmics. Drugs such as *cisapride, grepafloxacin, terfenadine,* and *astemizole* were withdrawn from the market because of severe and fatal arrhythmias. *Erythromycin, clarithromycin, pentamidine, moxifloxacin, levofloxacin, imipramine, desipramine, amitriptyline, doxepin, thioridazine, mesoridazine, haloperidol, risperidone, ziprasidone,* and *quetiapine* are some of the drugs known to prolong the QT interval. Caution should be exerted when combining several drugs with effects on the QT interval (for example, *quinidine* with *levofloxacin*) or when giving these drugs combined with azole antifungals (*fluconazole* and *itraconazole*). The latter are known to inhibit drug metabolism, leading to large increases in plasma drug concentrations.

C. Quinidine

Quinidine [KWIN-i-deen] is the prototype Class IA drug. Because of its concomitant Class III activity, it can actually

precipitate arrhythmias such as polymorphic ventricular tachycardia (torsades de pointes), which can degenerate into ventricular fibrillation. Because of the toxic potential of *quinidine*, calcium antagonists, such as *amiodarone* and *verapamil*, are increasingly replacing this drug in clinical use.

1. **Mechanism of action:** *Quinidine* binds to open and inactivated sodium channels and prevents sodium influx, thus slowing the rapid upstroke during Phase 0 (Figure 17.5). It also decreases the slope of Phase 4 spontaneous depolarization and inhibits potassium channels.
2. **Therapeutic uses:** *Quinidine* is used in the treatment of a wide variety of arrhythmias, including atrial, AV-junctional, and ventricular tachyarrhythmias. *Quinidine* is used to maintain sinus rhythm after direct-current cardioversion of atrial flutter or fibrillation and to prevent frequent ventricular tachycardia.

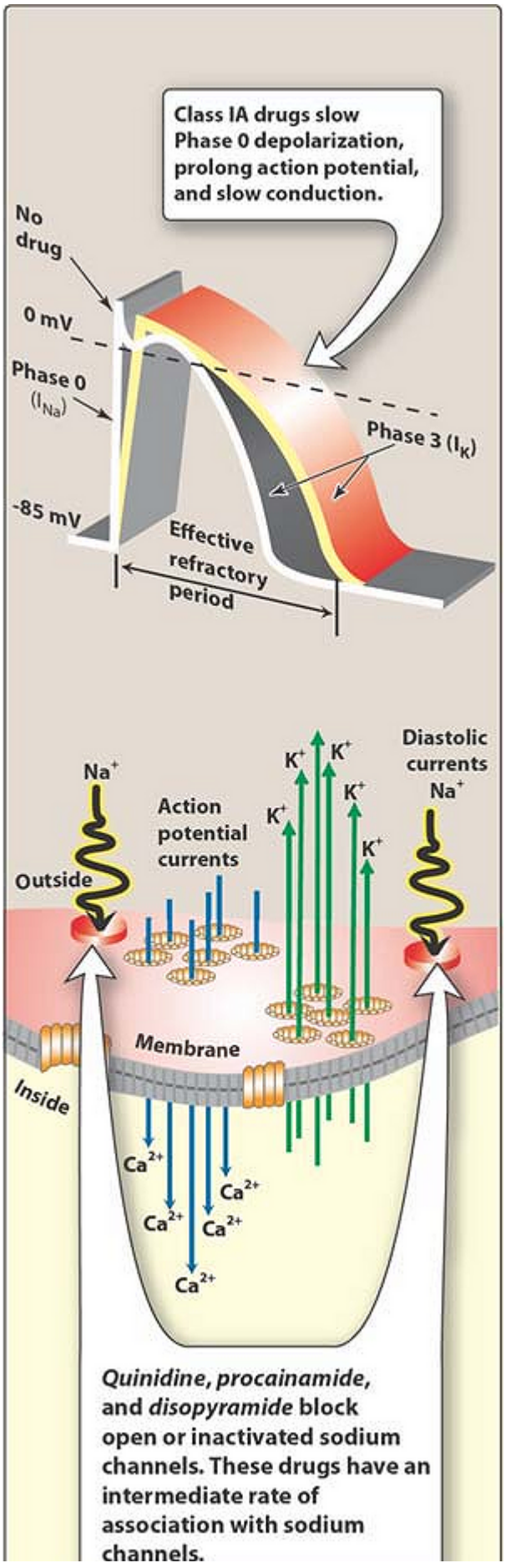

Class IA drugs slow Phase 0 depolarization, prolong action potential, and slow conduction.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period
Na+
Action potential currents
K+
Outside
Diastolic currents
Membrane
Inside
Ca2+
Quinidine, procainamide, and disopyramide block open or inactivated sodium channels. These drugs have an intermediate rate of association with sodium channels.

Figure 17.5 Schematic diagram of the effects of Class IA agents. INa and IK are transmembrane currents due to the movement of Na+ and K+, respectively.

3. **Pharmacokinetics:** *Quinidine sulfate* is rapidly and almost completely absorbed after oral administration. It undergoes extensive metabolism by the hepatic cytochrome P450 enzymes, forming active metabolites.

4. **Adverse effects:** A potential adverse effect of *quinidine* (or of any antiarrhythmic drug) is development of arrhythmia (torsades de pointes). *Quinidine* may cause SA and AV block or asystole. At toxic levels, the drug may induce ventricular tachycardia. Cardiotoxic effects are exacerbated by hyperkalemia. Nausea, vomiting, and diarrhea are commonly observed. Large doses of *quinidine* may induce the symptoms of cinchonism (for example, blurred vision, tinnitus, headache, disorientation, and psychosis). The drug has a mild Î±-adrenergic blocking action as well as an *atropine*-like effect. *Quinidine* can increase the steady-state concentration of *digoxin* by displacement of *digoxin* from tissue-binding sites (minor effect) and by decreasing *digoxin* renal clearance (major effect).

D. Procainamide

1. **Actions:** This Class IA drug, a derivative of the local anesthetic *procaine*, shows actions similar to those of *quinidine*.

2. **Pharmacokinetics:** *Procainamide* [proe-KANE-a-mide] is well-absorbed following oral administration. [Note: The intravenous route is rarely used, because hypotension occurs if the drug is infused too rapidly.] *Procainamide* has a relatively short half-life of 2 to 3 hours. A portion of the drug is acetylated in the liver to N-acetylprocainamide (NAPA), which has little effect on the maximum polarization of Purkinje fibers but prolongs the duration of the action potential. Thus, NAPA has properties of a Class III drug. NAPA is eliminated via the kidney, and dosages of *procainamide* may need to be adjusted in patients with renal failure.

3. **Adverse effects:** With chronic use, *procainamide* causes a high incidence of side effects, including a reversible lupus erythematosusâ€"like syndrome that develops in 25 to 30 percent of patients. Toxic concentrations of *procainamide* may cause asystole or induction of ventricular arrhythmias. Central nervous system (CNS) side effects include depression, hallucination, and psychosis. With this drug, gastrointestinal intolerance is less frequent than with *quinidine*.

E. Disopyramide

1. **Actions:** This Class IA drug shows actions similar to those of *quinidine*. *Disopyramide* [dye-soe-PEER-a-mide] produces a negative inotropic effect that is greater than the weak effect exerted by *quinidine* and *procainamide*, and unlike the latter drugs, *disopyramide* causes peripheral vasoconstriction. The drug may produce a clinically important decrease in myocardial contractility in patients with preexisting impairment of left ventricular function. *Disopyramide* is used in the treatment of ventricular arrhythmias as an alternative to *procainamide* or *quinidine*. Like *procainamide* and *quinidine*, it also has Class III activity.

2. **Pharmacokinetics:** Approximately half of the orally ingested drug is excreted unchanged by the kidneys. Approximately 30 percent of the drug is converted by the liver to the less active mono-N-dealkylated metabolite.

3. **Adverse effects:** *Disopyramide* shows effects of anticholinergic activity (for example, dry mouth, urinary retention, blurred vision, and constipation).

F. Lidocaine

Lidocaine [LYE-doe-kane] is a Class IB drug. The Class IB agents rapidly associate and dissociate from sodium channels. Thus, the actions of Class IB agents are manifested when the cardiac cell is depolarized or firing rapidly. Class IB drugs are particularly useful in treating ventricular arrhythmias. *Lidocaine* was the drug of choice for emergency treatment of cardiac arrhythmias.

1. **Actions:** *Lidocaine*, a local anesthetic, shortens Phase 3 repolarization and decreases the duration of the action potential (Figure 17.6).
2. **Therapeutic uses:** *Lidocaine* is useful in treating ventricular arrhythmias arising during myocardial ischemia, such as that experienced during a myocardial infarction. The drug does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias.
3. **Pharmacokinetics:** *Lidocaine* is given intravenously because of extensive first-pass transformation by the liver, which precludes oral administration. The drug is dealkylated and eliminated almost entirely by the liver; consequently, dosage adjustment may be necessary in patients with liver dysfunction or those taking drugs that lower hepatic blood flow, such as *propranolol*.
4. **Adverse effects:** *Lidocaine* has a fairly wide toxic-to-therapeutic ratio. It shows little impairment of left ventricular function and has no negative inotropic effect. CNS effects include drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions. Cardiac arrhythmias may also occur.

G. Mexiletine and tocainide

These Class IB drugs have actions similar to those of *lidocaine*, and they can be administered orally. *Mexiletine* [MEX-i-le-teen] is used for chronic treatment of ventricular arrhythmias associated with previous myocardial infarction. *Tocainide* [toe-KAY-nide] is used for treatment of ventricular tachyarrhythmias. *Tocainide* has pulmonary toxicity, which may lead to pulmonary fibrosis.

H. Flecainide

Flecainide [FLEK-a-nide] is a Class IC drug. These drugs slowly dissociate from resting sodium channels, and they show prominent effects even at normal heart rates. They are approved for refractory ventricular arrhythmias and for the prevention of paroxysmal atrial fibrillation/flutter associated with disabling symptoms and paroxysmal supraventricular tachycardia. However, recent data have cast serious doubts on the safety of the Class IC drugs.

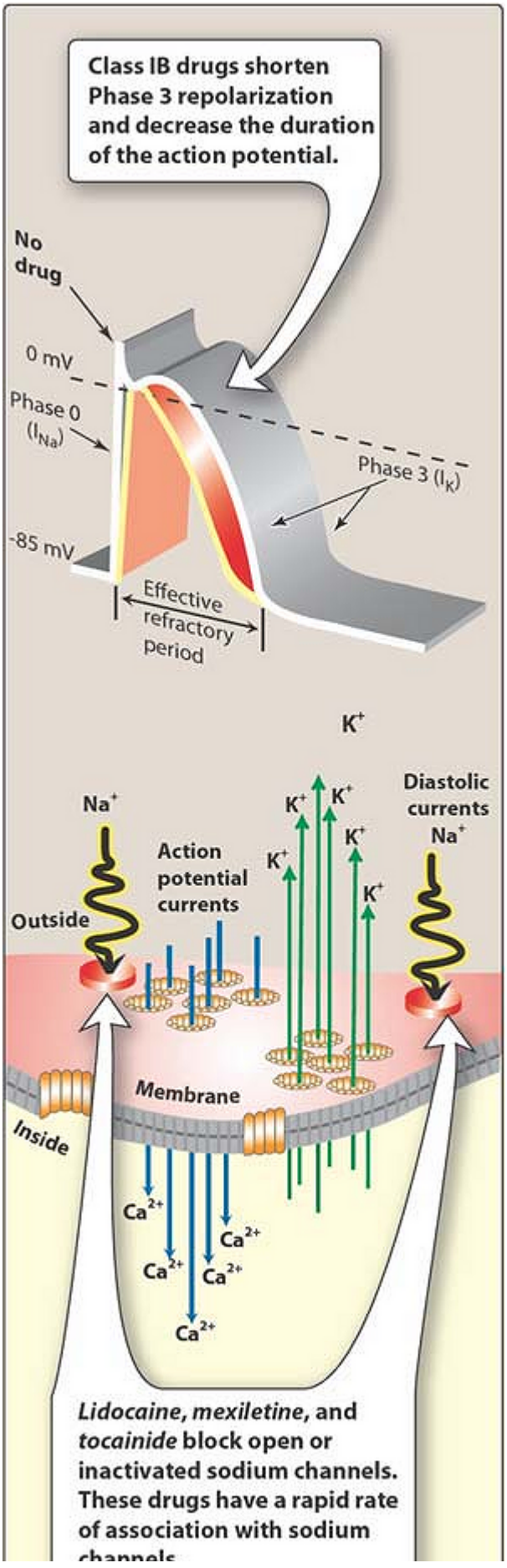

Class IB drugs shorten Phase 3 repolarization and decrease the duration of the action potential.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period
K^+
Na^+
Action potential currents
Outside
Diastolic currents Na^+
Membrane
Inside
Ca^{2+}
Lidocaine, *mexiletine*, and *tocainide* block open or inactivated sodium channels. These drugs have a rapid rate of association with sodium

Figure 17.6 Schematic diagram of the effects of Class IB agents. I_{Na} and I_K are transmembrane currents due to the movement of N_a+ and K+, respectively.

1. **Actions:** *Flecainide* suppresses Phase 0 upstroke in Purkinje and myocardial fibers (Figure 17.7). This causes marked slowing of conduction

   in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness. Automaticity is reduced by an increase in the threshold potential rather than a decrease in the slope of Phase 4 depolarization.

2. **Therapeutic uses:** *Flecainide* is useful in treating refractory ventricular arrhythmias. It is particularly useful in suppressing premature ventricular contraction. *Flecainide* has a negative inotropic effect and can aggravate congestive heart failure.

3. **Pharmacokinetics:** *Flecainide* is absorbed orally, undergoes minimal biotransformation, and has a half-life of 16 to 20 hours.

4. **Adverse effects:** *Flecainide* can cause dizziness, blurred vision, headache, and nausea. Like other Class IC drugs, *flecainide* can aggravate preexisting arrhythmias or induce life-threatening ventricular tachycardia that is resistant to treatment.

I. Propafenone

This Class IC drug shows actions similar to those of *flecainide*. *Propafenone* [proe-pa-FEEN-one], like *flecainide*, slows conduction in all cardiac tissues and is considered to be a broad-spectrum antiarrhythmic agent.

IV. Class II Antiarrhythmic Drugs

Class II agents are Î²-adrenergic antagonists. These drugs diminish Phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility. Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation and for AV-nodal reentrant tachycardia. [Note: In contrast to the sodium-channel blockers, Î²-blockers and Class III compounds, such as *sotalol* and *amiodarone*, are increasing in use.]

A. Propranolol

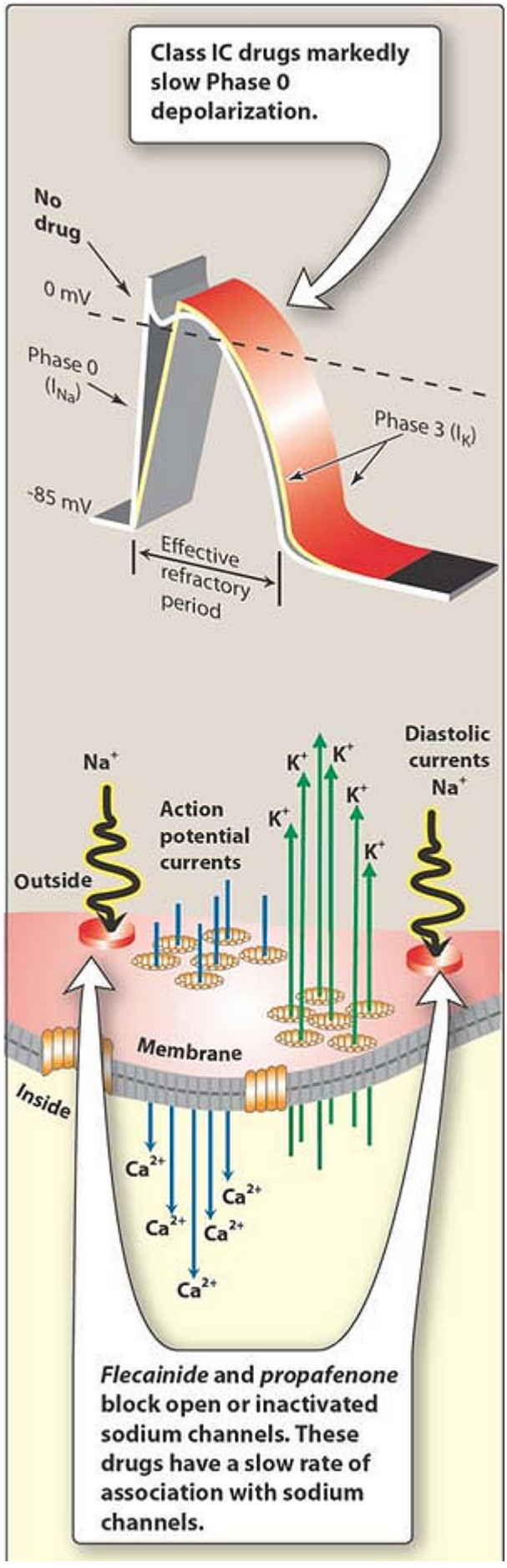
Propranolol [pro-PRAN-oh-lol] reduces the incidence of sudden arrhythmic death after myocardial infarction (the most common cause of death in this group of patients). The mortality rate in the first year after a heart attack is significantly reduced by *propranolol*, partly because of its ability to prevent ventricular arrhythmias.

B. Metoprolol

Metoprolol [me-TOE-pro-lol] is the Î²-adrenergic antagonist most widely used in the treatment of cardiac arrhythmias. Compared to propranolol, it reduces the risk of bronchospasm.

C. Esmolol

Esmolol [ESS-moe-lol] is a very short-acting Î²-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations.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0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period
Na+
Action potential currents
K+
Diastolic currents Na+
Outside
Membrane
Inside
Ca2+
Flecainide and propafenone block open or inactivated sodium channels. These drugs have a slow rate of association with sodium channels.

Figure 17.7 Schematic diagram of the effects of Class IC agents. I_{Na} and I_K are transmembrane currents due to the movement of Na+ and K+, respectively.

V. Class III Antiarrhythmic Drugs

Class III agents block potassium channels and, thus, diminish the outward potassium current during repolarization of cardiac cells. These agents prolong the duration of the action potential without altering Phase 0 of depolarization or the resting membrane potential (Figure 17.8). Instead, they prolong

the effective refractory period. All Class III drugs have the potential to induce arrhythmias.

A. Amiodarone

1. **Actions:** *Amiodarone* [a-MEE-oh-da-rone] contains iodine and is related structurally to thyroxine. It has complex effects, showing Class I, II, III, and IV actions. Its dominant effect is prolongation of the action potential duration and the refractory period. *Amiodarone* has antianginal as well as antiarrhythmic activity.
2. **Therapeutic uses:** *Amiodarone* is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias. Despite its side-effect profile, *amiodarone* is the most commonly employed antiarrhythmic.
3. **Pharmacokinetics:** *Amiodarone* is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks, and it distributes extensively in adipose issue. Full clinical effects may not be achieved until 6 weeks after initiation of treatment.
4. **Adverse effects:** *Amiodarone* shows a variety of toxic effects. After long-term use, more than half of patients receiving the drug show side effects that are severe enough to prompt its discontinuation. However, use of low doses reduces toxicity, while retaining clinical efficacy. Some of the more common effects include interstitial pulmonary fibrosis, gastrointestinal tract intolerance, tremor, ataxia, dizziness, hyper- or hypothyroidism, liver toxicity, photosensitivity, neuropathy, muscle weakness, and blue skin discoloration caused by iodine accumulation in the skin. As noted earlier, recent clinical trials have shown that *amiodarone* does not reduce the incidence of sudden death or prolong survival in patients with congestive heart failure.

B. Sotalol

Sotalol [SOE-ta-lol], although a class III antiarrhythmic agent, also has potent nonselective Î²-blocker activity. It is well established that Î²-blockers reduce mortality associated with acute myocardial infarction.

1. **Actions:** *Sotalol* blocks a rapid outward potassium current, known as the delayed rectifier. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period.
2. **Therapeutic uses:** Î²-Blockers are used for long-term therapy to decrease the rate of sudden death following an acute myocardial infarction. Î²-Blockers have a modest ability to suppress ectopic beats and to reduce myocardial oxygen demand. They have strong antifibrillatory effects, particularly in the ischemic myocardium. *Sotalol* was more effective in preventing recurrence of arrhythmia and in decreasing mortality than *imipramine, mexiletine, procainamide, propafenone*, and *quinidine* in patients with sustained ventricular tachycardia (Figure 17.9).

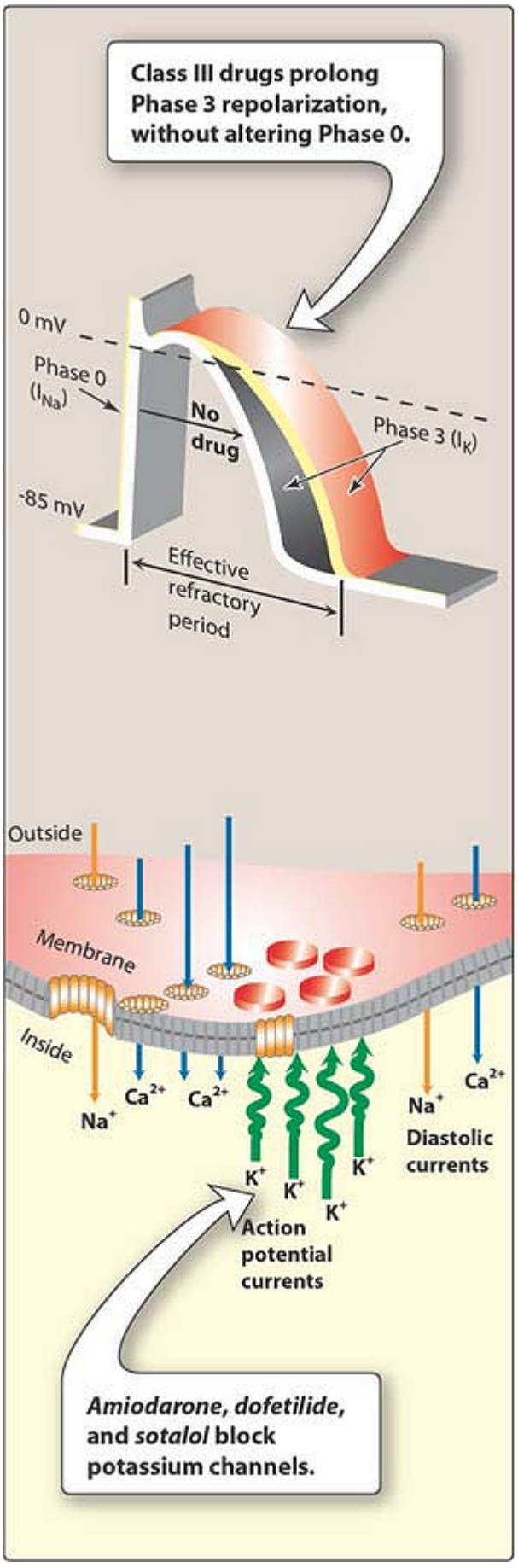
Class III drugs prolong Phase 3 repolarization, without altering Phase 0.
0 mV
Phase 0 (I_{Na})
No drug
Phase 3 (I_K)
-85 mV
Effective refractory period
Outside
Membrane
Inside
Na^+
Ca^{2+}
Ca^{2+}
K^+
K^+
K^+
Action potential currents
Na^+
Ca^{2+}
Diastolic currents
Amiodarone, *dofetilide*, and *sotalol* block potassium channels.

Figure 17.8 Schematic diagram of the effects of Class III agents. I_{Na} and I_K are transmembrane currents due to the movement of Na+ and K+, respectively.

3. **Adverse effects:** This drug also has the lowest rate of acute or long-term adverse effects. As with all drugs that prolong the QT interval,

the syndrome of torsade de pointes is a serious potential adverse effect, typically seen in three to four percent of patients.

C. Dofetilide

Dofetilide [doh-FET-il-ide] can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease with impaired left ventricular function. Because of the risk of proarrhythmia, *dofetilide* initiation is limited to the inpatient setting and is restricted to prescribers who have completed a specific manufacturer's training session. Along with *amiodarone* and Î²-blockers, *dofetilide* is the only antiarrhythmic drug that is recommended by experts for the treatment of atrial fibrillation in a wide range of patients. The half-life is 10 hours. Excretion is in the urine, with 80 percent as unchanged drug and 20 percent as inactive or minimally active metabolites.

