Treatment of Congestive Heart Failure

16

I. OVERVIEW OF CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a condition in which the heart is unable to pump sufficient blood to meet the needs of the body. CHF can be caused by an impaired ability of the cardiac muscle to contract or by an increased workload imposed on the heart. CHF is accompanied by abnormal increases in blood volume and interstitial fluid; the heart, veins, and capillaries are therefore generally dilated with blood. Hence the term "congestive" heart failure, since the symptoms include pulmonary congestion with left heart failure, and peripheral edema with right heart failure. Underlying causes of CHF include arteriosclerotic heart disease, 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 heart failure. The number of newly diagnosed patients with CHF is increasing because more individuals now survive acute myocardial infarction.

The therapeutic goal for CHF is to increase cardiac output. Three classes of drugs have been shown to be clinically effective in reducing symptoms and prolonging life: 1) vasodilators that reduce the load on the myocardium; 2) diuretic agents that decrease extracellular fluid volume; and 3) inotropic agents that increase the strength of contraction of cardiac muscle (Figure 16.1). [Note: These agents relieve the symptoms of cardiac insufficiency but do not reverse the underlying pathologic condition.] Knowledge of the physiology of cardiac muscle contraction is clearly essential to an understanding of the compensatory responses evoked by the failing heart, as well as the actions of drugs used to treat CHF.

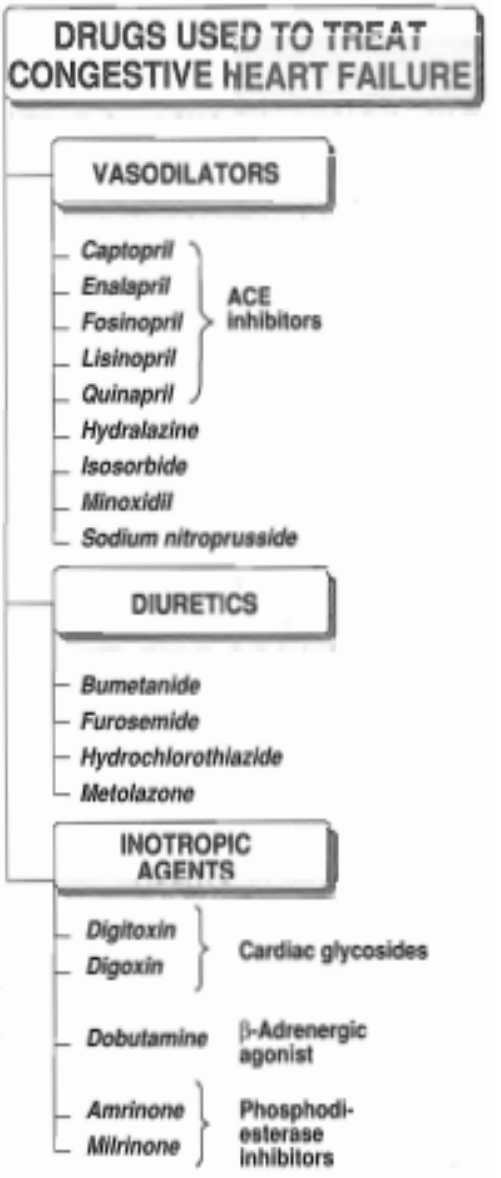

Figure 16.1
Summary of drugs used to treat congestive heart failure.