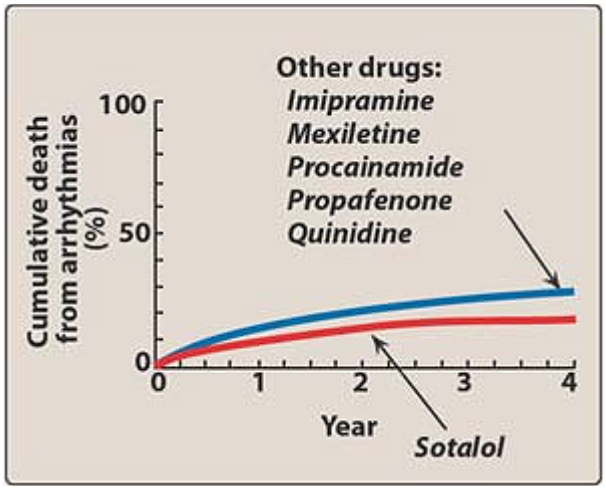

Figure 17.9 Comparison of *sotalol* with six other drugs with respect to deaths due to cardiac arrhythmias.

VI. Class IV Antiarrhythmic Drugs

Class IV drugs are calcium-channel blockers (see p. 223). They decrease the inward current carried by calcium, resulting in a decreased rate of Phase 4 spontaneous depolarization. They also slow conduction in tissues that are dependent on calcium currents, such as the AV node (Figure 17.10). Although voltage-sensitive calcium channels occur in many different tissues, the major effect of calcium-channel blockers is on vascular smooth muscle and the heart.

A. Verapamil and diltiazem

Verapamil [ver-AP-a-mil] shows greater action on the heart than on vascular smooth muscle, whereas *nifedipine*, a calcium-channel blocker used to treat hypertension (see p. 223), exerts a stronger effect on the vascular smooth muscle than on the heart. *Diltiazem* [dil-TYE-a-zem] is intermediate in its actions.

1. **Actions:** Calcium enters cells by voltage-sensitive channels and by receptor-operated channels that are controlled by the binding of agonists, such as catecholamines, to membrane receptors. Calcium-channel blockers, such as *verapamil* and *diltiazem*, are more effective against the voltage-sensitive channels, causing a decrease in the slow inward current that triggers cardiac contraction. *Verapamil* and *diltiazem* bind only to open, depolarized channels, thus preventing repolarization until the drug dissociates from the channel. These drugs are therefore use-dependent; that is, they block most effectively when the heart is beating rapidly, because in a normally paced heart, the calcium channels have time to repolarize and the bound drug dissociates from the channel before the next conduction pulse. By decreasing the inward current carried by calcium, *verapamil* and *diltiazem* slow conduction and prolong the effective refractory period in tissues that are dependent on calcium currents, such as the AV node. These drugs are therefore effective in treating arrhythmias that must traverse calcium-dependent cardiac tissues.
2. **Therapeutic uses:** *Verapamil* and *diltiazem* are more effective against atrial than against ventricular arrhythmias. They are useful in treating reentrant supraventricular tachycardia and in reducing

the ventricular rate in atrial flutter and fibrillation. In addition, these drugs are used to treat hypertension and angina.
3. **Pharmacokinetics:** *Verapamil* and *diltiazem* are absorbed after oral administration. *Verapamil* is extensively metabolized by the liver; thus, care should be taken when administering this drug to patients with hepatic dysfunction.
4. **Adverse effects:** *Verapamil* and *diltiazem* have negative inotropic properties and, therefore, may be contraindicated in patients with preexisting depressed cardiac function. Both drugs can also produce a decrease in blood pressure because of peripheral vasodilationâ€"an effect that is actually beneficial in treating hypertension.

VII. Other Antiarrhythmic Drugs

A. Digoxin

Digoxin [di-JOX-in] shortens the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in the AV node. *Digoxin* is used to control the ventricular response rate in atrial fibrillation and flutter. At toxic concentrations, *digoxin* causes ectopic ventricular beats that may result in ventricular tachycardia and fibrillation. [Note: This arrhythmia is usually treated with *lidocaine* or *phenytoin*.]

B. Adenosine

Adenosine [ah-DEN-oh-zeen] is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node. Intravenous *adenosine* is the drug of choice for abolishing acute supraventricular tachycardia. It has low toxicity but causes flushing, chest pain, and hypotension. *Adenosine* has an extremely short duration of action (approximately 15 seconds).

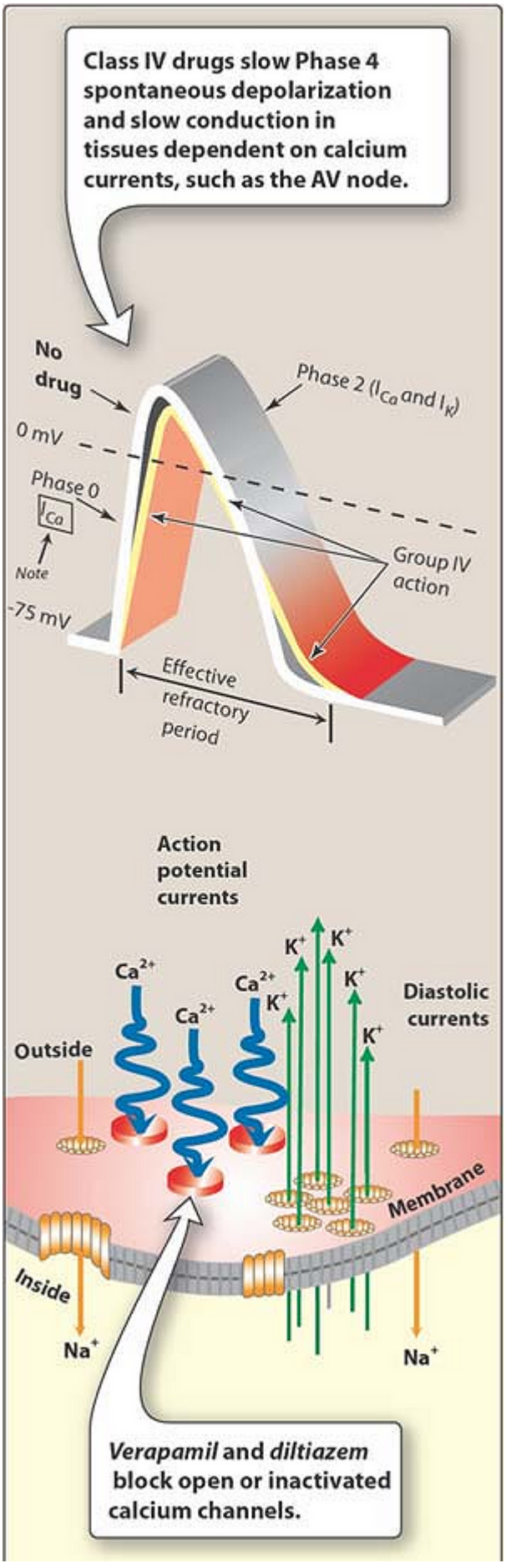
Class IV drugs slow Phase 4 spontaneous depolarization and slow conduction in tissues dependent on calcium currents, such as the AV node.
No drug
Phase 2 (I_{Ca} and I_K)
0 mV
Phase 0
I_{Ca}
Note
Group IV action
-75 mV
Effective refractory period
Action potential currents
Ca^{2+}
Ca^{2+}
Ca^{2+}
K^+
K^+
K^+
K^+
K^+
Diastolic currents
Outside
Membrane
Inside
Na^+
Na^+
Verapamil and *diltiazem* block open or inactivated calcium channels.

Figure 17.10 Schematic diagram of the effects of Class IV agents. I_{Ca} and I_K are transmembrane currents due to the movement of Ca2+ and K+, respectively.

Study Questions

Choose the ONE best answer.

17.1 A 66-year-old man had a myocardial infarct. Which one of the following would be appropriate prophylactic antiarrhythmic therapy?

A. Lidocaine.

B. Metoprolol.

C. Procainamide.

D. Quinidine.

E. Verapamil.

View Answer

17.2 Suppression of arrhythmias resulting from a reentry focus is most likely to occur if the drug:

A. Has vagomimetic effects on the AV node.

B. Is a Î²-blocker.

C. Converts a unidirectional block to a bidirectional block.

D. Slows conduction through the atria.

E. Has atropine-like effects on the AV node.

View Answer

17.3 A 57-year-old man is being treated for an atrial arrhythmia. He complains of headache, dizziness, and tinnitus. Which one of the following antiarrhythmic drugs is the most likely cause?

A. Amiodarone.

B. Procainamide.

C. Propranolol.

D. Quinidine.

E. Verapamil.

View Answer

17.4 A 58-year-old woman is being treated for chronic suppression of a ventricular arrhythmia. After 2 months of therapy, she complains about feeling tired all the time. Examination reveals a resting heart rate of 10 beats per minute lower than her previous rate. Her skin is cool and clammy. Laboratory test results indicate low thyroxin and elevated thyroid-stimulating hormone levels. Which of the following antiarrhythmic drugs is the likely cause of these signs and symptoms?

A. Amiodarone.

B. Procainamide.

C. Propranolol.

D. Quinidine.

E. Verapamil.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 18

Antianginal Drugs

I. Overview

Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms. It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia. The imbalance between oxygen delivery and utilization may result during exertion, from a spasm of the vascular smooth muscle, or from obstruction of blood vessels caused by atherosclerotic lesions. These transient episodes (15 seconds to 15 minutes) of myocardial ischemia do not cause cellular death, such as occurs in myocardial infarction. Three classes of drugs, used either alone or in combination, are effective in treating patients with stable angina: organic nitrates, Î²-blockers, and calcium-channel blockers (Figure 18.1). These agents lower the oxygen demand of the heart by affecting blood pressure, venous return, heart rate, and contractility. Lifestyle and risk factor modifications, especially cessation of smoking, are also important in the treatment of angina. [Note: Options other than medications for treating angina include angioplasty and coronary artery bypass surgery.]

II. Types of Angina

Angina pectoris has three overlapping patterns: 1) stable or typical angina, 2) unstable angina, and 3) Prinzmetal's or variant angina. They are caused by varying combinations of increased myocardial demand and decreased myocardial perfusion.

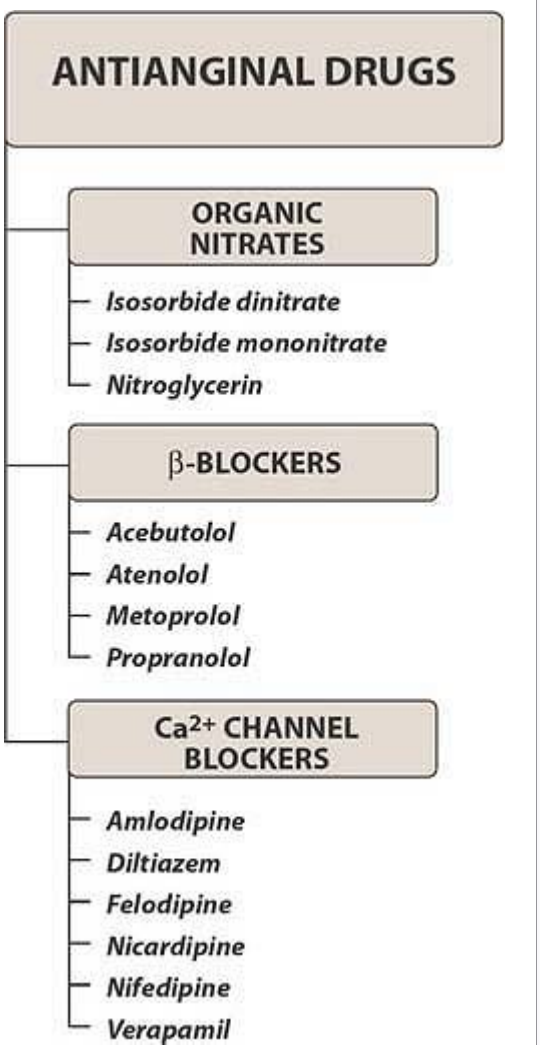

Figure 18.1 Summary of antianginal drugs.

A. Stable angina

Stable angina is the most common form of angina and, therefore, is called typical angina pectoris. It is characterized by a burning, heavy, or squeezing feeling in the chest. It is caused by the reduction of coronary perfusion due to a fixed obstruction produced by coronary atherosclerosis. The heart becomes vulnerable to ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload. Typical angina pectoris is promptly relieved by rest or *nitroglycerin* (a vasodilator).

B. Unstable angina

Unstable angina lies between stable angina on the one hand and myocardial infarction on the other. In unstable angina, chest pains occur with increased frequency and are precipitated by progressively

less effort. The symptoms are not relieved by rest or *nitroglycerin.* Unstable angina requires hospital admission and more aggressive therapy to prevent death and progression to myocardial infarction.

C. Prinzmetal's or variant or vasospastic angina

Prinzmetal's angina is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm. Symptoms are caused by decreased blood flow to the heart muscle due to spasm of the coronary artery. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal's angina generally responds promptly to coronary vasodilators, such as *nitroglycerin* and calcium-channel blockers.

D. Mixed forms of angina

Patients with advanced coronary artery disease may present with angina episodes during effort as well as at rest, suggesting the presence of a fixed obstruction associated with endothelial dysfunction.

III. Organic Nitrates

Organic nitrates (and nitrites) used in the treatment of angina pectoris are simple nitric and nitrous acid esters of glycerol. They differ in their volatility. For example, *isosorbide dinitrate* and *isosorbide mononitrate* are solids at room temperature, *nitroglycerin* is only moderately volatile, and *amyl nitrite* is extremely volatile. These compounds cause a rapid reduction in myocardial oxygen demand, followed by rapid relief of symptoms. They are effective in stable and unstable angina as well as in variant angina pectoris.

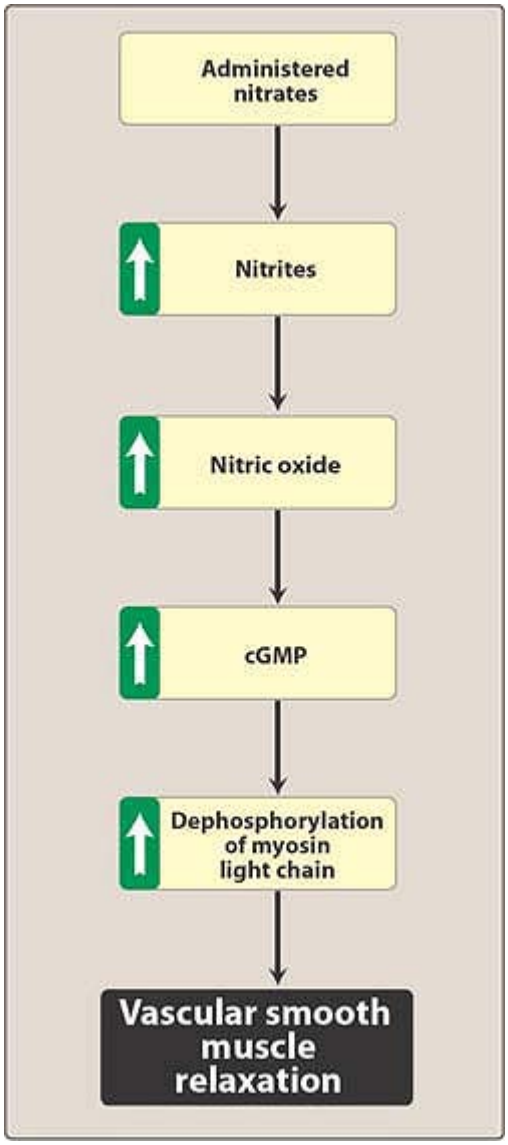

Figure 18.2 Effects of nitrates and nitrites on smooth muscle. cGMP = cyclic guanosine 3', 5'-monophosphate.

A. Mechanism of action

Nitrates decrease coronary vasoconstriction or spasm and increase perfusion of the myocardium by relaxing coronary arteries. In addition, they relax veins, decreasing preload and myocardial oxygen consumption. Organic nitrates, such as *nitroglycerin* [nye-troe-GLIS-er-in], which is also known as *glyceryl trinitrate*, are thought to relax vascular smooth muscle by their intracellular conversion to nitrite ions, and then to nitric oxide, which in turn activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (GMP).[1] Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation (Figure 18.2).

B. Effects on the cardiovascular system

All these agents are effective, but they differ in their onset of action and rate of elimination. For prompt relief of an ongoing attack of angina precipitated by exercise or emotional stress, sublingual (or spray form) *nitroglycerin* is

the drug of choice. At therapeutic doses, *nitroglycerin* has two major effects. First, it causes dilation of the large veins, resulting in pooling of blood in the veins. This diminishes preload (venous return to the heart) and reduces the work of the heart. Second, *nitroglycerin* dilates the coronary vasculature, providing an increased blood supply to the heart muscle. *Nitroglycerin* decreases myocardial oxygen consumption because of decreased cardiac work.

C. Pharmacokinetics

The time to onset of action varies from 1 minute for *nitroglycerin* to more than 1 hour for *isosorbide mononitrate* (Figure 18.3). Significant first-pass metabolism of *nitroglycerin* occurs in the liver. Therefore, it is common to take the drug either sublingually or via a transdermal patch, thereby avoiding this route of elimination. *Isosorbide mononitrate* owes its improved bioavailability and long duration of action to its stability against hepatic breakdown. Oral *isosorbide dinitrate* undergoes denitration to two mononitrates, both of which possess antianginal activity.

D. Adverse effects

The most common adverse effect of *nitroglycerin*, as well as of the other nitrates, is headache. From 30 to 60 percent of patients receiving intermittent nitrate therapy with long-acting agents develop headaches. High doses of organic nitrates can also cause postural hypotension, facial flushing, and tachycardia. *Sildenafil* potentiates the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.

E. Tolerance

Tolerance to the actions of nitrates develops rapidly. The blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily â€œnitrate-free intervalâ€ to restore sensitivity to the drug. This interval is typically 10 to 12 hours, usually at night, because demand on the heart is decreased at that time. *Nitroglycerin* patches are worn for 12 hours then removed for 12 hours. However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate-free interval in these patients should occur in the late afternoon. Patients who continue to have angina despite nitrate therapy may benefit by addition of another class of agent.

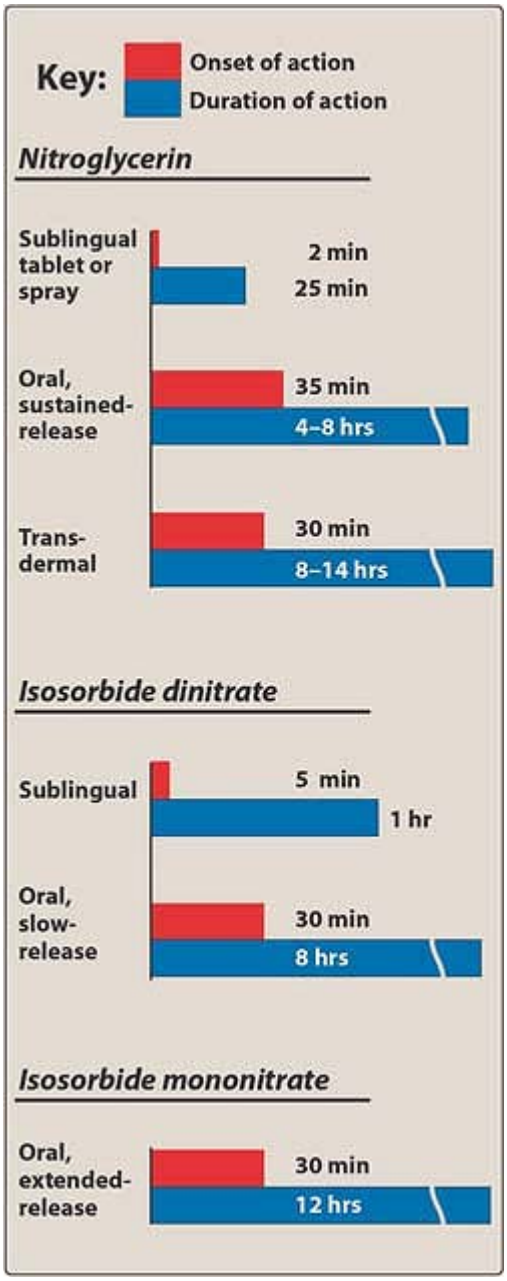

Figure 18.3 Time to peak effect and duration of action for some common organic nitrate preparations.

IV. Î²-Adrenergic Blockers

The Î²-adrenergicâ€"blocking agents decrease the oxygen demands of the myocardium by lowering both the rate and the force of contraction of the heart (see p. 86). They suppress the activation of the heart by blocking $Î²_1$ receptors, and they reduce the work of the heart by decreasing heart rate, contractility, cardiac output, and blood pressure. With Î²-blockers, the demand for oxygen by the myocardium is reduced both during exertion and at rest. *Propranolol* is the prototype for this class of compounds, but it is not cardioselective. Thus, other Î²-blockers, such as *metoprolol* or *atenolol*, are preferred. [Note: All Î²-blockers are nonselective at high doses and can inhibit $Î²_2$ receptors. This is particularly important to remember in the case of asthmatics.] Agents with intrinsic sympathomimetic activity (for example, *pindolol*) are less effective and should be avoided in angina. The

Î²-blockers reduce the frequency and severity of angina attacks. These agents are particularly useful in the treatment of patients with myocardial infarction and have been shown to prolong survival. The Î²-blockers can be used with nitrates to increase exercise duration and tolerance. They are, however, contraindicated in patients with asthma, diabetes, severe bradycardia, peripheral vascular disease, or chronic obstructive pulmonary disease. [Note: It is important not to discontinue Î²-blocker therapy abruptly. The dose should be gradually tapered off over 5 to 10 days to avoid rebound angina or hypertension.]

V. Calcium-Channel Blockers

Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. In turn, this promotes the activity of several adenosine triphosphateâ€“consuming enzymes, thereby depleting energy stores and worsening the ischemia. The calcium-channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium-channel blockers are therefore arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance. (See p. 206 for a description of the mechanism of action for this group of drugs.) At clinical doses, these agents affect primarily the resistance of vascular smooth muscle and the myocardium. [Note: *Verapamil* mainly affects the myocardium, whereas *nifedipine* exerts a greater effect on smooth muscle in the peripheral vasculature. *Diltiazem* is intermediate in its actions.] All calcium-channel blockers lower blood pressure. They may worsen heart failure due to their negative inotropic effect. [Note: Variant angina caused by spontaneous coronary spasm (either at work or at rest; Figure 18.4) rather than by increased myocardial oxygen requirement is controlled by organic nitrates or calcium-channel blockers; Î²-blockers are contraindicated.]

A. Nifedipine

Nifedipine [nye-FED-i-peen], a dihydropyridine derivative, functions mainly as an arteriolar vasodilator. This drug has minimal effect on cardiac conduction or heart rate. Other members of this class, *amlodipine, nicardipine*, and *felodipine*, have similar cardiovascular characteristics except for *amlodipine*, which does not affect heart rate or cardiac output. *Nifedipine* is administered orally, usually as extended-release tablets. It undergoes hepatic metabolism to products that are eliminated in both urine and the feces. The vasodilation effect of *nifedipine* is useful in the treatment of variant angina caused by spontaneous coronary spasm. *Nifedipine* can cause flushing, headache, hypotension, and peripheral edema as side effects of its vasodilation activity. As with all calcium-channel blockers, constipation is a problem. Because it has little to no sympathetic antagonistic action, *nifedipine* may cause reflex tachycardia if peripheral vasodilation is marked. [Note: The general consensus is that short-acting dihydropyridines should be avoided in coronary artery disease.]

B. Verapamil

The diphenylalkylamine *verapamil* [ver-AP-a-mil] slows cardiac atrioventricular (AV) conduction directly, and decreases heart rate, contractility, blood pressure, and oxygen demand. *Verapamil* causes greater negative inotropic effects than *nifedipine*, but it is a weaker vasodilator. The drug is extensively metabolized by the liver; therefore, care must be taken to adjust the dose in patients with liver dysfunction. *Verapamil* is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities. It also causes constipation. *Verapamil* should be used with caution in patients taking *digoxin,* because *verapamil* increases *digoxin* levels.

C. Diltiazem

Diltiazem [dil-TYE-a-zem] has cardiovascular effects that are similar to those of *verapamil*. Both drugs slow AV conduction and decrease the rate of firing of the sinus node pacemaker. *Diltiazem* reduces the heart

rate, although to a lesser extent than *verapamil*, and also decreases blood pressure. In addition, *diltiazem* can relieve coronary artery spasm and, therefore, is particularly useful in patients with variant angina. It is extensively metabolized by the liver. The incidence of adverse side effects is low (the same as those for other calcium-channel blockers). Interactions with other drugs are the same as those indicated for *verapamil*.

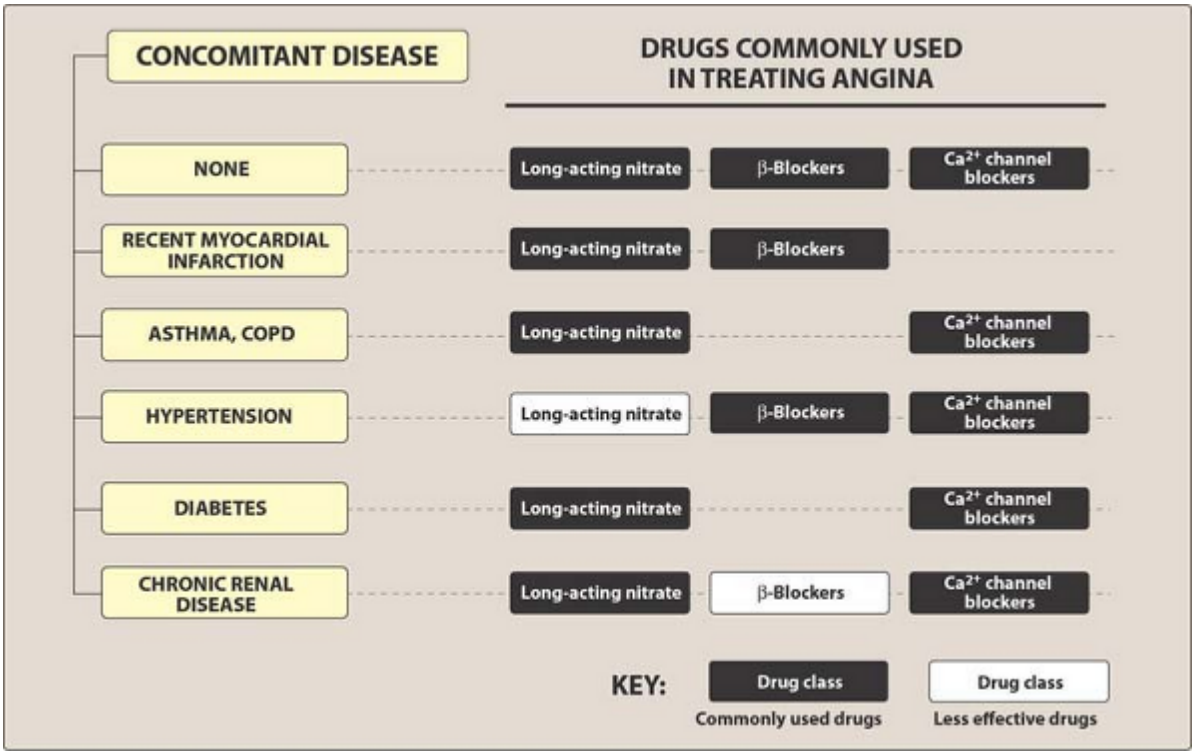

Figure 18.5 Treatment of angina in patients with concomitant diseases. COPD = chronic obstructive pulmonary disease.

Figure 18.5 summarizes the treatment of angina in patients with concomitant diseases.

Study Questions

Choose the ONE best answer.

18.1 A 56-year-old patient complains of chest pain following any sustained exercise. He is diagnosed with atherosclerotic angina. He is prescribed sublingual nitroglycerin for treatment of acute chest pain. Which of the following adverse effects is likely to be experienced by this patient?

A. Hypertension.

B. Throbbing headache.

C. Bradycardia.

D. Sexual dysfunction.

E. Anemia.

View Answer

18.2 The patient described in Question 18.1 is also prescribed propranolol to prevent episodes of angina. The Î²-blocker has the added benefit of preventing which of the following side effects of sublingual nitroglycerin?

A. Dizziness.

B. Methemoglobinemia.

C. Throbbing headache.

D. Reflex tachycardia.

E. Edema.

View Answer

18.3 A 68-year-old man has been successfully treated for exercise-induced angina for several years. He recently has been complaining about being awakened at night with chest pain. Which of the following drugs would be useful in preventing this patient's nocturnal angina?

A. Amyl nitrite.

B. Nitroglycerin (sublingual).

C. Nitroglycerin (transdermal).

D. Esmolol.

E. Hydralazine.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 19

Antihypertensives

I. Overview

Hypertension is defined as either a sustained systolic blood pressure (SBP) of greater than 140 mm Hg or a sustained diastolic blood pressure (DBP) of greater than 90 mm Hg. Hypertension results from increased peripheral vascular smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. In most cases, the cause of the increased vascular tone is unknown. Elevated blood pressure is an extremely common disorder, affecting approximately 15 percent of the population of the United States (60 million people). Although many of these individuals have no symptoms, chronic hypertensionâ€"either systolic or diastolicâ€"can lead to cerebrovascular accidents (strokes), congestive heart failure, myocardial infarction, and renal damage. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated. In recognition of the progressive nature of hypertension, the Seventh Report of the Joint National Committee classifies hypertension into four categories for the purpose of treatment management. The categories are normal (SBP/DBP, <120/<80), prehypertension (SBP/DBP, 120â€“139/80â€“89), stage 1 hypertension (SBP/DBP, 140â€“159/90 â€“99), and stage 2 hypertension (SBP/DBP >â€“ 160/>â€“ 100).

II. Etiology of Hypertension

Although hypertension may occur secondary to other disease processes, more than 90 percent of patients have essential hypertension, a disorder of unknown origin affecting the blood pressure regulating mechanism. A family history of hypertension increases the likelihood that an individual will develop hypertensive disease. The incidence of essential hypertension is four-fold more frequent among blacks than among whites. It occurs more often among middle-aged males than among middle-aged females, and its prevalence increases with age and obesity. Environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking, further predispose an individual to the occurrence of hypertension. Figure 19.1 summarizes the drugs used to treat hypertension.]

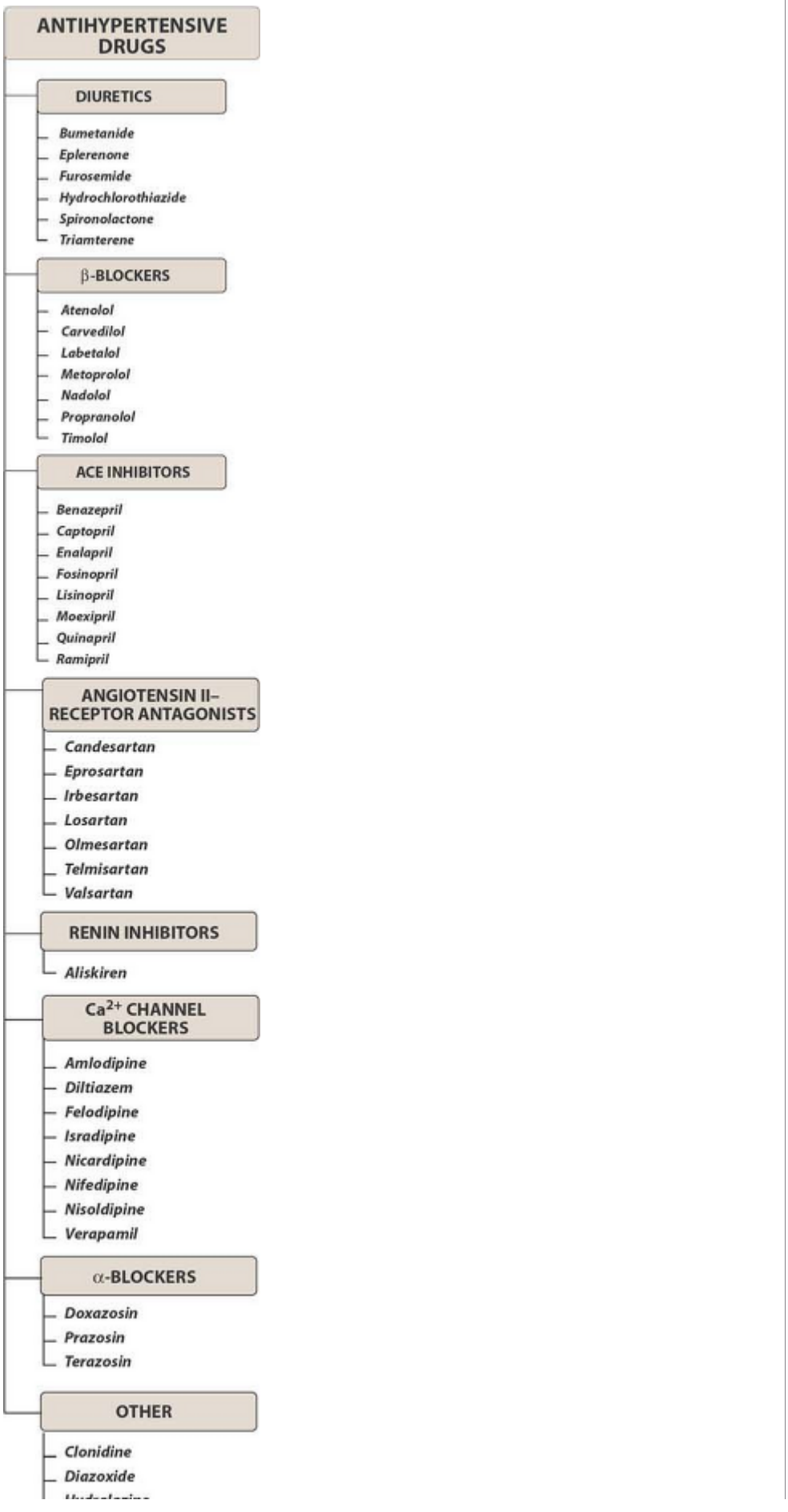
ANTIHYPERTENSIVE DRUGS
DIURETICS
Bumetanide
Eplerenone
Furosemide
Hydrochlorothiazide
Spironolactone
Triamterene
β-BLOCKERS
Atenolol
Carvedilol
Labetalol
Metoprolol
Nadolol
Propranolol
Timolol
ACE INHIBITORS
Benazepril
Captopril
Enalapril
Fosinopril
Lisinopril
Moexipril
Quinapril
Ramipril
ANGIOTENSIN II–RECEPTOR ANTAGONISTS
Candesartan
Eprosartan
Irbesartan
Losartan
Olmesartan
Telmisartan
Valsartan
RENIN INHIBITORS
Aliskiren
Ca2+ CHANNEL BLOCKERS
Amlodipine
Diltiazem
Felodipine
Isradipine
Nicardipine
Nifedipine
Nisoldipine
Verapamil
α-BLOCKERS
Doxazosin
Prazosin
Terazosin
OTHER
Clonidine
Diazoxide

Figure 19.1 Summary of antihypertensive drugs. ACE = angiotensin-converting enzyme.

III. Mechanisms for Controlling Blood Pressure

Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system, particularly the arterial intima (endothelium). Arterial blood pressure is directly proportional to the product of the cardiac output and the peripheral vascular resistance (Figure 19.2). Cardiac output and peripheral resistance are controlled mainly by two overlapping control mechanisms: the baroreflexes, which are mediated by the sympathetic nervous system, and the renin-angiotensin-aldosterone system (Figure 19.3). Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.

A. Baroreceptors and the sympathetic nervous system

Baroreflexes involving the sympathetic nervous system are responsible for the rapid, moment-to-moment regulation of blood pressure. A fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output. These changes result in a compensatory rise in blood pressure (see Figure 19.3).

B. Renin-angiotensin-aldosterone system

The kidney provides for the long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of Î²-adrenoceptors) by releasing the enzyme renin (see Figure 19.3). Low sodium intake and greater sodium loss also increase renin release. This peptidase converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II in the presence of angiotensin-converting enzyme (ACE). Angiotensin II is the body's most potent circulating vasoconstrictor, constricting both arterioles and veins, causing an increase in blood pressure. Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration. Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin IIâ€“AT1 receptors.

IV. Treatment Strategies

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. The relationship between blood pressure and the risk of a cardiovascular event is continuous, and thus lowering of even moderately elevated blood pressure significantly reduces cardiovascular disease. The newly added classification of â€œprehypertensionâ€ recognizes this relationship and emphasizes the need for decreasing blood pressure in the general population by education and adoption of blood pressureâ€“lowering behaviors. Mild hypertension can often be controlled with a single drug; however, most patients require more than one drug to achieve blood pressure control. Current recommendations are to initiate therapy with a thiazide diuretic unless there are compelling reasons to employ other drug classes (Figure 19.4). If blood pressure is inadequately controlled, a second

drug is added, with the selection based on minimizing the adverse effects of the combined regimen. A Î²-blocker is usually added if the initial drug was a diuretic, or a diuretic is usually added if the first drug was a Î²-blocker. A vasodilator can be added as a third step for those patients who still fail to respond. However, angiotensin

IIâ€“converting enzyme inhibitors, angiotensin IIâ€“AT1 receptor blockers, and calcium-channel blockers can also be used to initiate therapy.

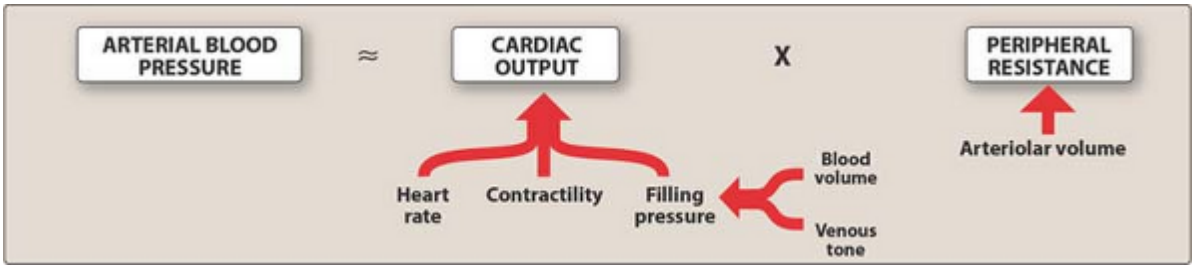

Figure 19.2 Major factors influencing blood pressure.

A. Individualized care

Certain subsets of the hypertensive population respond better to one class of drug than they do to another. For example, black patients

respond well to diuretics and calcium-channel blockers, but therapy with Î²-blockers or ACE inhibitors is often less effective. Similarly, calcium-channel blockers, ACE inhibitors, and diuretics are favored for treatment of hypertension in the elderly, whereas Î²-blockers and Î±-antagonists are less well tolerated. Furthermore, hypertension may coexist with other diseases that can be aggravated by some of the antihypertensive drugs. For example, Figure 19.4 shows the preferred therapy in hypertensive patients with various concomitant diseases. In such cases, it is important to match antihypertensive drugs to the particular patient. Figure 19.5 shows the frequency of concomitant disease in the hypertensive patient population.

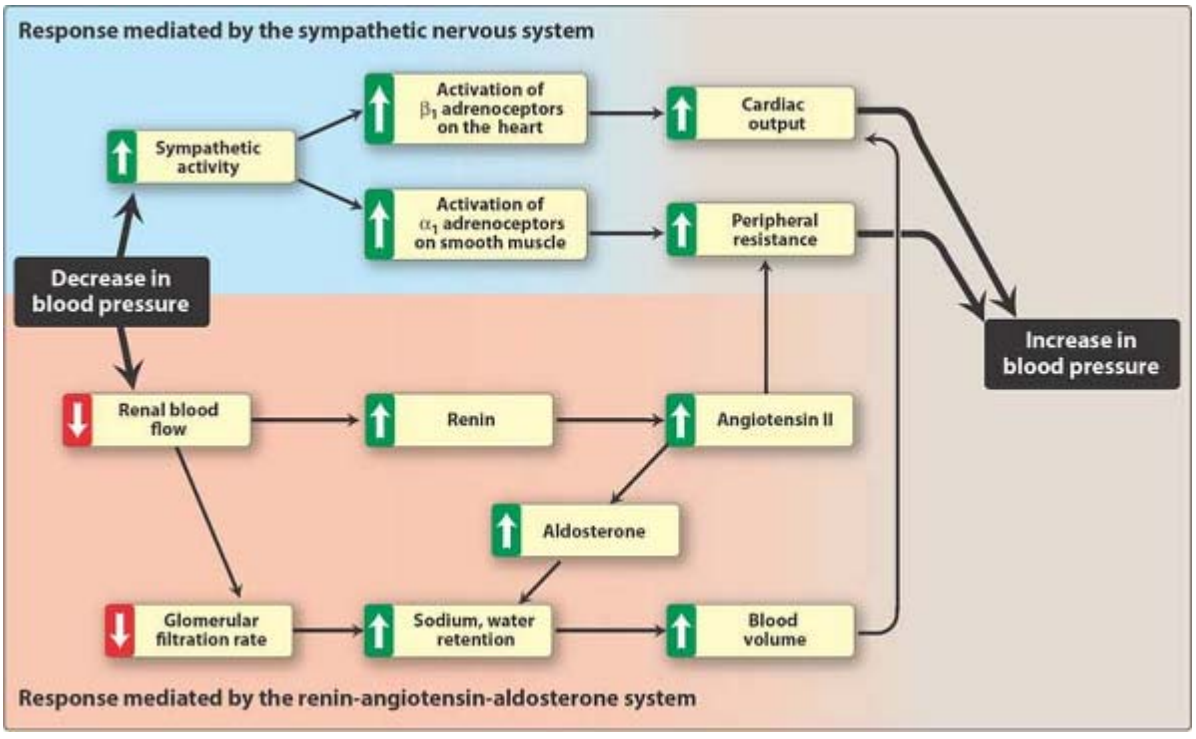

Figure 19.3 Response of the autonomic nervous system and the renin-angiotensin-aldosterone system to a decrease in blood pressure.

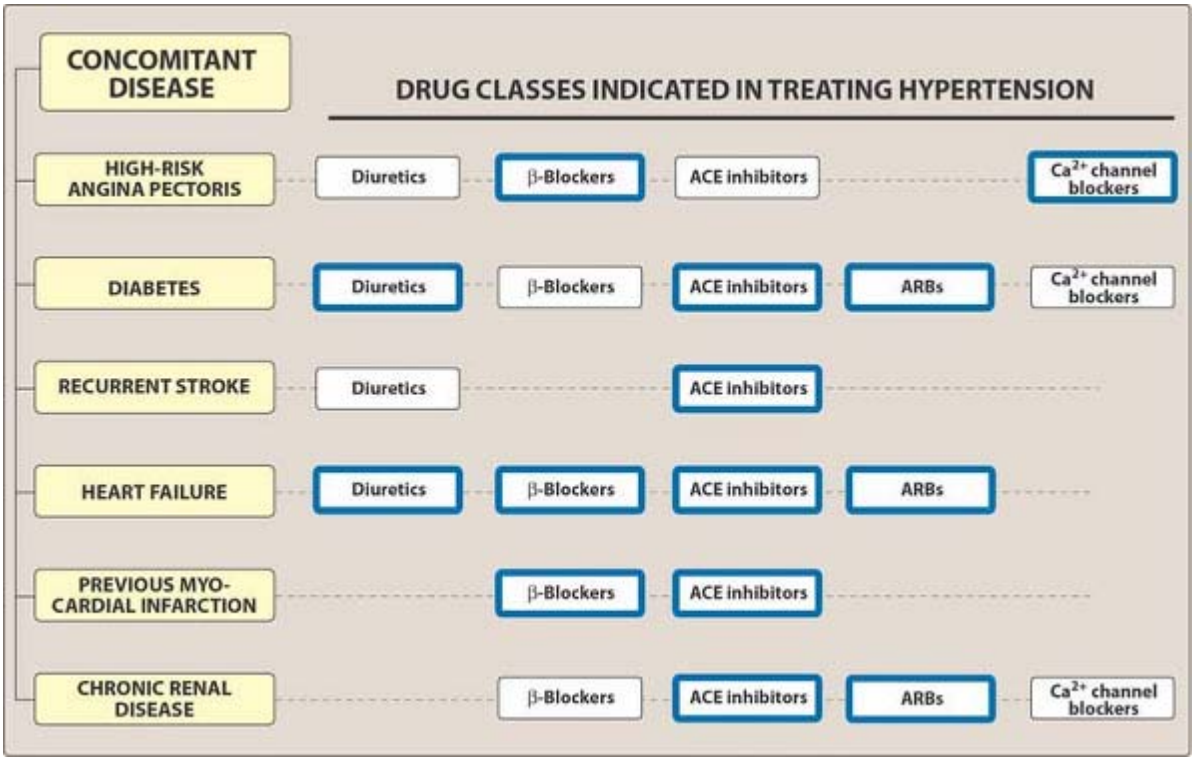

Figure 19.4 Treatment of hypertension in patients with concomitant diseases. Drug classes shown in blue boxes provide improvement in outcome (for example diabetes or renal disese) independent of blood pressure . [Note: ARBs are an alternative to ACE inhibitors.] ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

B. Patient compliance in antihypertensive therapy

Lack of patient compliance is the most common reason for failure of antihypertensive therapy. The hypertensive patient is usually asymptomatic and is diagnosed by routine screening before the occurrence of overt end-organ damage. Thus, therapy is generally directed at preventing future disease sequelae rather than relieving the patient's present discomfort. The adverse effects associated with the hypertensive therapy may influence the patient more than the future benefits.

For example, Î²-blockers can decrease libido and induce impotence in males, particularly middle-aged and elderly men. This drug-induced sexual dysfunction may prompt the patient to discontinue therapy. Thus, it is important to enhance compliance by carefully selecting a drug regimen that both reduces adverse effects and minimizes the number of doses required daily.

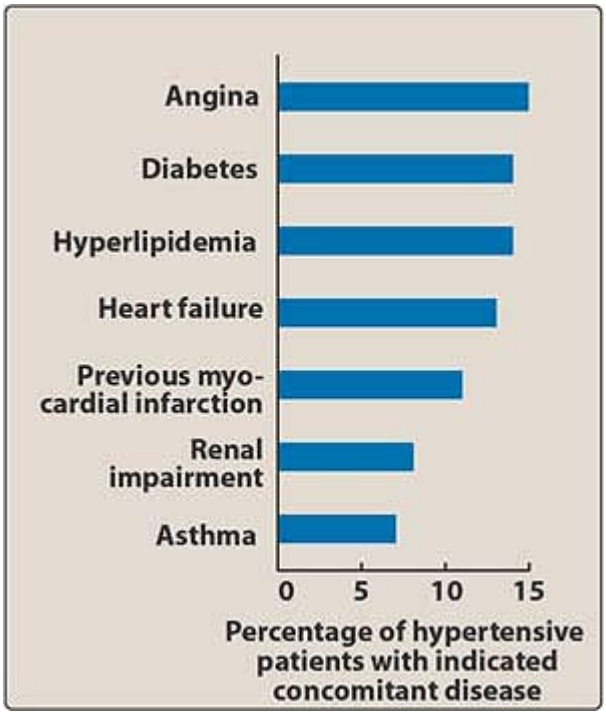

Figure 19.5 Frequency of occurrence of concomitant disease among the hypertensive patient population.

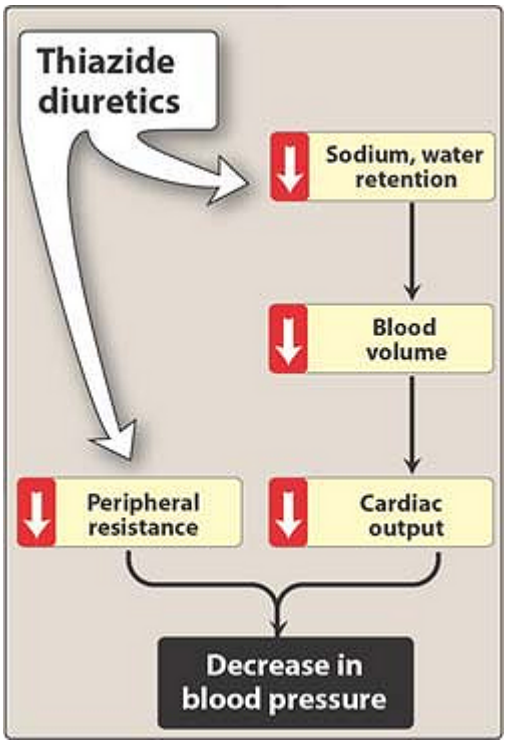

Figure 19.6 Actions of thiazide diuretics.

V. Diuretics

Diuretics can be used as first-line drug therapy for hypertension unless there are compelling reasons to choose another agent. Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and congestive heart failure, all of which can cause mortality. Recent data suggest that diuretics are superior to Î²-blockers for treating hypertesnion in older adults.

A. Thiazide diuretics

All oral diuretic drugs are effective in the treatment of hypertension, but the thiazides have found the most widespread use.

1. **Actions:** Thiazide diuretics, such as *hydrochlorothiazide* [hye-droe-klor-oh-THYE-a-zide], lower blood pressure initially by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow (Figure 19.6). With long-term treatment, plasma volume approaches a normal value, but peripheral resistance decreases. Potassium-sparing diuretics are often used combined with thiazides.

2. **Therapeutic uses:** Thiazide diuretics decrease blood pressure in both the supine and standing positions, and postural hypotension is rarely observed except in elderly, volume-depleted patients. These agents counteract the sodium and water retention observed with other agents used in the treatment of hypertension (for example, *hydralazine*). Thiazides are therefore useful in combination therapy with a variety of other antihypertensive agents, including Î²-blockers, ACE inhibitors, angiotensin-receptor blockers, and potassium-sparing diuretics. Thiazide diuretics are particularly useful in the treatment of black or elderly patients. They are not effective in patients with inadequate kidney function (creatinine clearance, <50 mL/min). Loop diuretics may be required in these patients.

3. **Pharmacokinetics:** Thiazide diuretics are orally active. Absorption and elimination rates vary considerably, although no clear advantage is present for one agent over another. All thiazides are ligands for the organic acid secretory system of the nephron, and as such, they may compete with uric acid for elimination.

4. **Adverse effects:** Thiazide diuretics induce hypokalemia and hyperuricemia in 70 percent of patients and hyperglycemia in 10 percent of patients. Hypomagnesemia may also occur. Serum potassium levels should be monitored closely in patients who are predisposed to cardiac arrhythmias (particularly individuals with left ventricular hypertrophy, ischemic heart disease, or chronic heart failure) and who are concurrently being treated with both thiazide diuretics and *digoxin.*

B. Loop diuretics

The loop diuretics act promptly, even in patients with poor renal function or who have not responded to thiazides or other diuretics. Loop diuretics cause decreased renal vascular resistance and increased renal blood flow. [Note: Loop diuretics increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease it.]

C. Potassium-sparing diuretics.

Amiloride [a-MIL-oh-ride] and *triamterene* [tri-AM-ter-een] (inhibitors of epithelial sodium transport at the late distal and collecting ducts) as well as *spironolactone* [speer-on-oh-LAK-tone] and *eplerenone* [eh-PLEH-reh-none] (aldosterone-receptor antagonists) reduce potassium loss in the urine. *Spironolactone* has the additional benefit of diminishing the cardiac remodeling that occurs in heart failure. (A complete discussion of diuretics is found in Chapter 22, p. 257.)

VI. Î²-Adrenoceptor Blocking Agents

Î²-Blockers are currently recommended as first-line drug therapy for hypertension when when concomitant disease is present (see Figure 19.4)â€”for example, with heart failure. These drugs are efficacious but have some contraindications.

A. Actions

The Î²-blockers reduce blood pressure primarily by decreasing cardiac output (Figure 19.7). They may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone. The prototype Î²-blocker is *propranolol* [proe PRAN-oh-lol], which acts at both $Î²_1$ and $Î²_2$ receptors. Selective blockers of $Î²_1$ receptors, such as *metoprolol* [met-OH-pro-lol] and *atenolol* [ah-TEN-oh-lol], are among the most commonly prescribed Î²-blockers. The selective Î²-blockers may be administered cautiously to hypertensive patients who also have asthma, for which *propranolol* is contraindicated due to its blockade of $Î²_2$-mediated bronchodilation. (See p. 220 for a

discussion of the Î²-blockers). The Î²-blockers should be employed cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

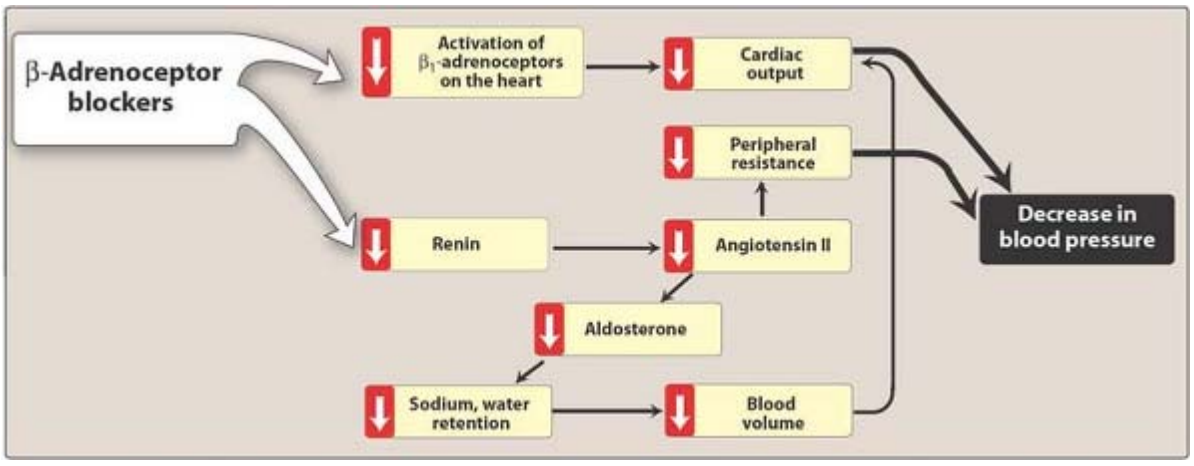

Figure 19.7 Actions of Î²-adrenoceptor blocking agents.

B. Therapeutic uses

1. **Subsets of the hypertensive population:** The Î²-blockers are more effective for treating hypertension in white than in black patients and in young compared to elderly patients. [Note: Conditions that discourage the use of Î²-blockers (for example, severe chronic obstructive lung disease, chronic congestive heart failure, or severe symptomatic occlusive peripheral vascular disease) are more commonly found in the elderly and in diabetics.]
2. **Hypertensive patients with concomitant diseases:** The Î²-blockers are useful in treating conditions that may coexist with hypertension, such as supraventricular tachyarrhythmia, previous myocardial infarction, angina pectoris, chronic heart failure, and migraine headache.

C. Pharmacokinetics

The Î²-blockers are orally active. *Propranolol* undergoes extensive and highly variable first-pass metabolism. The Î²-blockers may take several weeks to develop their full effects.

D. Adverse effects

1. **Common effects:** The Î²-blockers may cause bradycardia and CNS side effects such as fatigue, lethargy, insomnia, and hallucinations; these drugs can also cause hypotension (Figure 19.8). The Î²-blockers may decrease libido and cause impotence. [Note: Drug-induced sexual dysfunction can severely reduce patient compliance.]
2. **Alterations in serum lipid patterns:** The Î²-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing plasma triacylglycerol.
3. **Drug withdrawal:** Abrupt withdrawal may induce angina, myocardial infarction, or even sudden death in patients with ischemic heart disease. Therefore, the dose of these drugs must be tapered over 2 to 3 weeks in patients with hypertension and ischemic heart disease.

Figure 19.8 Some adverse effects of Î²-blockers.

VII. ACE Inhibitors

The ACE inhibitors, such as *enalapril* [e-NAL-ah-pril] or *lisinopril* [lye-SIN-oh-pril], are recommended when the preferred first-line agents (diuretics or Î²-blockers) are contraindicated or ineffective. Despite their widespread use, it is not clear if antihypertensive therapy with ACE inhibitors increases the risk of other major diseases.

A. Actions

The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing

cardiac output, rate, or contractility. These drugs block the ACE that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II (Figure 19.9). The converting enzyme is also responsible for the breakdown of bradykinin. ACE inhibitors decrease angiotensin II and increase bradykinin levels. Vasodilation

occurs as a result of the combined effects of lower vasoconstriction caused by diminished levels of angiotensin II and the potent vasodilating effect of increased bradykinin. By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

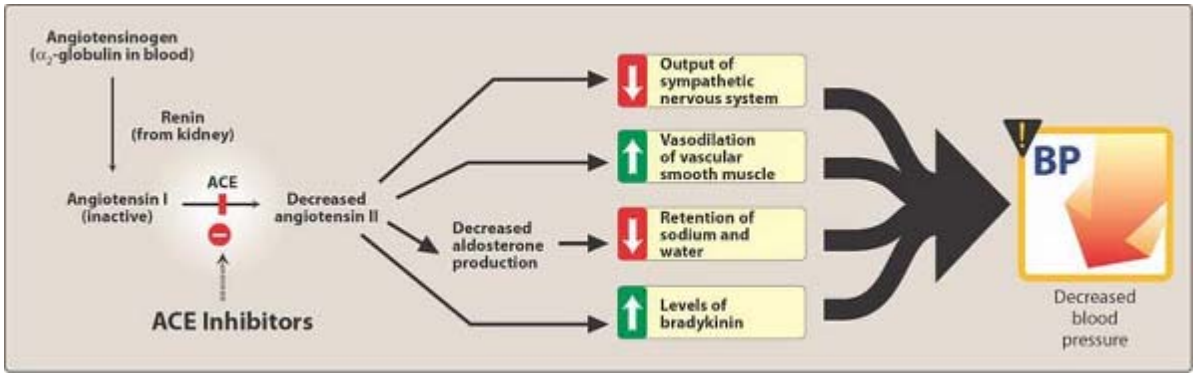

Figure 19.9 Effects of angiotensin-converting enzyme (ACE) inhibitors.

B. Therapeutic uses

Like Î²-blockers, ACE inhibitors are most effective in hypertensive patients who are white and young. However, when used in combination with a diuretic, the effectiveness of ACE inhibitors is similar in white and black patients with hypertension. Along with the angiotensin-receptor blockers, ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria. ACE inhibitors are also effective in the management of patients with chronic heart failure. ACE inhibitors are a standard in the care of a patient following a myocardial infarction. Therapy is started 24 hours after the end of the infarction.

C. Adverse effects

Common side effects include dry cough, rash, fever, altered taste, hypotension (in hypovolemic states), and hyperkalemia (Figure 19.10). The dry cough, which occurs in about 10 percent of patients, is thought to be due to increased levels of bradykinin in the pulmonary tree. Potassium levels must be monitored, and potassium supplements (or a high postasium diets) or potassium-sparing diuretics are contraindicated. Angioedema is a rare but potentially life-threatening reaction and may also be due to increased levels of bradykinin. Because of the risk of angioedema and first-dose syncope, ACE inhibitors may be first administered in the physician's office with close observation. Reversible renal failure can occur in patients with severe bilateral renal artery stenosis. ACE inhibitors are fetotoxic and should not be used by women who are pregnant.

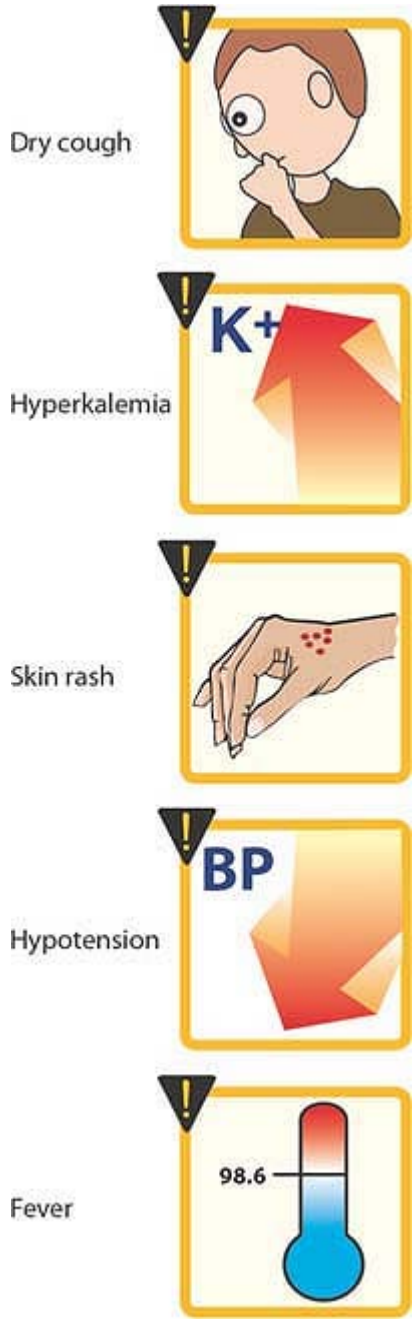

Figure 19.10 Some common adverse effects of the ACE inhibitors.

VIII. Angiotensin Iiâ€“Receptor Antagonists

The angiotensin Iiâ€“receptor blockers (ARBs) are alternatives to the ACE inhibitors. These drugs block the AT1 receptors. *Losartan* [LOW-sar-tan], is the prototypic ARB; currently, there are six additional ARBs. Their pharmacologic effects are similar to those of ACE inhibitors in that they produce

arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention. ARBs do not increase bradykinin levels. ARBs decrease the nephrotoxicity of diabetes, making them

an attractive therapy in hypertensive diabetics. Their adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased. ARBs are also fetotoxic. [Note: The ARBs are discussed more fully in Chapter 16.]

IX. Renin Inhibitors

A selective renin inhibitor, *aliskiren* [a-LIS-ke-rin] has been released for the treatment of hypertension. *Aliskiren* directly inhibits renin and, thus, acts earlier in the renin-angiotensin-aldosterone system than ACE inhibitors or ARBs. It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides. It can also be combined other antihypertensives, such diuretics, ACE inhibitors, ARBs, or calcium-channel blockers. *Aliskiren* can cause diarrhea, especially at the higher doses. *Aliskiren* can also cause cough and angioedema but probably less often than ACE inhibitors. The drug is contraindicated during pregnancy. The combination of maximum doses of *aliskiren* and *valsartan* decreased blood pressure more than maximum doses of either agent alone but not more than would be expected with dual therapy consisting of agents of different classes. Hyperkalemia was significantly more common in patients who received both *valsarta*n and *aliskiren*.

X. Calcium-Channel Blockers

Calcium-channel blockers are recommended when the preferred first-line agents are contraindicated or ineffective. They are effective in treating hypertension in patients with angina or diabetes. High doses of short-acting calcium-channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

A. Classes of calcium-channel blockers

The calcium-channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications (Figure 19.11).

1. **Diphenylalkylamines:** *Verapamil* [ver-AP-ah-mil] is the only member of this class that is currently approved in the United States. *Verapamil* is the least selective of any calcium-channel blocker and has significant effects on both cardiac and vascular smooth muscle cells. It is used to treat angina, supraventricular tachyarrhythmias, and migraine headache.

2. **Benzothiazepines:** *Diltiazem* [dil-TYE-ah-zem] is the only member of this class that is currently approved in the United States. Like *verapamil, diltiazem* affects both cardiac and vascular smooth muscle cells; however, it has a less pronounced negative inotropic effect on the heart compared to that of *verapamil*. *Diltiazem* has a favorable side-effect profile.

3. **Dihydropyridines:** This rapidly expanding class of calcium-channel blockers includes the first-generation *nifedipine* [ni-FED-i-peen] and five second-generation agents for treating cardiovascular disease: *amlodipine* [am-LOE-di-peen], *felodipine* [fe-LOE-di-peen], *isradipine*

[iz-RA-di-peen], *nicardipine* [nye-KAR-de-peen], and *nisoldipine* [ni-SOLD-i-peen]. These second-generation calcium-channel blockers differ in pharmacokinetics, approved uses, and drug interactions. All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart. They are therefore particularly attractive in treating hypertension. Some of the newer agents, such as *amlodipine* and *nicardipine*, have the advantage that they show little interaction with other cardiovascular drugs, such as *digoxin* or *warfarin*, which are often used concomitantly with calcium-channel blockers.

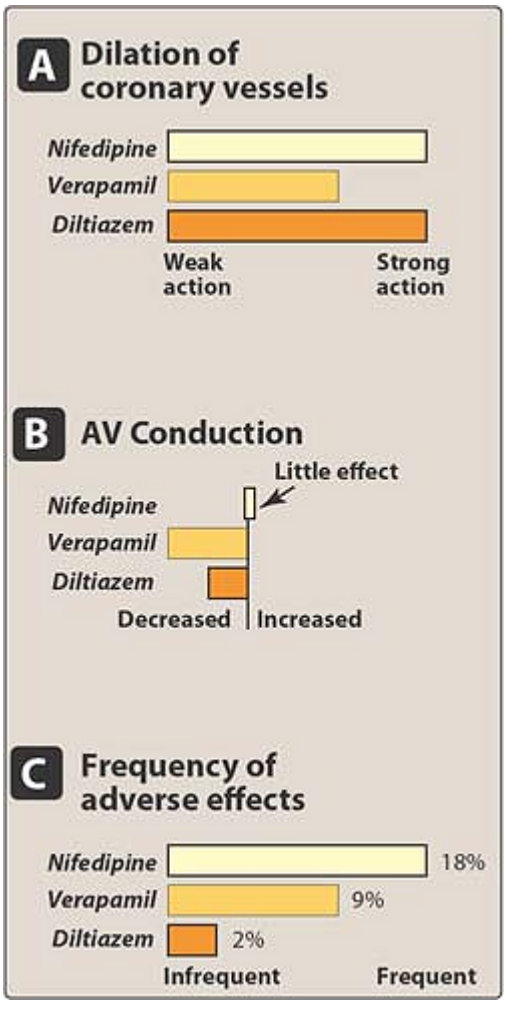

Figure 19.11 Actions of calcium-channel blockers.

B. Actions

The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium enters muscle cells through special voltage-sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium. Calcium-channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles.

C. Therapeutic uses

Calcium-channel blockers have an intrinsic natriuretic effect and, therefore, do not usually require the addition of a diuretic. These agents are

useful in the treatment of hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease (Figure 19.12). Black hypertensives respond well to calcium-channel blockers.

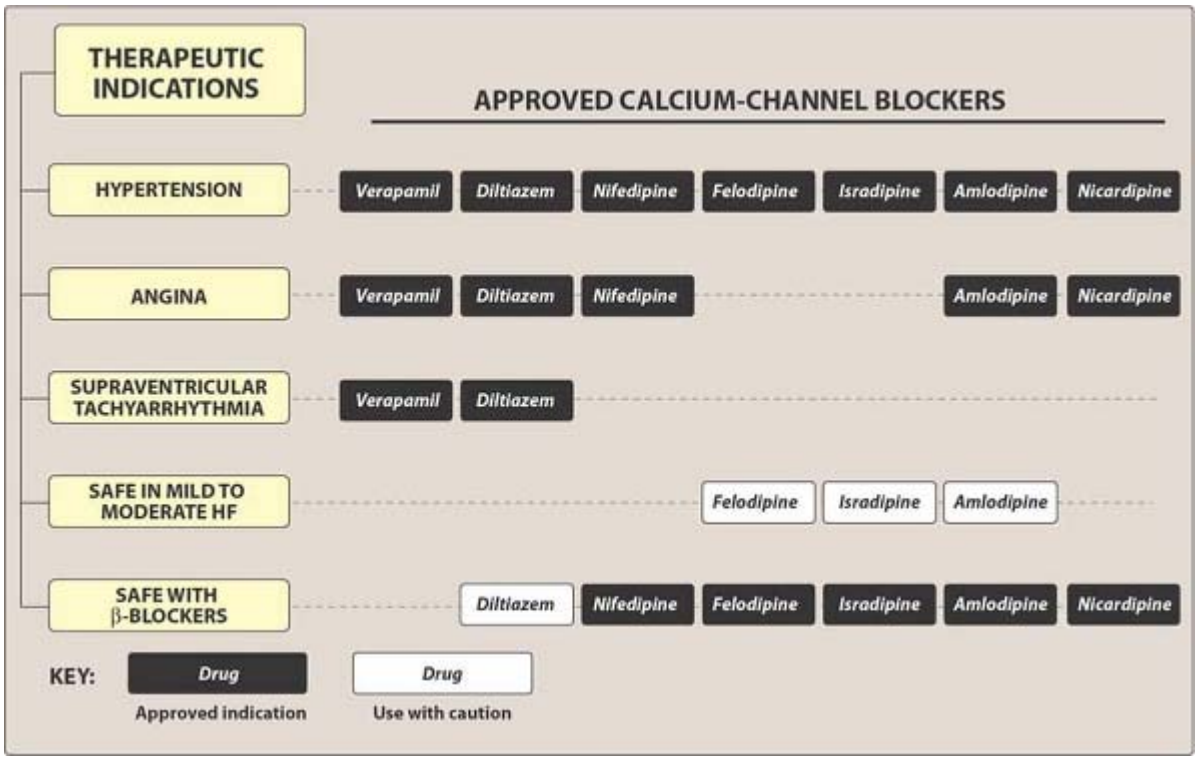

Figure 19.12 Some therapeutic applications of calcium channel blockers. HF = heart failure.

D. Pharmacokinetics

Most of these agents have short half-lives (3â€“8 hours) following an oral dose. Treatment is required three times a day to maintain good control of hypertension. Sustained-release preparations are available and permit less frequent dosing. *Amlodipine* has a very long half-life and does not required a sustained-release formulation.

E. Adverse effects

Constipation occurs in 10 percent of patients treated with *verapamil*. Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines (Figure 19.13). *Verapamil* should be avoided in patients with congestive heart failure or with atrioventricular block due to its negative inotropic (force of cardiac muscle contraction) and dromotropic (velocity of conduction) effects.

XI. Î±-Adrenoceptor Blocking Agents

Prazosin [PRAY-zo-sin], *doxazosin* [dox-AH-zoe-sin], and *terazosin* [ter-AH-zoe-sin] produce a competitive block of $\hat{I}\pm_1$-adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle. These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate. Therefore, long-term tachycardia does not occur, but salt and water retention does. Postural hypotension may occur in some individuals. *Prazosin* is used to treat mild to moderate hypertension and is prescribed in combination with *propranolol* or a diuretic for additive effects. Reflex tachycardia and first-dose syncope are almost universal adverse effects. Concomitant use of a $\hat{I}^2$-blocker may be necessary to blunt the short-term effect of reflex tachycardia. An increased rate of congestive heart failure occurs in patients taking *doxazosin* alone compared to those taking a thiazide diuretic alone. Because of the side-effect profile, development of tolerance, and the advent of safer antihypertensives, Î±-blockers are seldom used in the

treatment of hypertension. *Tamsulosin*, an a_1â€“blocker with greater selectivity for prostate muscle, has been used in the treatment of prostate hyperplasia.

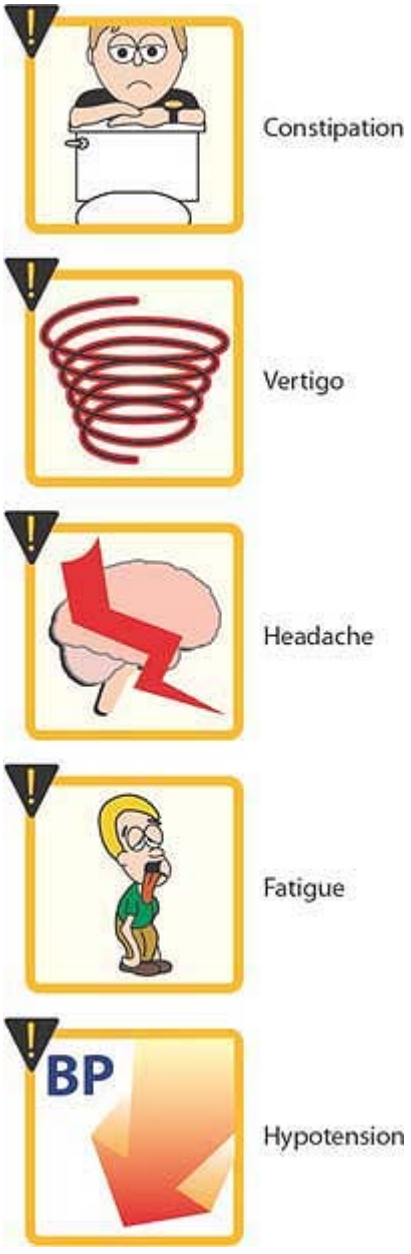

Figure 19.13 Some common adverse effects of the calcium-channel blockers.

XII. Î±- Î²- Adrenoceptor Blocking Agents

Labetalol [la-BET-ah-lol] and *carvedilol* [kar-VEH-di-lol] block both a_1- and b_1- and b_2- receptors. *Carvedilol,* although an effective antihypertensive, is mainly used in the treatment of heart failure. *Carvedilol* has been shown to reduce mortality associated with heart failure.

XIII. Centrally Acting Adrenergic Drugs

A. Clonidine

This Î±$_2$-agonist diminishes central adrenergic outflow. *Clonidine* [KLOE-ni-deen] is used primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs. *Clonidine* does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated

by renal disease. *Clonidine* is absorbed well after oral administration and is excreted by the kidney. Because it may cause sodium and water retention, *clonidine* may be administered in combination with a diuretic. Adverse effects are generally mild, but the drug can produce sedation and drying of the nasal mucosa. Rebound hypertension occurs following abrupt withdrawal of *clonidine*. The drug should therefore be withdrawn slowly if the clinician wishes to change agents.

B. Î±-Methyldopa

This Î±$_2$-agonist is converted to methylnorepinephrine centrally to diminish the adrenergic outflow from the CNS. This leads to reduced total peripheral resistance and a decreased blood pressure. Cardiac output is not decreased, and blood flow to vital organs is not diminished. Because blood flow to the kidney is not diminished by its use, Î±-*methyldopa* [meth-ill-DOE-pa] is especially valuable in treating hypertensive patients with renal insufficiency. The most common side effects of Î±-*methyldopa* are sedation and drowsiness. It has been used in hypertensive pregnant patients.

XIV. Vasodilators

The direct-acting smooth muscle relaxants, such as *hydralazine* and *minoxidil*, have traditionally not been used as primary drugs to treat hypertension. Vasodilators act by producing relaxation of vascular smooth muscle, which decreases resistance and, therefore, blood pressure. These agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals. Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be blocked by concomitant use of a diuretic and a Î²-blocker.

A. Hydralazine

This drug causes direct vasodilation, acting primarily on arteries and arterioles. This results in a decreased peripheral resistance, which in turn prompts a reflex elevation in heart rate and cardiac output. *Hydralazine* [hye-DRAL-ah-zeen] is used to treat moderately severe hypertension. It is almost always administered in combination with a Î²-blocker, such as *propranolol* (to balance the reflex tachycardia), and a diuretic (to decrease sodium retention). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance. *Hydralazine* monotherapy is an accepted method of controlling blood pressure in pregnancy-induced hypertension. Adverse effects of *hydralazine* therapy include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina. A lupus-like syndrome can occur with high dosage, but it is reversible on discontinuation of the drug.

B. Minoxidil

This drug causes dilation of resistance vessels (arterioles) but not of capacitance vessels (venules). *Minoxidil* [mi-NOX-i-dill] is administered orally for treatment of severe to malignant hypertension that is refractory to other drugs. Reflex tachycardia and fluid retention may be severe and require the concomitant use of a loop diuretic and a Î²-blocker.

Minoxidil causes serious sodium and water retention, leading to volume overload, edema, and congestive heart failure. [Note: *Minoxidil* treatment also causes hypertrichosis (the growth of body hair). This drug is now used

topically to treat male pattern baldness.]

XV. Hypertensive Emergency

Hypertensive emergency is a rare but life-threatening situation in which the DBP is either >150 mm Hg (with SBP >210 mm Hg) in an otherwise healthy person or >130 mm Hg in an individual with preexisting complications, such as encephalopathy, cerebral hemorrhage, left ventricular failure, or aortic stenosis. The therapeutic goal is to rapidly reduce blood pressure.

A. Sodium nitroprusside

Nitroprusside [nye-troe-PRUSS-ide] is administered intravenously and causes prompt vasodilation with reflex tachycardia. It is capable of reducing blood pressure in all patients regardless of the cause of hypertension (Figure 19.14). The drug has little effect outside the vascular system, acting equally on arterial and venous smooth muscle. [Note: Because *nitroprusside* also acts on the veins, it can reduce cardiac preload.] *Nitroprusside* is metabolized rapidly (half-life of minutes) and requires continuous infusion to maintain its hypotensive action. *Sodium nitroprusside* exerts few adverse effects except for those of hypotension caused by overdose. *Nitroprusside* metabolism results in cyanide ion production. Although cyanide toxicity is rare, it can be effectively treated with an infusion of *sodium thiosulfate* to produce thiocyanate, which is less toxic and is eliminated by the kidneys. [Note: *Nitroprusside* is poisonous if given orally because of its hydrolysis to cyanide.] Nitroprusside is light sensitive, and when in solution, it should be protected from light.

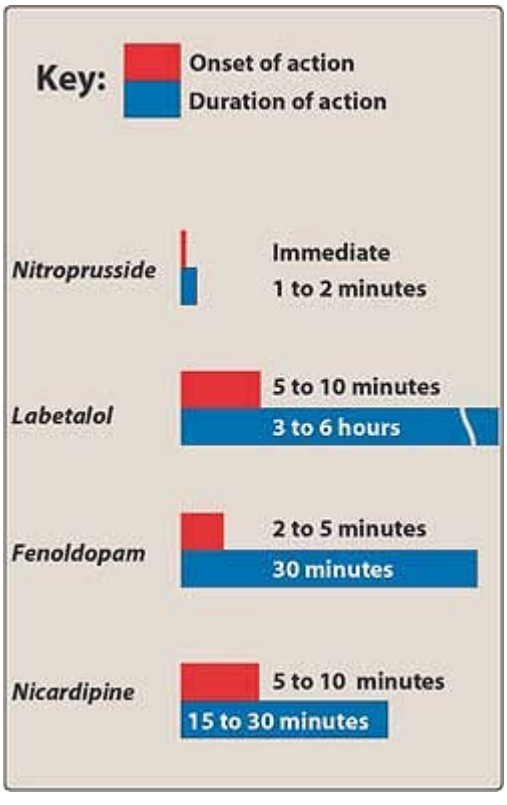

Figure 19.14 Time to peak effect and duration of action for some drugs used in hypertensive emergency.

B. Labetalol

Labetalol [lah-BET-a-lole] is both an Î±- and a Î²-blocker and is given as an intravenous bolus or infusion in

hypertensive emergencies. *Labetalol* does not cause reflex tachycardia. *Labetalol* carries the contraindications of a nonselective Î²-blocker. The major limitation is a longer half-life, which precludes rapid titration (see Figure 19.14)

C. Fenoldopam

Fenoldopam [feh-NOL-doh-pam] is a peripheral dopamine-1 receptor agonist that is given as an intravenous infusion. Unlike other parenteral antihypertensive agents, *fenoldopam* maintains or increases renal perfusion while it lowers blood pressure. *Fenoldopam* can be safely used in all hypertensive emergencies and may be particularly beneficial in patients with renal insufficiency. The drug is contraindicated in patients with glaucoma.

D. Nicardipine

Nicardipine, a calcium-channel blocker, can be given as an intravenous infusion. The initial dose is 5 mg/h and can be increased to a maximum of 15 mg/h. The major limitation of *nicardipine* in treating hypertensive emergency is its long half-time (approximately 8 hours), which precludes rapid titration.

Study Questions

Choose the ONE best answer.

19.1 A 45-year-old man has recently been diagnosed with hypertension and started on monotherapy designed to reduce peripheral resistance and prevent NaCl and water retention. He has developed a persistent cough. Which of the following drugs would have the same benefits but would not cause cough?

A. Losartan.

B. Nifedipine.

C. Prazosin.

D. Propranolol.

View Answer

19.2 Which one of the following drugs may cause a precipitous fall in blood pressure and fainting on initial administration?

A. Atenolol.

B. Hydrochlorothiazide.

C. Nifedipine.

D. Prazosin.

E. Verapamil.

View Answer

19.3 Which one of the following antihypertensive drugs can precipitate a hypertensive crisis following abrupt cessation of therapy?

A. Clonidine.

B. Diltiazem.

C. Enalapril.

D. Losartan.

E. Hydrochlorothiazide.

View Answer

19.4 A 48-year-old hypertensive patient has been successfully treated with a thiazide diuretic for the last 5 years. Over the last 3 months, his diastolic pressure has steadily increased, and he has been started on an additional antihypertensive medication. He complains of several instances of being unable to achieve an erection and that he is no longer able to complete three sets of tennis. The second antihypertensive medication is most likely which one of the following?

A. Captopril.

B. Losartan.

C. Minoxidil.

D. Metoprolol.

E. Nifedipine.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 20

Blood Drugs

I. Overview

This chapter describes drugs that are useful in treating three important dysfunctions of blood: thrombosis, bleeding, and anemia. Thrombosisâ€"the formation of an unwanted clot within a blood vesselâ€"is the most common abnormality of hemostasis. Thrombotic disorders include acute myocardial infarction, deep-vein thrombosis, pulmonary embolism, and acute ischemic stroke. These are treated with drugs such as anticoagulants and fibrinolytics. Bleeding disorders involving the failure of hemostasis are less common than thromboembolic diseases. These disorders include hemophilia, which is treated with transfusion of Factor VIII prepared by recombinant DNA techniques, and vitamin K deficiency, which is treated with dietary supplements of the vitamin. Anemias caused by nutritional deficiencies, such as the commonly encountered iron-deficiency anemia, can be treated with either dietary or pharmaceutical supplementation. However, individuals with anemias that have a genetic basis, such as sickle-cell disease, can benefit from additional treatment. See Figure 20.1 for a summary of drugs affecting the blood.

II. Thrombus VS. Embolus

First, a few definitions to clarify the discussion of undesirable blood clots: A clot that adheres to a vessel wall is called a thrombus, whereas an intravascular clot that floats in the blood is termed an embolus. Thus, a detached thrombus becomes an embolus. Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients. Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by surface lesions on endothelial cells caused by atherosclerosis. Arterial thrombosis usually consists of a platelet-rich clot. In contrast, venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade, frequently as a result of a defect in the normal hemostatic defense mechanisms. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.

III. Platelet Response to Vascular Injury

Physical trauma to the vascular system, such as a puncture or a cut, initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade. This results in the formation of a platelet-fibrin plug (clot) at the site of the puncture. The creation of an unwanted

thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system rather than an external physical trauma.

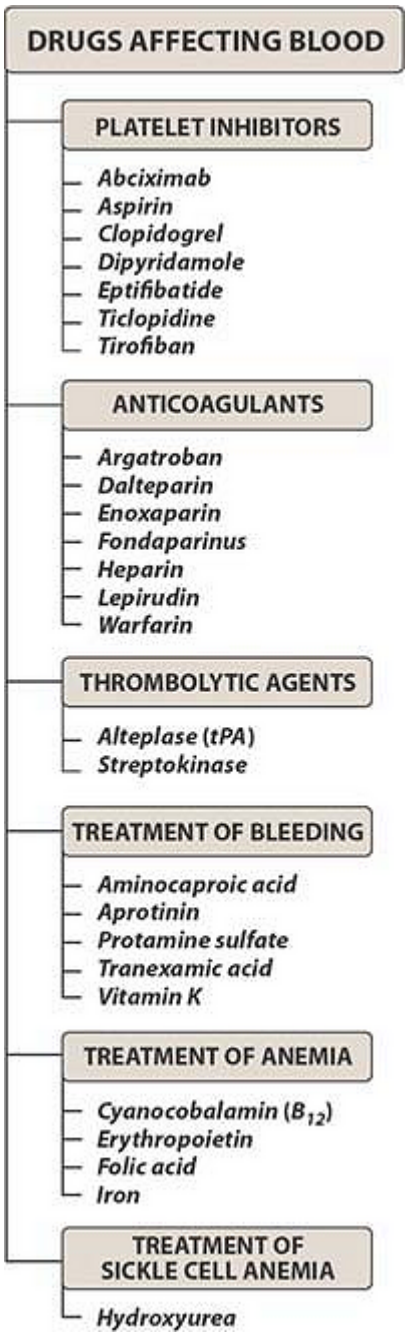

Figure 20.1 Summary of drugs used in treating dysfunctions of the blood.

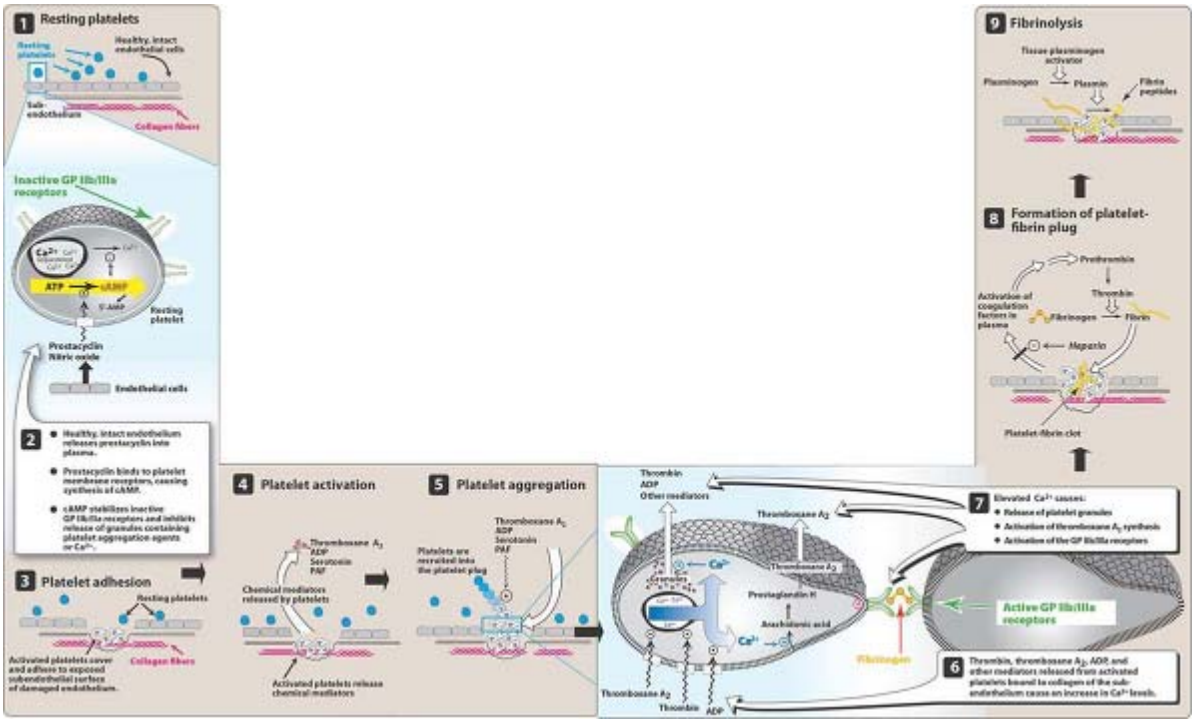

Figure 20.2 Formation of a hemostatic plug. PAF = platelet-activation factor.

A. Resting platelets

Platelets act as vascular sentries, monitoring the integrity of the endothelium. In the absence of injury, resting platelets circulate freely, because the balance of chemical signals indicates that the vascular system is not damaged (Figure 20.2).

1. **Chemical mediators synthesized by endothelial cells:** Chemical mediators, such as prostacyclin and nitric oxide, are synthesized by intact endothelial cells and act as inhibitors of platelet aggregation. Prostacyclin (prostaglandin I_2) acts by binding to platelet membrane receptors that are coupled to the synthesis of cyclic adenosine monophosphate (cAMP; Figure 20.2)â€"an intracellular messenger.[1] Elevated levels of intracellular cAMP are associated with a decrease in intracellular Ca^{2+}. This leads to inhibition of platelet activation and the subsequent release of platelet aggregation agents. [Note: The drug *dipyridamole* inhibits the enzyme phosphodiesterase, which inactivates cAMP, thus prolonging its active life.] Damaged endothelial cells synthesize less prostacyclin, resulting in a localized reduction in prostacyclin levels. The binding of prostacyclin to platelet receptors is decreased, resulting in lower levels of intracellular cAMP, which leads to platelet aggregation.

2. **Roles of thrombin, thromboxanes, and collagen:** The platelet membrane also contains receptors that can bind thrombin, thromboxanes,[2] and exposed collagen.[3] In the intact, normal vessel, circulating levels of thrombin and thromboxane are low, and the intact

endothelium covers the collagen in the subendothelial layers. The corresponding platelet receptors are thus unoccupied and remain inactive; as a result, platelet activation and aggregation are not initiated. However, when occupied, each of these receptor types triggers a series of reactions leading to the release into the circulation of intracellular granules by the platelets. This ultimately stimulates platelet aggregation.

B. Platelet adhesion

When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the subendothelium (see Figure 20.2). This triggers a complex series of chemical reactions, resulting in platelet activation.

C. Platelet activation

Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue. This causes morphologic changes in the platelets (Figure 20.3) and the release of platelet granules containing chemical mediators, such as adenosine diphosphate (ADP), thromboxane A_2, serotonin, platelet-activation factor, and thrombin (see Figure 20.2). These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby. These receptors function as sensors that are activated by the signals sent from the adhering platelets. The previously dormant platelets become activated and start to aggregateâ€"actions mediated by several messenger systems that ultimately result in elevated levels of Ca^{2+} and a decreased concentration of cAMP within the platelet.

D. Platelet aggregation

The increase in cytosolic Ca^{2+} accompanying activation is due to a release of sequestered stores within the platelet (see Figure 20.2). This leads to 1) the release of platelet granules containing mediators, such

as ADP and serotonin that activate other platelets; 2) activation of thromboxane A_2 synthesis; and 3) activation of the glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen and, ultimately, regulate platelet-platelet interaction and thrombus formation (see Figure 20.2). Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation. This leads to an avalanche of platelet aggregation, because each activated platelet can recruit other platelets (Figure 20.4).

E. Formation of a clot

Local stimulation of the coagulation cascade by tissue factors released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (Factor IIa). In turn, thrombinâ€"a serine proteaseâ€"catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the plug. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet-fibrin plug (see Figure 20.2).

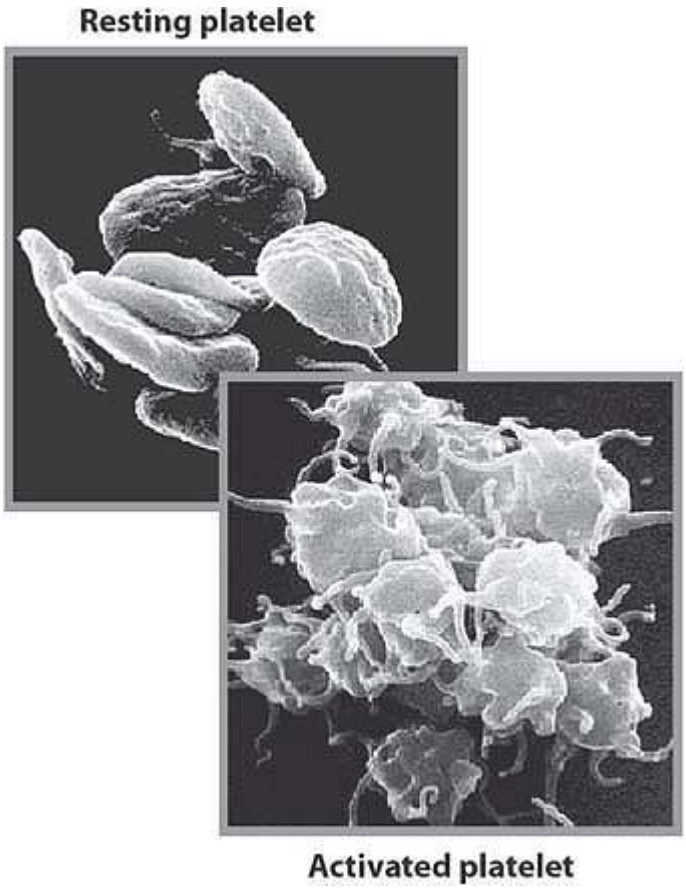

Figure 20.3 Scanning electron micrograph of platelets.

F. Fibrinolysis

During plug formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators in the tissue (see Figure 20.2). Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal. At present, a number of fibrinolytic enzymes are available for treatment of myocardial infarctions, pulmonary emboli, or ischemic stroke.

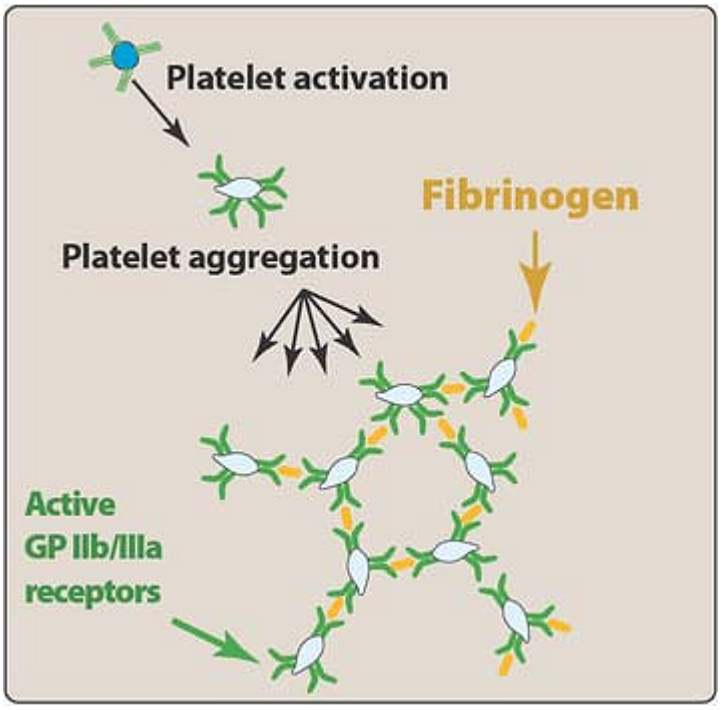

Figure 20.4 Activation and aggregation of platelets. GP = glycoprotein.

IV. Platelet Aggregation Inhibitors

Platelet aggregation inhibitors decrease the formation or the action of chemical signals that promote platelet aggregation. The last step in this response to vascular trauma depends on a family of membrane GP receptors thatâ€"after activationâ€"can bind adhesive proteins, such as fibrinogen, von Willebrand factor, and fibronectin. The most important of these is the GP IIb/IIIa receptor that ultimately regulates platelet-platelet interaction and thrombus formation. Thus, platelet activation agents, such as thromboxane A_2, ADP, thrombin, serotonin, and collagen, all promote the conformational change necessary for the GP IIb/IIIa receptor to bind ligands, particularly fibrinogen. Fibrinogen simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and aggregation (see Figure 20.4). The platelet aggregation inhibitors described below inhibit cyclooxygenase-1 (COX-1) or block GP IIb/IIIa or ADP receptors, thereby interfering in the signals that promote platelet aggregation. Since these agents have different mechanisms of actions, synergistic or additive effects may be achieved when agents from different classes are combined. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in myocardial infarction.

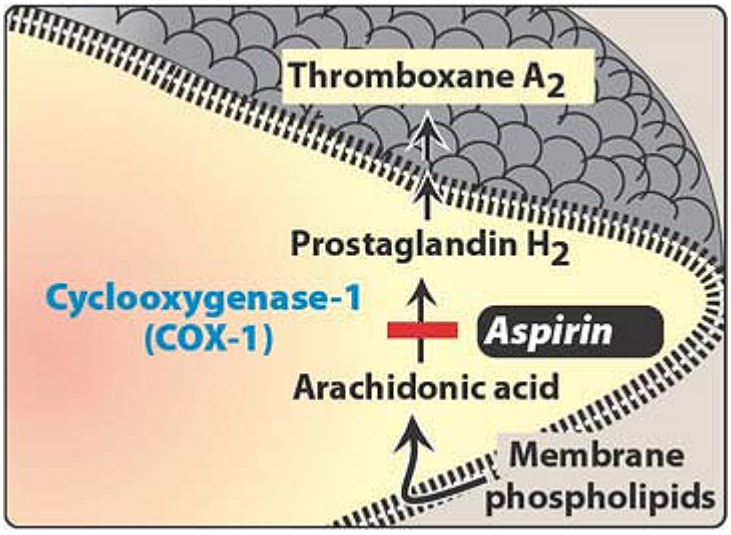

Figure 20.5 *Aspirin* irreversibly inhibits platelet cyclooxygenase-1.

A. Aspirin

Stimulation of platelets by thrombin, collagen and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids.[4] Arachidonic acid is first converted

to prostaglandin H_2 by COX-1 (Figure 20.5); prostaglandin H_2 is further metabolized to thromboxane A_2, which is released into plasma. Thromboxane A_2 produced by the aggregating platelets further promotes the clumping process that is essential to the rapid formation of a hemostatic plug. *Aspirin* [AS-pir-in] inhibits thromboxane A_2 synthesis from arachidonic acid in platelets by irreversible acetylation of a serine, resulting in a blockade of arachidonate to the active site and, thus, inhibition of COX-1 (Figure 20.6). This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thus impeding platelet aggregation. The inhibitory effect is rapid, apparently occurring in the portal circulation. The *aspirin*-induced suppression of thromboxane A_2 synthetase and the resulting suppression of platelet aggregation last for the life of the anucleate plateletâ€"approximately 7 to 10 days. *Aspirin* is currently employed in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent myocardial infarction, and to decrease mortality in preâ€“ and postâ€“myocardial infarct patients. The recommended dose of *aspirin* ranges from 81 to 325 mg, with side effects determining the dose chosen. Bleeding time is prolonged by *aspirin* treatment, causing complications that include an increased incidence of hemorrhagic stroke as well as gastrointestinal bleeding, especially at higher doses of the drug. *Aspirin* is frequently used in combination with other drugs having anticlotting propertiesâ€"for example, *heparin* or *clopidogrel*. Nonsteroidal anti-inflammatory drugs, such as *ibuprofen,* inhibit COX-1 by transiently competing at the catalytic site. *Ibuprofen*, if taken concomitantly with, or 2 hours prior to *aspirin*, can obstruct the access of *aspirin* to the serine residue and, thereby, antagonize the platelet inhibition by *aspirin*. Therefore, *aspirin* should be taken at least 30 minutes before *ibuprofen* or at least 8 hours after *ibuprofen*. Although *celecoxib* (a selective COX-2 inhibitorâ€"see Chapter 39) does not interfere in the antiaggregation activity of *aspirin*, there is some evidence that it may contribute to cardiovascular events by shifting the balance of chemical mediators in favor of thromboxane A_2.

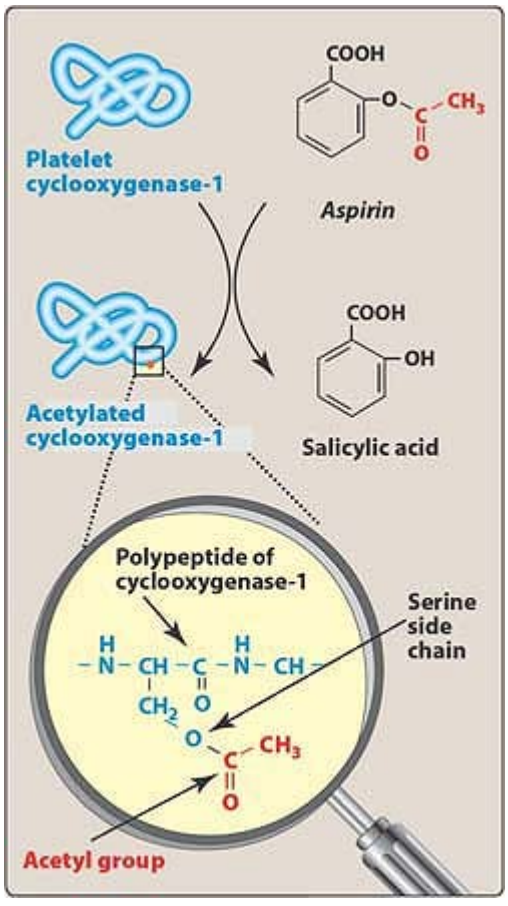

Figure 20.6 Acetylation of *cyclooxygenase*-1 by *aspirin*.

B. Ticlopidine and clopidogrel

Ticlopidine [ti-KLOE-pi-deen] and *clopidogrel* (kloh-PID-oh-grel) are closely related thienopyridines that also block platelet aggregation, but by a mechanism different from that of *aspirin*.

1. **Mechanism of action:** These drugs irreversibly inhibit the binding of ADP to its receptors on platelets and, thus, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other (Figure 20.7).

2. **Therapeutic use:** Although *ticlopidine* and *clopidogrel* are similar in both structure and mechanism of action, their therapeutic uses are different. *Ticlopidine* is approved for the prevention of transient ischemic attacks and strokes for patients with prior cerebral thrombotic event. It is also used as adjunct therapy with *aspirin* following coronary stent implantation to decrease the incidence of stent thrombosis. However, due to its life-threatening hematologic adverse reactions, including neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia, it is generally reserved for patients who are intolerant to other therapies.*Clopidogrel* is approved for prevention of atherosclerotic events following recent myocardial infarction, stroke, or established peripheral arterial disease. It is also approved for prophylaxis of thrombotic events in acute coronary syndrome (unstable angina or non-Q-wave

myocardial infarction). Additionally, *clopidogrel* is used to prevent thrombotic events associated with percutaneous coronary intervention with or without coronary stent. Compared to *ticlopidine, clopidogrel* is the

preferred agent in ischemic heart disease events, because there is more data to support use of *clopidogrel* in these cardiac patients. Furthermore, *clopidogrel* has a better overall side-effect profile, although TTP may also occur with this agent.

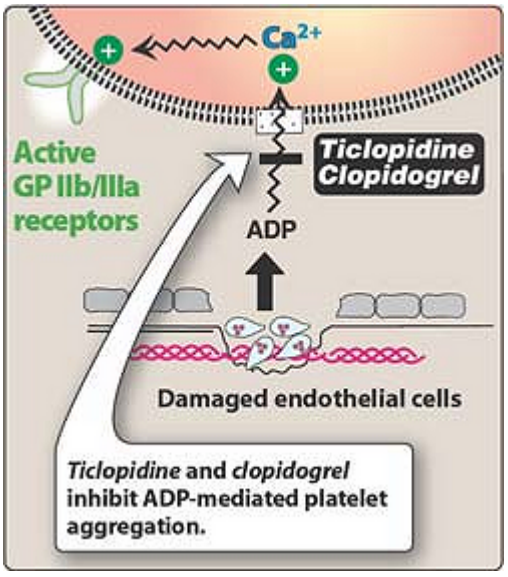

Figure 20.7 Mechanism of action of *ticlopidine* and *clopidogrel*. GP = glycoprotein.

3. **Pharmacokinetics:** Food interferes with the absorption of *ticlopidine* but not with *clopidogrel*. After oral ingestion, both drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by the cytochrome P450 system to active metabolites that are yet to be identified. The maximum effect is achieved in 3 to 5 days; when treatment is suspended, the platelet system requires time to recover. Elimination of the drugs and metabolites occurs by both the renal and fecal routes. *Ticlopidine* has a black box warning due to the severe hematologic adverse reactions associated with its use. Both drugs can cause prolonged bleeding for which there is no antidote. Serious adverse effects of *ticlopidine* include neutropenia, TTP, and aplastic anemia requiring frequent blood monitoring, especially during the first 3 months of treatment. *Clopidogrel* causes fewer adverse reactions, and the incidence of neutropenia is lower. However, TTP has been reported as an adverse effect for both drugs. Because these drugs can inhibit cytochrome P450, they may interfere with the metabolism of drugs such as *phenytoin, tolbutamide, warfarin, fluvastatin*, and *tamoxifen* if taken concomitantly. Indeed, *phenytoin* toxicity has been reported when taken with *ticlopidine*.

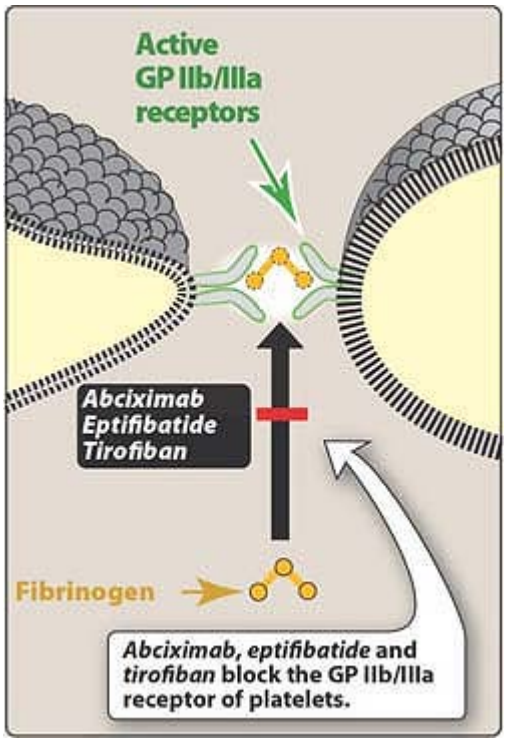

Figure 20.8 Mechanism of action of glycoprotein (GP) IIb/IIIaâ€“receptor blockers.

C. Abciximab

The realization of the key role of the platelet GP IIb/IIIa receptor in stimulating platelet aggregation directed attempts to block this receptor on activated platelets. This led to the development of a chimeric monoclonal antibody, *abciximab* [ab-SIKS-eh-mab], which is composed of the constant regions of human immunoglobulin joined to the Fab fragments of a murine monoclonal antibody directed against the GP IIb/IIIa complex. By binding to GP IIb/IIIa, the antibody blocks the binding of fibrinogen and von Willebrand factor; consequently, aggregation does not occur (Figure 20.8). *Abciximab* is given intravenously along with *heparin* or *aspirin* as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications. After cessation of infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours. The major adverse effect of *abciximab* therapy is the potential for bleeding, especially if the drug is used with anticoagulants or if the patient has a clinical hemorrhagic condition. *Abciximab* is expensive, limiting its use in some settings.

D. Eptifibatide and tirofiban

These two antiplatelet drugs act similarly to *abciximab*â€”namely, blocking the GP IIb/IIIa receptor (see Figure 20.8). *Eptifibatide* [ep-ti-FIB-ih-tide] is a cyclic peptide that binds to GP IIb/IIIa at the site that interacts with the arginine-glycine-aspartic acid sequence of fibrinogen. *Tirofiban* [tye-roe-FYE-ban] is not a peptide, but it blocks the same site as *eptifibatide*. These compounds, like *abciximab*, can decrease the incidence of thrombotic complications associated with acute coronary syndromes. When intravenous infusion is stopped, these agents are rapidly cleared from the plasma, but their effect can persist for as long as 4 hours. [Note: Only intravenous formulations are available, because oral preparations

of GP IIb/IIIa blockers are too toxic.] *Eptifibatide* and its metabolites are excreted by the kidney. *Tirofiban* is

excreted unchanged by the kidney. The major adverse effect of both drugs is bleeding. Figure 20.9 summarizes the effects of the GP IIb/IIIaâ€“receptor antagonists on death and myocardial infarction.

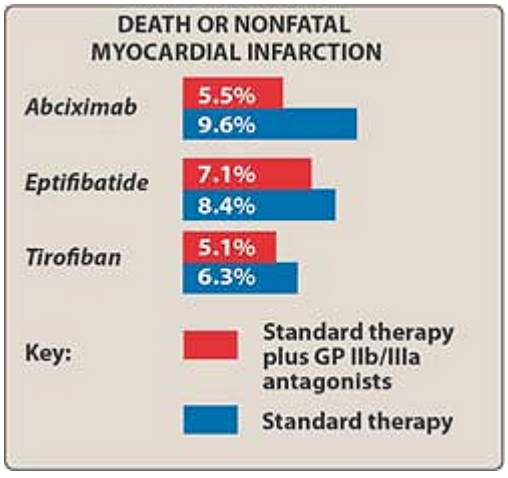

Figure 20.9 Effects of glycoprotein (GP) IIb/IIIaâ€“ receptor antagonists on the incidence of death or nonfatal myocardial infarction following percutaneous transluminal coronary angioplasty. [Note: Data are from several studies; thus, reported incidence of complications with standard therapy, such as as *heparin*, is not the same for each drug.]

E. Dipyridamole

Dipyridamole [dye-peer-ID-a-mole], a coronary vasodilator, is employed prophylactically to treat angina pectoris. It is usually given in combination with *aspirin or warfarin*; it is ineffective when used alone. *Dipyridamole* increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, resulting in decreased thromboxane A_2 synthesis. It may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces (see Figure 20.2). The meager data available suggest that *dipyridamole* makes only a marginal contribution to the antithrombotic action of *aspirin*. In combination with *warfarin*, however, *dipyridamole* is effective for inhibiting embolization from prosthetic heart valves.

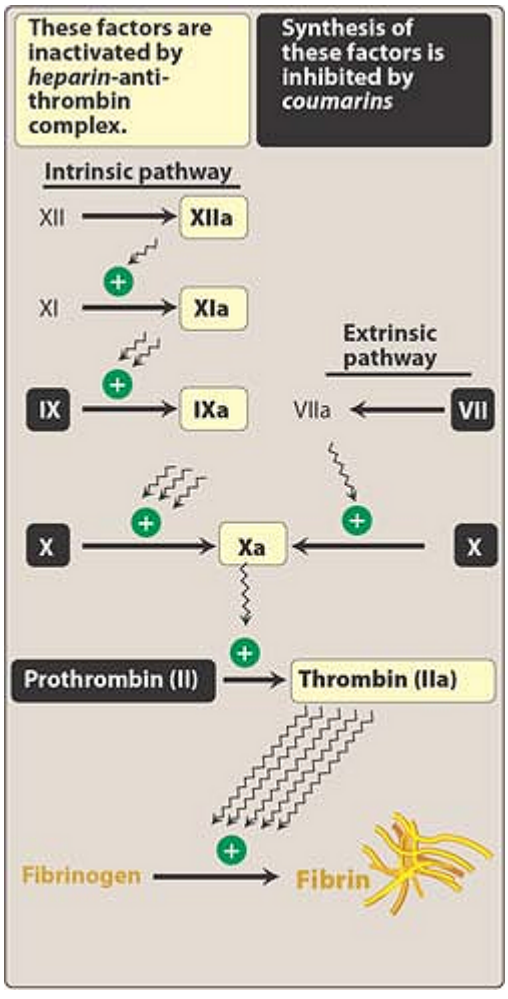

Figure 20.10 Formation of fibrin clot.

V. Blood Coagulation

The coagulation process that generates thrombin consists of two interrelated pathwaysâ€"the extrinsic and the intrinsic systems. The extrinsic system, which is probably the more important system in vivo, is initiated by the activation of clotting Factor VII by tissue factor, or thromboplastin. Tissue factor is a lipoprotein that is expressed by activated endothelial cells, activated leukocytes, subendothelial fibroblasts, and subendothelial smooth muscle cells at the site of vascular injury. The intrinsic system is triggered by the activation of clotting Factor XII, following its contact in vitro with glass or highly charged surfaces. In vivo, this pathway may be initiated by Factor XII contact with charged cell surfaces containing phospholipids.

A. Formation of fibrin

Both systems involve a cascade of enzyme reactions that sequentially transform various plasma factors (proenzymes) to their active (enzymatic) forms. They ultimately produce Factor Xa, which converts prothrombin (Factor II) to thrombin (Factor IIa, Figure 20.10). Thrombin plays a key role in coagulation, because it is responsible for generation of fibrin, the GP that forms the mesh-like matrix of the blood clot. If thrombin is not formed or if its function is impeded (for example, by antithrombin III), coagulation is inhibited. Each step in the activation process is catalytic; for example, one unit of activated Factor X (Xa) can potentially generate 40 units of thrombin. This will

result in the production of large amounts of fibrin at the site of injury.

B. Role of cell surfaces

Each reaction involved with the coagulation cascade takes place at a localized activated cell surface where a phospholipid-based protein-protein complex has formed. This complex consists of membrane surfaces provided by phospholipid (primarily phosphatidyl serine) of activated platelets or activated endothelial cells, an enzyme (an activated coagulation factor), a substrate (the proenzyme form of the downstream coagulation factor), and a cofactor. Ca^{2+} is essential in this process, bridging the anionic phospholipids and Î³-carboxyglutamic acid residues of the clotting factors. [Note: Removal of Ca^{2+} with calcium chelators such as ethylenediamine tetra-acetic acid or citrate is used to prevent clotting in a test tube].

C. Inhibitors of coagulation

It is important that coagulation is restricted to the local site of vascular injury. Endogenously, there are several inhibitors of coagulation factors, including protein C, protein S, antithrombin III, and tissue factor pathway inhibitor. The mechanism of action of several anticoagulant agents, including *heparin* and *heparin*-related products, involves activation of these endogenous inhibitors (primarily antithrombin III).

VI. Anticoagulants

The anticoagulant drugs either inhibit the action of the coagulation factors (the thrombin inhibitors, such as *heparin* and *heparin*-related agents) or interfere with the synthesis of the coagulation factors (the vitamin K antagonists, such as *warfarin*).

A. Thrombin inhibitors: heparin and low-molecular-weight heparins (LMWHs)

Heparin [HEP-a-rin] is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi. *Heparin* normally occurs as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown. It is extracted for commercial use from porcine intestine. Unfractionated *heparin* is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights (Figure 20.11). It is strongly acidic because of the presence of sulfate and carboxylic acid groups (Figure 20.12). [Note: In this discussion, the term *heparin* will indicate the unfractionated form of the drug.] The realization that low-molecular-weight forms of *heparin* (*LMWHs*) can also act as anticoagulants led to the isolation of *enoxaparin* [e-NOX-a-par-in], the first *LMWH* (<6000) available in the United States. The *LMWHs* are heterogeneous compounds (one-third the size of unfractionated *heparin*) produced by the chemical or enzymatic depolymerization of unfractionated *heparin*. Because they are free of some of the drawbacks associated with the polymer, they are replacing the use of *heparin* in many clinical situations. *Heparin* is used in the prevention of venous thrombosis and the treatment of a variety of thrombotic diseases, such as pulmonary embolism and acute myocardial infarction.

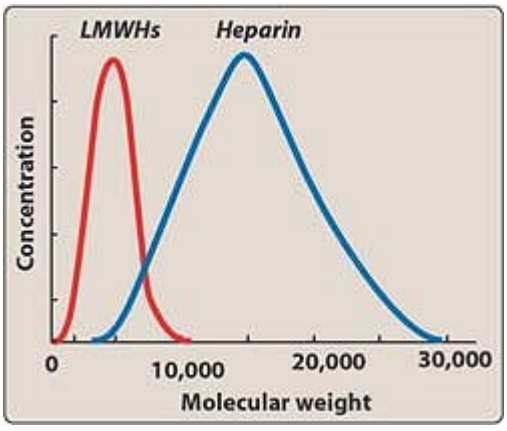

Figure 20.11 Typical molecular weight distributions of *low-molecular-weight heparins (LMWHs)* and heparin.

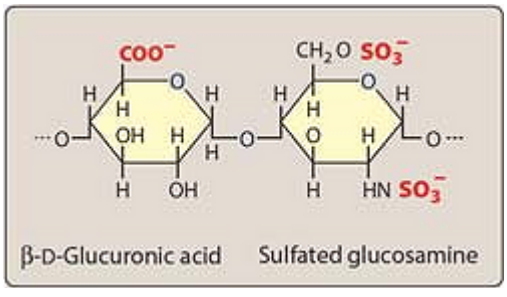

Figure 20.12 Disaccharide component of *heparin* showing negative charges due to carboxyl and sulfate groups.

1. **Mechanism of action:** *Heparin* acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors (Figure 20.13). Antithrombin III is an Î±-globulin. It inhibits serine proteases, including several of the clotting factorsâ€"most importantly, thrombin (Factor IIa) and Factor Xa (see Figure 20.10). In the absence of *heparin*, antithrombin III interacts very slowly with thrombin and Factor Xa. *Heparin* molecules bind antithrombin III inducing a conformational change that accelerates its rate of action about 1000-fold. *Heparin* also serves as a catalytic template for the interaction of antithrombin III and the activated coagulation factors. *Heparin* serves as a true catalyst, allowing antithrombin III to rapidly combine with and inhibit circulating thrombin and Factor Xa (Figure 20.14). In contrast, *LMWHs* complex with antithrombin III and inactivate Factor Xaâ€"including that located on platelet surfacesâ€"but do not bind as avidly to thrombin. Indeed, *LMWHs* are less likely than *heparin* to activate resting platelets. [Note: A unique pentasaccharide sequence contained in *heparin* and *LMWHs* permits their binding to antithrombin III (see Figure 20.14).]

2. **Therapeutic uses:** *Heparin* and the *LMWHs* limit the expansion of thrombi by preventing fibrin formation. *Heparin* has been the major antithrombotic drug for the treatment of acute deep-vein thrombosis and pulmonary embolism. The incidence of recurrent thromboembolic episodes is also decreased. Clinically, *heparin* is used prophylactically to prevent postoperative venous thrombosis in patients undergoing elective surgery (for example, hip replacement) and those in the acute phase of myocardial infarction. Coronary artery rethrombosis after thrombolytic treatment is reduced with *heparin*. The drug is also used in extracorporeal devices (for example, dialysis machines) to prevent thrombosis. *Heparin* and *LMWHs* are the anticoagulants of choice for treating pregnant women with prosthetic heart valves or venous thromboembolism, because these agents do not cross the placenta (due to their large size and negative charge). *Heparin* has the advantage of speedy onset of action, which is rapidly terminated on suspension of therapy. However, it is being supplanted by the *LMWHs*, such as *enoxaparin* and *dalteparin*, because they can be conveniently injected subcutaneously on a patient weightâ€“adjusted basis, have predictable therapeutic effects, and have a more predictable pharmacokinetic profile (Figure 20.15). Specifically, *LMWHs* do not require the same intense monitoring that *heparin* needs, subsequently saving laboratory costs as well as nursing time and costs. Therefore, these advantages make *LMWHs* useful for inpatient and outpatient therapy.

3. **Pharmacokinetics:**

    a. **Absorption:** Whereas the anticoagulant effect with *heparin* occurs within minutes of intravenous administration (or 1 to 2 hours after subcutaneous injection), the maximum antiâ€“Factor Xa activity of the *LMWHs* occurs about 4 hours after subcutaneous injection. (This is in comparison to the vitamin Kâ€“antagonist anticoagulants, such as *warfarin*, the activity of which requires 8 to 12 hours.) *Heparin* must be given parenterally, either in a deep subcutaneous site or intravenously,

because the drug does not readily cross membranes (Figure 20.16). The *LMWHs* are administered subcutaneously. [Note: Intramuscular administration of either agent is contraindicated because of hematoma formation.] *Heparin* is often administered intravenously in a bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of *heparin* for 7 to 10 days, titrating the dose so that the activated partial thromboplastin time (aPTT) is 1.5- to 2.5-fold that of the normal control. It is usually not necessary to obtain such an index with the *LMWHs* because the plasma levels and pharmacokinetics of these drugs are predictable, However, for those patients with renal impairment, the dose should be reduced to account for decreased renal function.

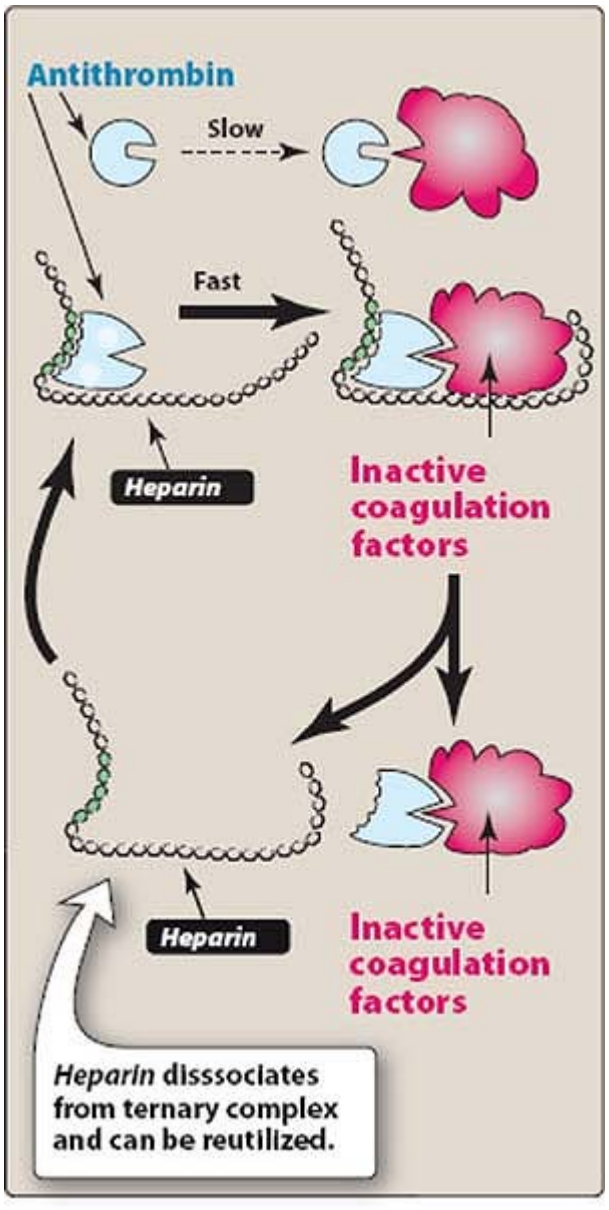

Figure 20.13 *Heparin* accelerates inactivation of coagulation factors by antithrombin.

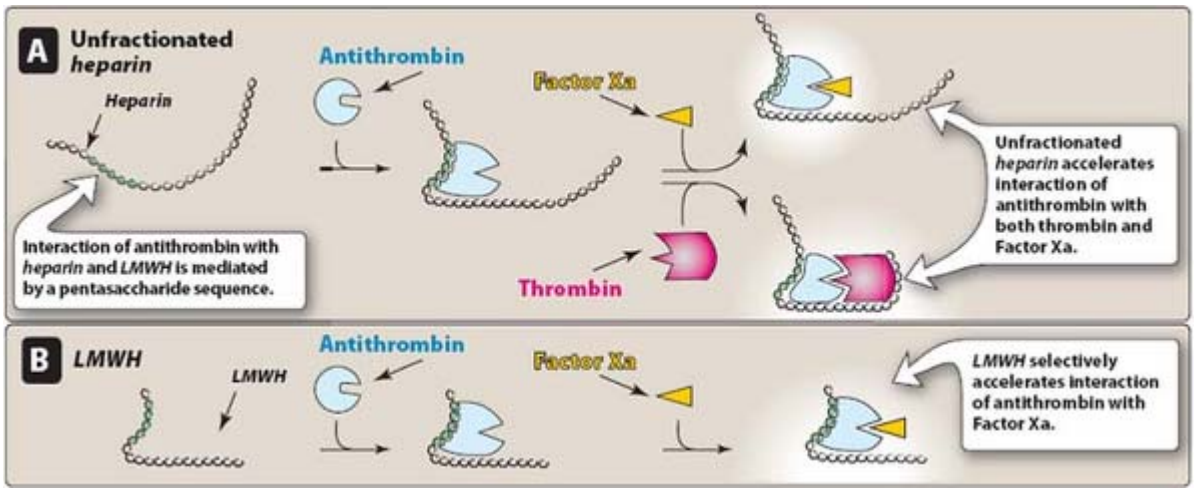

Figure 20.14 *Heparin- and low-molecular-weight heparin (LMWH)*â€“mediated inactivation of thrombin or Factor Xa.

DRUG CHARACTERISTIC	*HEPARIN*	*LMWHs*
Intravenous half-life	2 hours	4 hours
Anticoagulant response	Variable	Predicable
Bioavailability:	20%	90%
Major adverse effect	Frequent bleeding	Less frequent bleeding
Setting for therapy	Hospital	Hospital and outpatient

Figure 20.15 Some properties of *heparin* and *lowmolecular-weight heparins (LMWHs)*

b. **Fate:** In the blood, *heparin* binds to many proteins that neutralize its activity, thereby causing resistance to the drug. Although generally restricted to the circulation, *heparin* is taken up by the monocyte/macrophage system, and it undergoes depolymerization and desulfation to inactive products. [Note: *Heparin* therefore has a longer half-life in patients with hepatic cirrhosis.] The inactive metabolites as well as some of the parent *heparin* and *LMWHs* are excreted into the urine. Therefore, renal insufficiency also prolongs the half-life. Neither *heparin* nor the *LMWHs* cross the placental barrier. The half-life of *heparin* is approximately 1.5 hours, whereas the half-life of the *LMWHs* is two to four times longer than that of *heparin*, ranging from around 3 to 7 hours.

4. **Adverse effects:** Despite early hopes of fewer side effects with *LMWHs*, complications have proven to be similar to those seen with *heparin.* However, exceptions are thromboembolic problems, which are less common.

a. **Bleeding complications:** The chief complication of *heparin* therapy is hemorrhage (Figure 20.17). Careful monitoring of the bleeding time is required to minimize this problem. Excessive bleeding may be managed by ceasing administration of the drug or by treating with *protamine sulfate*. Infused slowly, the latter combines ionically with *heparin* to form a stable, 1:1 inactive complex. It is very important that the dosage of *protamine sulfate* is carefully titrated (1 mg for every 100 units of *heparin* administered) because *heparin sulfate* is a weak anticoagulant and excess amounts may trigger bleeding episodes or worsen bleeding potential.

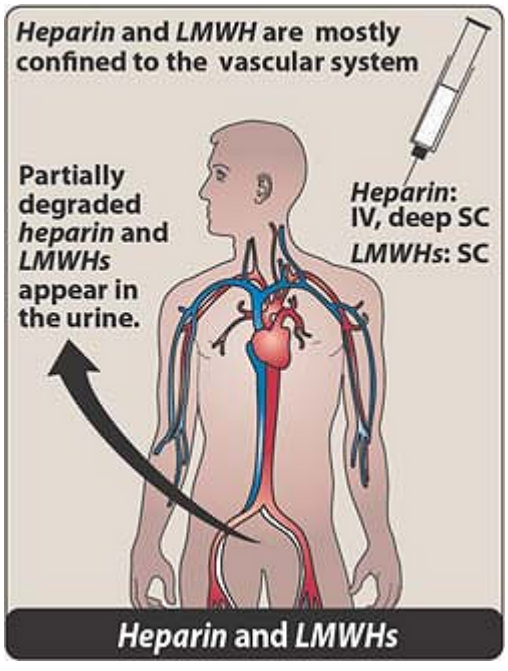

Figure 20.16 Administration and fate of *heparin* and *low-molecularweight heparins (LMWHs)*.

b. **Hypersensitivity reactions:** *Heparin* preparations are obtained from porcine sources and, therefore, may be antigenic. Possible adverse reactions include chills, fever, urticaria, or anaphylactic shock.

c. **Thrombosis:** Chronic or intermittent administration of *heparin* can lead to a reduction in antithrombin III activity, thus decreasing the inactivation of coagulation factors and, thereby, increasing the risk of thrombosis. To minimize this risk, low-dose *heparin* therapy is usually employed.

d. **Thrombocytopenia:** This condition, in which circulating blood contains an abnormally small number of platelets, is a common abnormality among hospital patients and can be caused by a variety of factors. One of these is associated with the use of *heparin* and is called *heparin*-induced thrombocytopenia (HIT). Two types of this abnormality have been identified. Type I is common and involves a mild decrease in platelet number due to nonimmunologic mechanisms. Type I usually occurs within the first 5 days of treatment and is not serious. In Type II, platelets are activated by an immunoglobulin Gâ€“mediated reaction with a *heparin*â€“platelet Factor 4 complex, causing platelet aggregation and release of platelet contents. This can result in thrombocytopenia and thrombosisâ€”dangerous complications of *heparin* therapy occurring between the fifth and fourteenth days of treatmentâ€”that range from mild to life-threatening. Platelet counts can drop 50 percent or more, and thromboembolic complications can develop. Although Type II is relatively rare, the wide use of *heparin* has resulted in a greater recognition of its role in thrombocytopenia. It is imperative that *heparin* therapy be discontinued in such patients. *Heparin* can be

replaced by another anticoagulant, such as *lepirudin* or *argatroban* (see below).

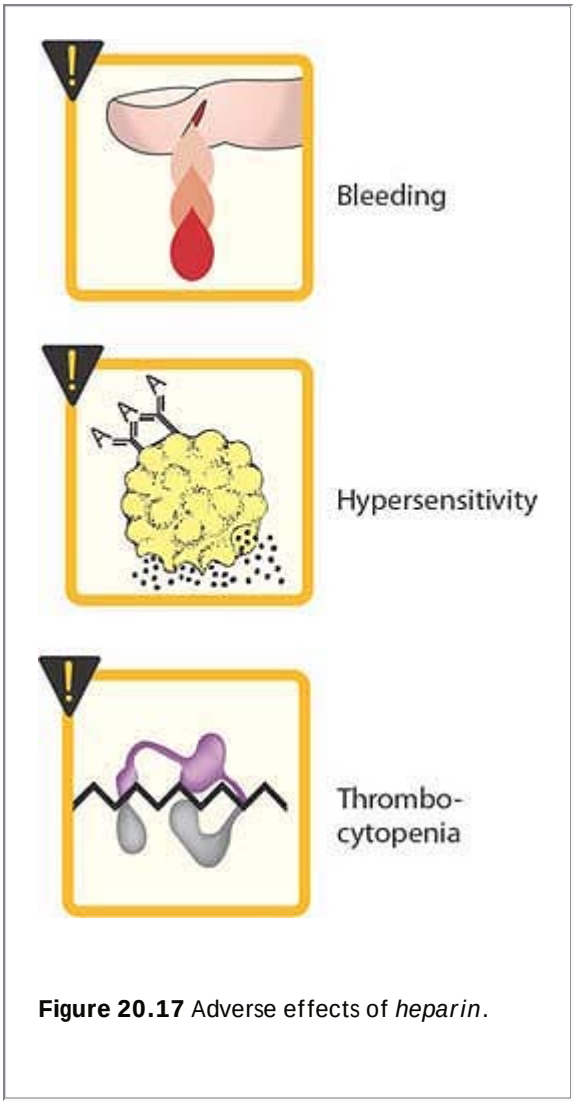

Figure 20.17 Adverse effects of *heparin*.

e. **Heparin** may produce abnormal liver function tests, and osteoporosis has been observed in patients on long term *heparin* therapy.

f. **Contraindications:** *Heparin* is contraindicated for patients who are hypersensitive to it, have bleeding disorders, are alcoholics, or are having or have had recent surgery of the brain, eye, or spinal cord.

B. Other parenteral anticoagulants

1. **Lepirudin:** A highly specific, direct thrombin antagonist, *lepirudin* [leh-PEE-roo-din] is a polypeptide that is closely related to *hirudin*â€"a thrombin inhibitor derived from medicinal leech saliva. *Lepirudin* is produced in yeast cells by recombinant DNA technology. One molecule of *lepirudin* binds to one molecule of thrombin, resulting in blockade of the thrombogenic activity of thrombin. It has little effect on platelet aggregation. Administered intravenously (Figure 20.18), *lepirudin* is effective in the treatment of HIT and other thromboembolic disorders, and it can prevent further thromboembolic complications. *Lepirudin* has a half-life of about 1 hour, and it undergoes hydrolysis. The parent drug and its fragments are eliminated in the urine. Bleeding is the major adverse effect of treatment with *lepirudin*, and it can be exacerbated by concomitant thrombolytic therapy, such as treatment with *streptokinase* or *alteplase*. About half the patients receiving *lepirudin* develop antibodies. However, the drug-antibody complex retains anticoagulant activity. Because renal elimination of the complex is slower than that of the free drug, the anticoagulant effect may be increased. It is

important to monitor the aPTT and renal function when a patient is receiving *lepirudin*.

2. **Argatroban:** *Argatroban* [ar-GA-troh-ban] is a parenteral anticoagulant that is a small molecule that direct inhibits thrombin. *Argatroban*

is used prophylactically for the treatment of thrombosis in patients with HIT, and it is also approved for use during percutaneous coronary interventions in patients who have or are at risk for developing HIT. *Argatroban* is metabolized in the liver and has a half life of about 50 minutes. It is monitored by aPTT. The patient's hemoglobin and hematocrit must also be monitored. Because *argatroban* is metabolized in the liver, it may be used in patients with renal dysfunction but it should be used cautiously in patients with hepatic impairment. As with other agents in this class, the major side effect is bleeding.

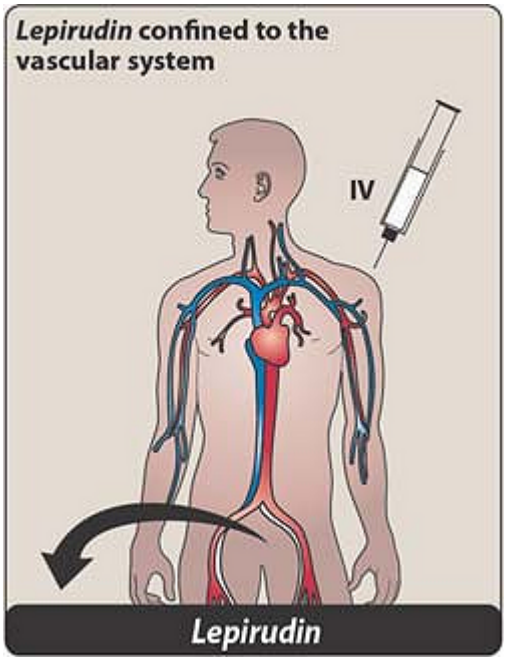

Figure 20.18 Administration of *lepirudin*.

3. **Fondaparinux:** *Fondaparinux* [fawn-da-PEH-rih-nox] is the first in a new class of pentasaccharide anticoagulants that is purely synthetically, derived with no variable biologic activity. It has been recently approved by the U.S. Food and Drug Administration for use in the prophylaxis of deep-vein thrombosis that could lead to pulmonary embolism in patients undergoing hip fracture surgery, hip replacement surgery, and knee replacement surgery. This agent selectively inhibits only Factor Xa. By selectively binding to antithrombin III, *fondaparinux* potentiates (300- to 1000-fold) the innate neutralization of Factor Xa by antithrombin III. It is well absorbed from the subcutaneous route with a predictable pharmacokinetic profile. *Fondaparinux* requires less monitoring than *heparin*. *Fondaparinux* is eliminated in urine mainly as unchanged drug with an elimination half-life of 17 to 21 hours. It is contraindicated in patients with severe renal impairment (<30 mL/min). Bleeding episodes are the major side effect of *fondaparinux* therapy. Thrombocytopenia, in particular Type II thrombocytopenia, is not a problem, and this agent may be used in patients with HIT.

C. Vitamin K antagonists

The coumarin anticoagulants, which include *warfarin* [WAR-far-in], and *dicumarol* [dye-KOO-ma-role] (*bishydroxycoumarin*), owe their action to their ability to antagonize the cofactor functions of vitamin K. The only

therapeutically relevant coumarin anticoagulant is *warfarin*. Initially used as a rodenticide, *warfarin* is now widely employed clinically as an oral anticoagulant. With the availability of the *LMWHs* and platelet aggregate inhibitors, however, use of the vitamin K antagonists is decreasing. The potential morbidity associated with the use of *warfarin* makes it important to identify those patients who are truly at risk for thrombosis. Even careful monitoring to keep the prothrombin time at 1.5- to 2.5-fold longer than normal values does not prevent bleeding complications in about 20 percent of the patients.

1. **Mechanism of action:** Several of the protein coagulation factors (including Factors II, VII, IX, and X; see Figure 20.10) require vitamin K as a cofactor for their synthesis by the liver. These factors undergo vitamin Kâ€“dependent posttranslational modification, whereby a number of their glutamic acid residues are carboxylated to form *Î³*-carboxyglutamic acid residues (Figure 20.19). The *Î³*-carboxyglutamyl residues bind calcium ions, which are essential for interaction between the coagulation factors and platelet membranes.

In the carboxylation reactions, the vitamin Kâ€“dependent carboxylase fixes CO_2 to form the new COOH group on glutamic acid. The reduced vitamin K cofactor is converted to vitamin K epoxide during the reaction. Vitamin K is regenerated from the epoxide by vitamin K epoxide reductaseâ€”the enzyme that is inhibited by *warfarin*. *Warfarin* treatment results in the production of clotting factors with diminished activity (10%â€“40% of normal), because they lack sufficient *Î³*-carboxyglutamyl side chains. Unlike *heparin*, the anticoagulant effects of *warfarin* are not observed until 8 to 12 hours after drug administration, but peak effects may be delayed for 72 to 96 hoursâ€”the time required to deplete the pool of circulating clotting factors. The anticoagulant effects of *warfarin* can be overcome by the administration of vitamin K. However, reversal following administration of vitamin K takes approximately 24 hours (the time necessary for degradation of already synthesized clotting factors).

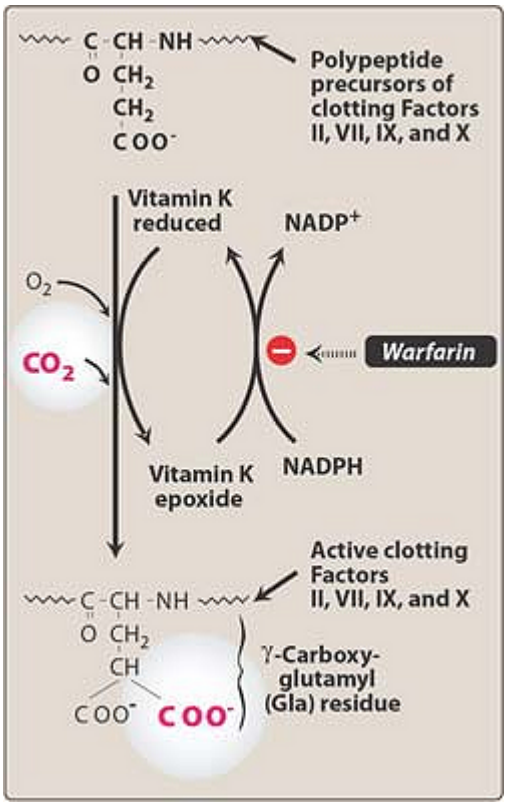

Figure 20.19 Mechanism of action of *warfarin*. NADP+ = oxidized form of nicotinamide-adenine dinucleotide phosphate; NADPH = reduced form of nicotinamide-adenine dinucleotide phosphate.

2. **Therapeutic uses:** *Warfarin* is used to prevent the progression or recurrence of acute deep-vein thrombosis or pulmonary embolism after initial *heparin* treatment. It is also used for the prevention of venous thromboembolism during orthopaedic or gynecologic surgery. Prophylactically, it is used in patients with acute myocardial infarction, prosthetic heart valves, or chronic atrial fibrillation.

3. **Pharmacokinetics:**

   a. **Absorption:** *Warfarin* is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation). Although food may delay absorption, it does not affect the extent of absorption of the drug. *Warfarin* is 99 percent bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk. However, drugs that have a greater affinity for the albumin binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity. *Warfarin* readily crosses the placental barrier. The mean half life of *warfarin* is approximately 40 hours, but this value is highly variable among individuals. Prothrombin time, a measure of the extrinsic pathway, may be used to monitor *warfarin* therapy. In the 1990s, the international normalized ratio (INR) was adopted to monitor *warfarin* concentration. The INR corrects for variations that would occur with different thromboplastin reagents, between different hospitals, or when a single hospital gets a new lot of reagent. The goal of *warfarin* therapy is an INR of 2 to 3 for most indications and 2.5 to 3.5 in patients with mechanical heart valves.

   b. **Fate:** The products of *warfarin* metabolism, catalyzed by the cytochrome P450 system, are inactive. After conjugation to glucuronic acid, they are excreted in the urine and stool.

4. **Adverse effects:**

   a. **Bleeding disorders:** The principal untoward reaction caused by *warfarin* treatment is hemorrhage. Therefore, it is important to frequently monitor and adjust the anticoagulant effect. Minor bleeding may be treated by withdrawal of the drug and administration of oral vitamin K_1; severe bleeding requires that greater doses of the vitamin be given intravenously. Whole blood, frozen plasma, or plasma concentrates of the blood factors may also be employed to arrest hemorrhaging. Skin lesions

   and necrosis are rare complications of *warfarin* therapy and are observed primarily in women. Purple toe syndrome, a painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with *warfarin* therapy.

   b. **Drug interactions:** *Warfarin* has numerous drug interactions that may potentiate or attenuate its anticoagulant effect. The list of interacting drugs is extensive. A summary of some of the important interactions is shown in Figure 20.20.

   c. **Disease states:** Vitamin K deficiency, hepatic disease that impairs synthesis of the clotting factors or affects *warfarin* metabolism, and hypermetabolic states that increase catabolism of the vitamin Kâ€“dependent clotting factors can all influence the hypoprothrombinemic state of the patient and augment the response to the oral anticoagulants.

   d. **Contraindications:** *Warfarin* should never be used during pregnancy, because it is teratogenic and can cause abortion as well as birth defects.

VII. Thrombolytic Drugs

Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasminâ€”a serine protease that hydrolyzes fibrin and, thus, dissolves clots (Figure 20.21). *Streptokinase*, one of the first such agents to be approved, causes a systemic fibrinolytic state that can lead to bleeding problems. *Alteplase* acts more locally on the thrombotic fibrin to produce fibrinolysis. Figure 20.22 compares these commonly used thrombolytic agents. Clinical experience has shown nearly equal efficacy between *streptokinase* and *alteplase*. Unfortunately, thrombolytic therapy is unsuccessful in about 20 percent of infarcted arteries, and about 15 percent of the arteries that are opened will later close again. In the case of acute myocardial infarction, the thrombolytic drugs are reserved for those instances when angioplasty is not an option or until the patient can be taken to a facility that performs percutaneous coronary interventions. Fibrinolytic drugs may lyse both normal and pathologic thrombi.

A. Common characteristics of thrombolytic agents

1. **Mechanism of action:** The thrombolytic agents share some common features. All act either directly or indirectly to convert plasminogen to plasmin, which in turn cleaves fibrin, thus lysing thrombi (see Figure 20.21). Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation, because clots become more resistant to lysis as they age. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregability and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as *aspirin*, or antithrombotics, such as *heparin*.

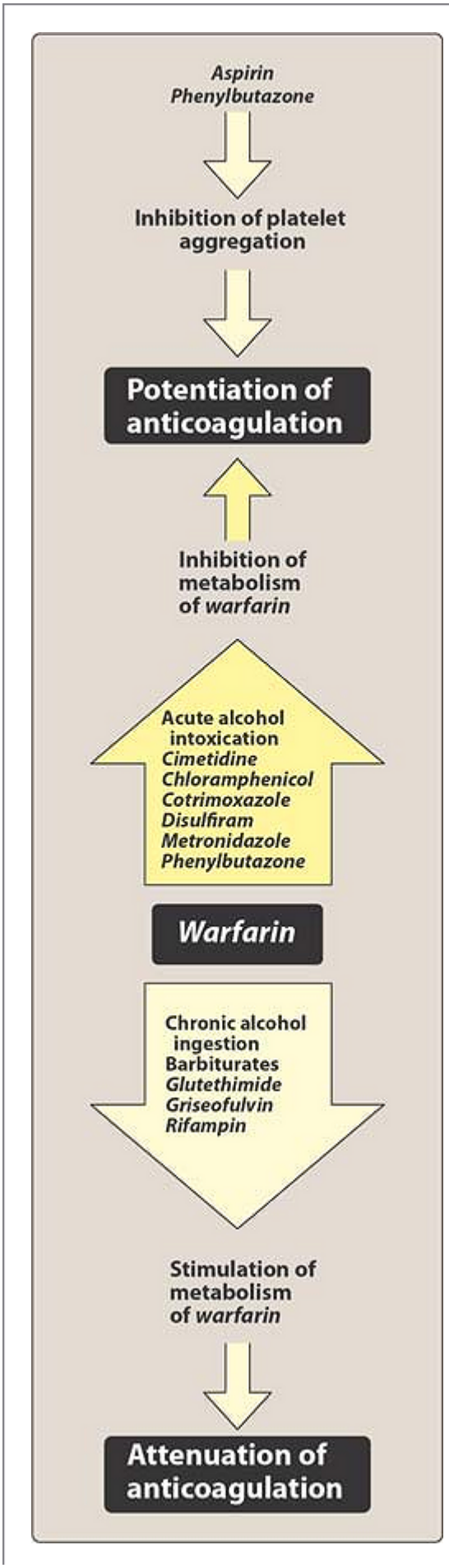
Aspirin
Phenylbutazone
Inhibition of platelet aggregation
Potentiation of anticoagulation
Inhibition of metabolism of warfarin
Acute alcohol intoxication
Cimetidine
Chloramphenicol
Cotrimoxazole
Disulfiram
Metronidazole
Phenylbutazone
Warfarin
Chronic alcohol ingestion
Barbiturates
Glutethimide
Griseofulvin
Rifampin
Stimulation of metabolism of warfarin
Attenuation of anticoagulation

Figure 20.20 Drugs affecting the anticoagulant effect of *warfarin*.

2. **Therapeutic uses:** Originally used for the treatment of deep-vein thrombosis and serious pulmonary embolism, thrombolytic drugs are now being used less frequently for these conditions. Their

tendency to cause bleeding has also blunted their used in treating acute myocardial infarction or peripheral arterial thrombosis. However, thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions. Thrombolytic agents are also used to dissolve clots that result in strokes.

3. **Pharmacokinetics:** For myocardial infarction, intracoronary delivery of the drugs is the most reliable in terms of achieving recanalization. However, cardiac catheterization may not be possible in the 2- to 6-hour â€œtherapeutic window,â€ beyond which significant myocardial salvage becomes less likely. Thus, thrombolytic agents are usually administered intravenously, because this route is rapid, is inexpensive, and does not have the risks of catheterization.

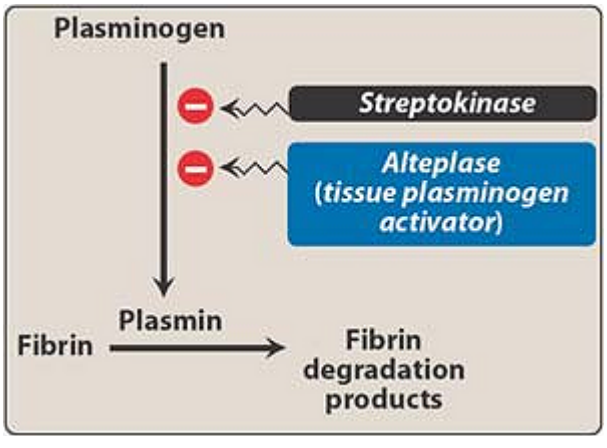

Figure 20.21 Activation of plasminogen by fibrinolytic agents.

4. **Adverse effects:** The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major side effect. For example, a previously unsuspected lesion, such as a peptic ulcer, may hemorrhage following injection of a thrombolytic agent (Figure 20.23). These drugs are contraindicated in patients with healing wounds, pregnancy, history of cerebrovascular accident, or metastatic cancer. Continued presence of thrombogenic stimuli may cause rethrombosis after lysis of the initial clot.

B. Alteplase

Alteplase [AL-te-place] (formerly known as *tissue plasminogen activator*, or *tPA*) is a serine protease originally derived from cultured human melanoma cells. It is now obtained as a product of recombinant DNA technology.

1. **Mechanism of action:** *Alteplase* has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. Thus, *alteplase* is said to be â€œfibrin selective,â€ and at low doses, it has the advantage of lysing only fibrin, without unwanted degradation of

other proteinsâ€”notably fibrinogen. This contrasts with *streptokinase*, which acts on free plasminogen and induces a general fibrinolytic state. [Note: At dose levels of *alteplase* currently in use clinically, circulating plasminogen may be activated, resulting in hemorrhage.]

2. **Therapeutic uses:** *Alteplase* is approved for the treatment of myocardial infarction, massive pulmonary embolism, and acute ischemic stroke. *Alteplase* seems to be superior to *streptokinase* in dissolving older clots and, ultimately, may be approved for other applications. *Alteplase,* administered within 3 hours of the onset of ischemic stroke, significantly improves clinical outcomeâ€”that is, the patient's ability to perform activities of daily living (Figure 20.24). *Reteplase* (*Retavase*) is similar to *alteplase* and can be used as an alternative.

3. **Pharmacokinetics:** *Alteplase* has a very short half-life (about 5 minutes) and, therefore, is administered as a total dose equal to 0.9 mg/kg. Ten percent of the total dose injected intravenously as a bolus and the remaining drug is administered over 60 minutes.

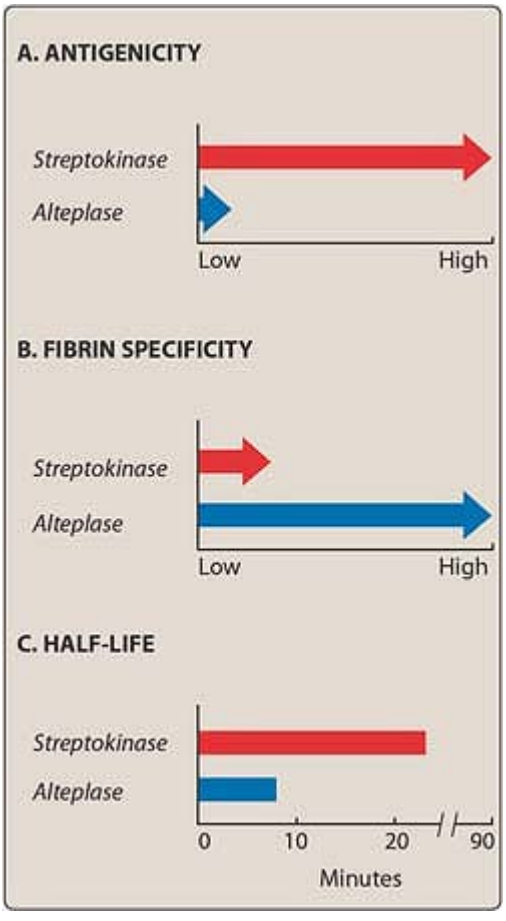

Figure 20.22 A comparison of *streptokinase* and *alteplase*.

4. **Adverse effects:** Bleeding complications, including gastrointestinal and cerebral hemorrhages, may occur.

C. Streptokinase

Streptokinase [strep-toe-KYE-nase] is an extracellular protein purified from culture broths of Group C Î²-hemolytic streptococci.[6]

1. **Mechanism of action:** *Streptokinase* has no enzymic activity. Instead, it forms an active one-to-one complex with plasminogen. This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin (Figure 20.25). In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen as well as clotting Factors V and VII (Figure 20.26).

2. **Therapeutic uses:** *Streptokinase* is approved for use in acute pulmonary embolism, deep-vein thrombosis, acute myocardial infarction, arterial thrombosis, and occluded access shunts.

3. **Pharmacokinetics:** *Streptokinase* therapy is instituted within 4 hours of a myocardial infarction and is infused for 1 hour. Its half-life is less than half an hour. Thromboplastin time is monitored and maintained at two- to five-fold the control value. On discontinuation of treatment, either *heparin* or oral anticoagulants may be administered.

4. **Adverse effects:**

    a. **Bleeding disorders:** Activation of circulating plasminogen by *streptokinase* leads to elevated levels of plasmin, which may precipitate bleeding by dissolving hemostatic plugs (see Figure 20.23). In the rare instance of life-threatening hemorrhage, *aminocaproic acid* may be administered.

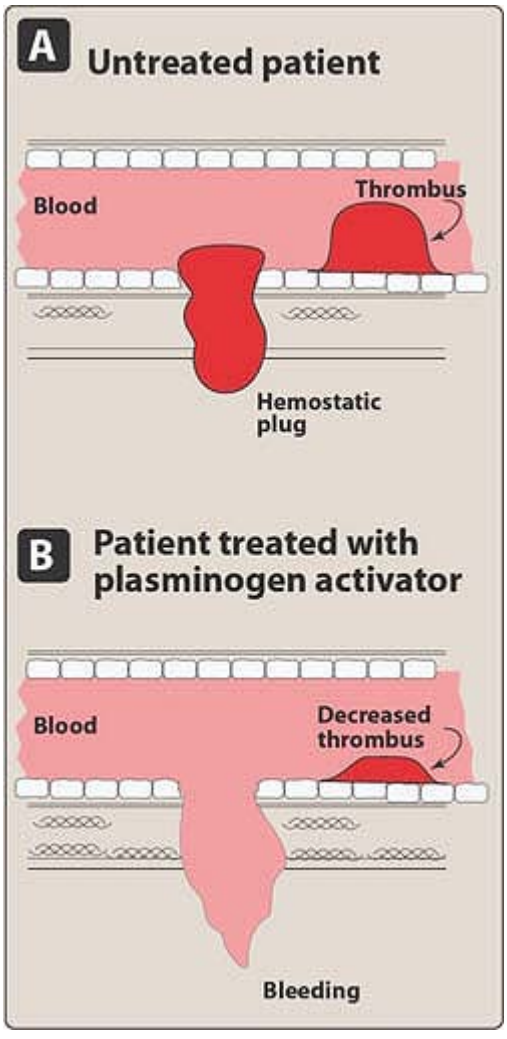

Figure 20.23 Degradation of an unwanted thrombus and a beneficial hemostatic plug by plasminogen activators.

b. **Hypersensitivity:** *Streptokinase* is a foreign protein and is antigenic. Rashes, fever, and rarely, anaphylaxis occur. Because most individuals have had a streptococcal infection sometime in their lives, circulating antibodies against *streptokinase* are likely to be present in most patients. These antibodies can combine with *streptokinase* and neutralize its fibrinolytic properties. Therefore, sufficient quantities of *streptokinase* must be administered to overwhelm the antibodies and provide a therapeutic concentration of plasmin. Fever, allergic reactions, and therapeutic failure may be associated with the presence of antistreptococcal antibodies in the patient. The incidence of allergic reactions is approximately 3 percent.

D. Anistreplase (anisoylated plasminogen streptokinase activator complex

Anistreplase is a preformed complex of *streptokinase* and plasminogen and it is considered to be a prodrug. *Streptokinase* must be released, and only plasminogen to which it was associated will get converted to plasmin.

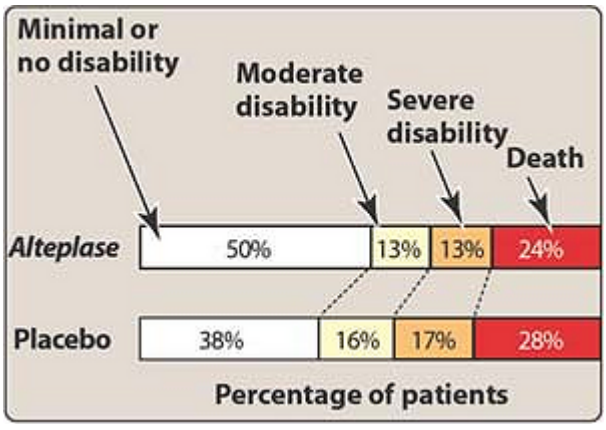

Figure 20.24 Outcome at 12 months of stroke patients treated with *alteplase* within 3 hours of the onset of symptoms compared to those treated with placebo.

VIII. Drugs Used to Treat Bleeding

Bleeding problems may have their origin in naturally occurring pathologic conditions, such as hemophilia, or as a result of fibrinolytic states that may arise after gastrointestinal surgery or prostatectomy. The use of anticoagulants may also give rise to hemorrhage. Certain natural proteins and vitamin K, as well as synthetic antagonists, are effective in controlling this bleeding. For example, hemophilia is a consequence of a deficiency in plasma coagulation factors, most frequently Factors VIII and IX. Concentrated preparations of these factors are available from human donors. However, these preparations carry the risk of transferring viral infections. Blood transfusion is also an option for treating severe hemorrhage.

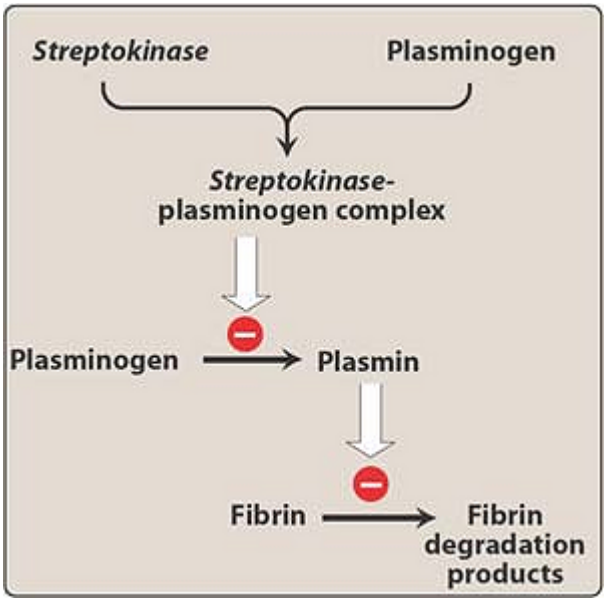

Figure 20.25 Mechanism of action of *streptokinase*.

A. Aminocaproic acid and tranexamic acid

Fibrinolytic states can be controlled by the administration of *aminocaproic* [a-mee-noe-ka-PROE-ic] *acid* or *tranexamic* [tran-ex-AM-ic] *acid*. Both agents are synthetic, inhibit plasminogen activation, are orally active, and are excreted in the urine. A potential side effect of treatment is intravascular thrombosis.

B. Protamine sulfate

Protamine [PROE-ta-meen] *sulfate* antagonizes the anticoagulant effects of *heparin*. This protein is derived from fish sperm or testes and is high in arginine content, which explains its basicity. The positively charged *protamine* interacts with the negatively charged *heparin*, forming a stable complex without anticoagulant activity. Adverse effects of drug administration include hypersensitivity as well as dyspnea, flushing, bradycardia, and hypotension when rapidly injected.

C. Vitamin K

That vitamin K_1 (*phytonadione*) administration can stem bleeding problems due to the oral anticoagulants is not surprising, because those substances act by interfering with the action of the vitamin (see Figure 20.19). The response to vitamin K is slow, requiring about 24 hours (time to synthesize new coagulation factors). Thus, if immediate hemostasis is required, fresh-frozen plasma should be infused.

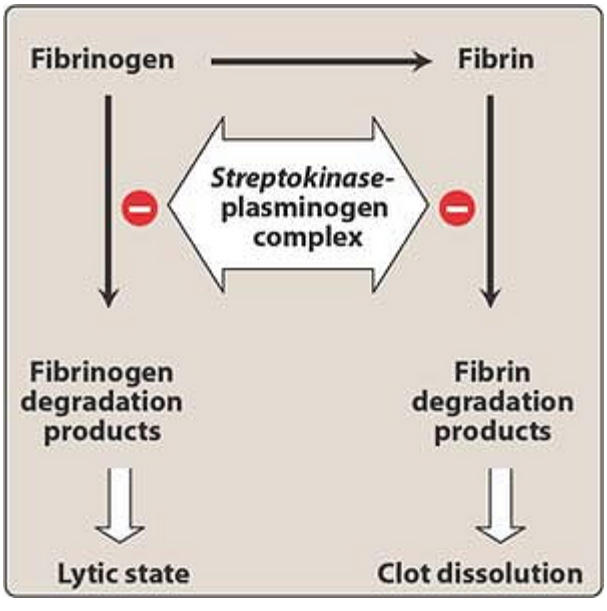

Figure 20.26 Streptokinase degrades both fibrin and fibrinogen.

D. Aprotinin

Aprotinin [ah-PRO-ti-nin] is a serine protease inhibitor that stops bleeding by blocking plasmin. It can inhibit *streptokinase*. It is approved for prophylactic use to reduce perioperative blood loss and the need for blood

transfusion in patients undergoing cardiopulmonary bypass surgery. *Aprotinin* may cause renal dysfunction and hypersensitivity (anaphylactic) reactions. In addition, *aprotinin* should not be administered to patients who have already been exposed to the drug within the previous 12 months due to the possibility of anaphylactic reactions.

IX. Agents Used to Treat Anemia

Anemia is defined as a below-normal plasma hemoglobin concentration resulting from a decreased number of circulating red blood cells or an abnormally low total hemoglobin content per unit of blood volume. Anemia can be caused by chronic blood loss, bone marrow abnormalities, increased hemolysis, infections, malignancy, endocrine deficiencies, renal failure, and

a number of other disease states. Anemia can be at least temporarily corrected by transfusion of whole blood. A large number of drugs cause toxic effects on blood cells, hemoglobin production, or erythropoietic organs, which in turn may cause anemia. In addition, nutritional anemias are caused by dietary deficiencies of substances such as iron, folic acid, or vitamin B_{12} (cyanocobalamin) that are necessary for normal erythropoiesis.

A. Iron

Iron is stored in intestinal mucosal cells as ferritin (an iron-protein complex) until needed by the body. Iron deficiency results from acute or chronic blood loss, from insufficient intake during periods of accelerated growth in children, or in heavily menstruating or pregnant women. Thus, iron deficiency results from a negative iron balance due to depletion of iron stores and/or inadequate intake, culminating in hypochromic microcytic anemia (due to low iron and small-sized red blood cells). Supplementation with *ferrous sulfate* is required to correct the deficiency. Gastrointestinal disturbances caused by local irritation are the most common adverse effects of iron supplements.

B. Folic acid

The primary use of *folic acid* is in treating deficiency states that arise from inadequate levels of the vitamin. Folate deficiency may be caused by 1) increased demand (for example, pregnancy and lactation), 2) poor absorption caused by pathology of the small intestine, 3) alcoholism, or 4) treatment with drugs that are dihydrofolate reductase inhibitors (for example, *methotrexate* or *trimethoprim*). A primary result of folic acid deficiency is megaloblastic anemia (large-sized red blood cells), which is caused by diminished synthesis of purines and pyrimidines. This leads to an inability of erythropoietic tissue to make DNA and, thereby, proliferate[7] (Figure 20.27). [Note: To avoid neurological complications of vitamin B_{12} deficiency, it is important to evaluate the basis of the megaloblastic anemia prior to instituting therapy. Vitamin B_{12} and folate deficiency causes similar symptoms (see below).] *Folic acid* is well absorbed in the jejunum unless pathology is present. If excessive amounts of the vitamin are ingested, they are excreted in the urine and feces. Oral *folic acid* administered has no known toxicity.

C. Cyanocobalamin (vitamin B12)

Deficiencies of vitamin B_{12} can result from either low dietary levels or, more commonly, poor absorption of the vitamin due to the failure of gastric parietal cells to produce intrinsic factor (as in pernicious anemia) or a loss of activity of the receptor needed for intestinal uptake of the vitamin.[8] Intrinsic factor is a GP produced by the parietal cells of the stomach and it is required for vitamin B_{12} absorption. In patients with bariatric surgery (surgical gastrointestinal treatment for obesity), vitamin B_{12} supplementation is required in large oral doses, sublingually or once a month by the parenteral route. Nonspecific malabsorption syndromes or gastric resection can also cause vitamin B_{12} deficiency. The vitamin may be administered orally (for dietary deficiencies), intramuscularly,

or deep subcutaneously (for pernicious anemia). [Note: *Folic acid* administration alone reverses the hematologic abnormality and, thus, masks the B_{12} deficiency, which can then proceed to severe neurologic dysfunction and disease. Therefore, megaloblastic anemia should not be treated with *folic acid* alone but, rather, with a combination of *folate* and vitamin B_{12}.] Therapy must be continued for the remainder of the life of a patient suffering from pernicious anemia. There are no known adverse effects of this vitamin.

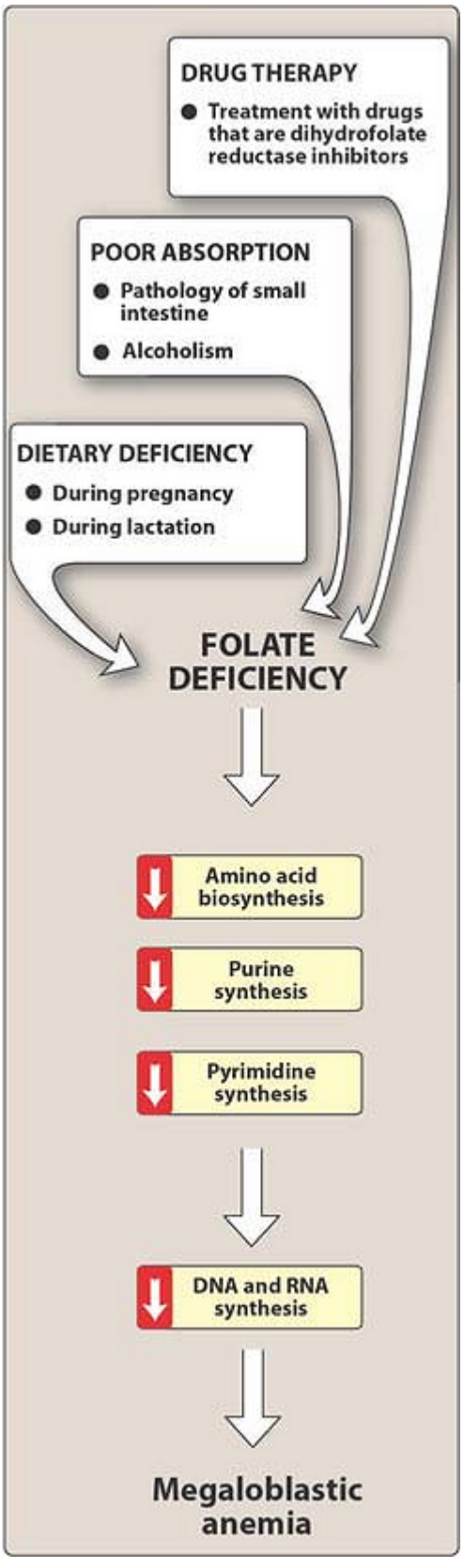

Figure 20.27 Causes and consequences of folic acid depletion.

D. Erythropoietin and darbepoetin

Erythropoietin [ee-rith-ro-POI-eh-tin] is a GP, normally made by the kidney, that regulates red blood cell proliferation and differentiation in bone marrow. Human *erythropoietin*, produced by recombinant DNA technology, is effective in the treatment of anemia caused by end-stage renal disease, anemia associated with human immunodeficiency virus infection, and anemia in some cancer patients. *Darbepoetin* [dar-be-POE-e-tin] is a long-acting version of *erythropoietin* that differs from *erythropoietin* by the addition of two carbohydrate chains, which improves its biologic activity. Therefore, *darbepoetin* has decreased clearance and has a half life about three times that of *erythropoietin*. Due to its delayed onset of action, *darbepoetin* has no value in acute treatment of anemia. Supplementation with iron may be required to assure an adequate response. The protein is usually administered intravenously in renal dialysis patients, but the subcutaneous route is preferred. Side effects are generally well tolerated but may include elevation in blood pressure and arthralgia in some cases. [Note: The former may be due to increases in peripheral vascular resistance and/or blood viscosity.] When *erythropoietin* is used to target hemoglobin concentration >12 g/dL, serious and life-threatening cardiovascular events, increased risk of death, shortened time to tumor progression and/or decreased survival have been observed. The recommendations for all patients receiving *erythropoietin* include a minimum effective dose that does not exceed a hemoglobin level of 12 g/dL, and this should not rise more than 1 g/dL over a 2-week period.

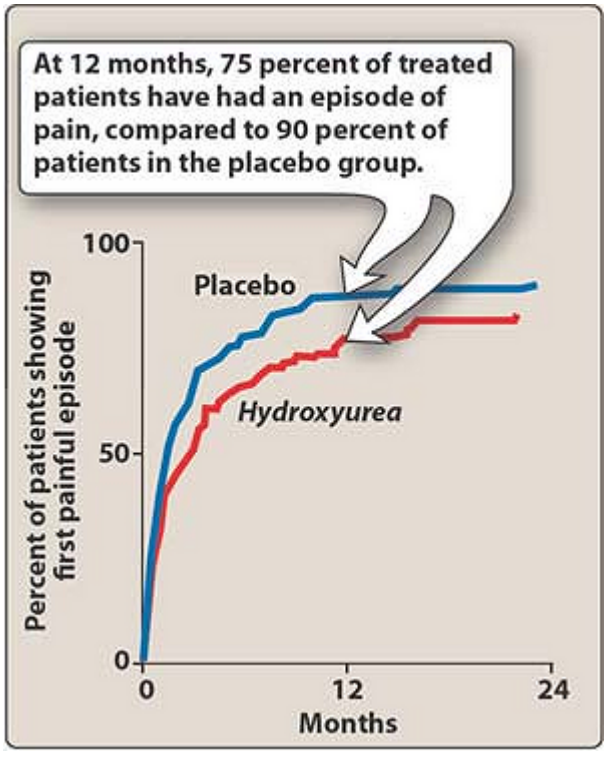

Figure 20.28 Effect of treatment with hydroxyurea on the percentage of sickle-cell patients experiencing first painful episode.

X. Agents Used to Treat Sickle-Cell Disease

Clinical trials have shown that *hydroxyurea* can relieve the painful clinical course of sickle-cell disease (Figure 20.28). *Hydroxyurea* is currently also being used to treat chronic myelogenous leukemia and polycythemia vera. In sickle-cell disease, the drug apparently increases fetal hemoglobin levels, thus diluting the abnormal hemoglobin S (HbS).[9] This process takes several months. Polymerization of HbS is delayed in the treated patients so that painful

crises are not caused by sickled cells blocking capillaries and causing tissue anoxia. Important side effects of *hydroxyurea* include bone marrow suppression and cutaneous vasculitis. It is important that *hydroxyurea* is administered under the supervision of a physician experienced in the treatment of sickle-cell disease.

Study Questions

Choose the ONE best answer.

20.1 A 22-year-old woman who experienced pain and swelling in her right leg presented at the emergency room. An ultrasound study showed thrombosis in the popliteal vein. The patient, who was in her second trimester of pregnancy, was treated for 7 days with intravenous unfractionated heparin. The pain resolved during the course of therapy, and the patient was discharged on Day 8. Which one of the following drugs would be most appropriate out-patient follow-up therapy for this patient, who lives 100 miles from the nearest hospital?

A. Warfarin.

B. Aspirin.

C. Alteplase.

D. Unfractionated heparin.

E. Low-molecular-weight heparin (LMWH).

View Answer

20.2 A 60-year-old man is diagnosed with deep-vein thrombosis. The patient was treated with a bolus of heparin, and a heparin drip was started. One hour later, he was bleeding profusely from the intravenous site. The heparin therapy was suspended, but the bleeding continued. Protamine was administered intravenously, and the bleeding resolved. The protamine:

A. Degraded the heparin.

B. Inactivates antithrombin.

C. Activates the coagulation cascade.

D. Activates tissue-plasminogen activator.

E. Ionically combines with heparin.

View Answer

20.3 A 54-year-old male with a prosthetic aortic valve replacement complained to his family physician of black and tarry stools. Physical examination and vital signs were unremarkable except for subconjunctival hemorrhages and bleeding gums. Stools tested positive for heme, and hematuria was observed. The patient has been receiving oral warfarin since his valve replacement 1 year earlier. Prothrombin time was found to be significantly elevated. Which one of the following therapies would provide the most rapid recovery from the observed bleeding secondary to warfarin treatment?

A. Intravenous vitamin K.

B. Transfusion of fresh-frozen plasma.

C. Intravenous protamine.

D. Immediate withdrawal of warfarin treatment.

E. Intravenous administration of anti-warfarin antibodies.