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by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
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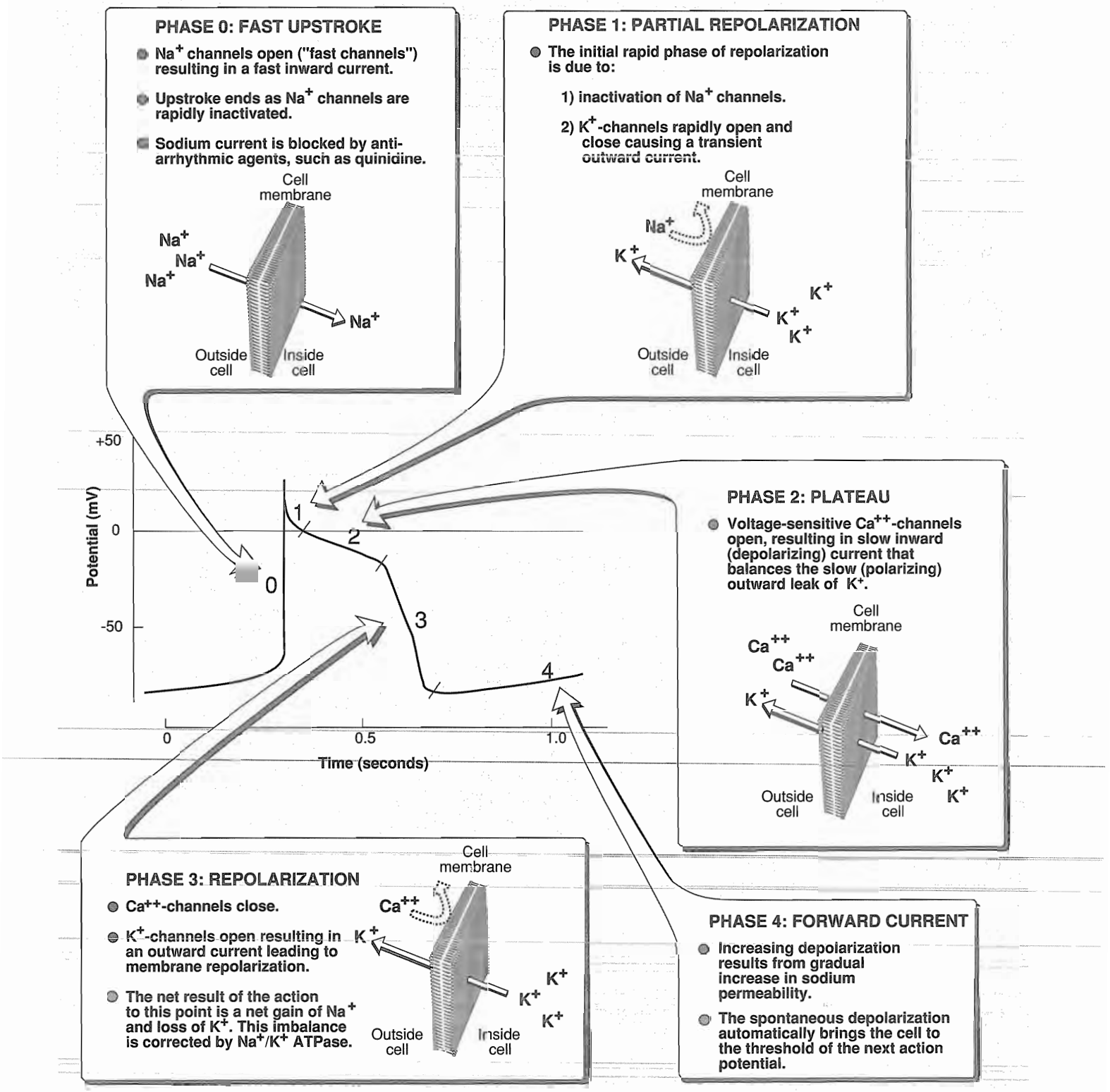


Figure 16.2
Action potential of a Purkinje fiber.

II. PHYSIOLOGY OF MUSCLE CONTRACTION

The myocardium, like smooth and skeletal muscle, responds to stimulation by depolarization of the membrane; this is followed by shortening of the contractile proteins and ends with relaxation and return to the resting state (Figure 16.2). However, unlike skeletal muscle, which shows graded contractions depending on the number of muscle cells 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 "pacemaker" cells located in the sinoatrial (SA), and atrioventricular (AV) nodes. The cardiac cells also have an unusually long action potential, which can be divided into five phases (0 to 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 either adenosine triphosphate (ATP)- or voltage-sensitive.

B. Cardiac contraction

The contractile machinery of the myocardial cell is essentially the same as 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 increase the sensitivity of the contractile machinery to calcium) result in an increase in the 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 two sources. The first is from outside the cell, where opening of voltage-sensitive calcium channels causes an immediate rise in free cytosolic calcium. The second source is the release of calcium 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 (Figure 16.3).

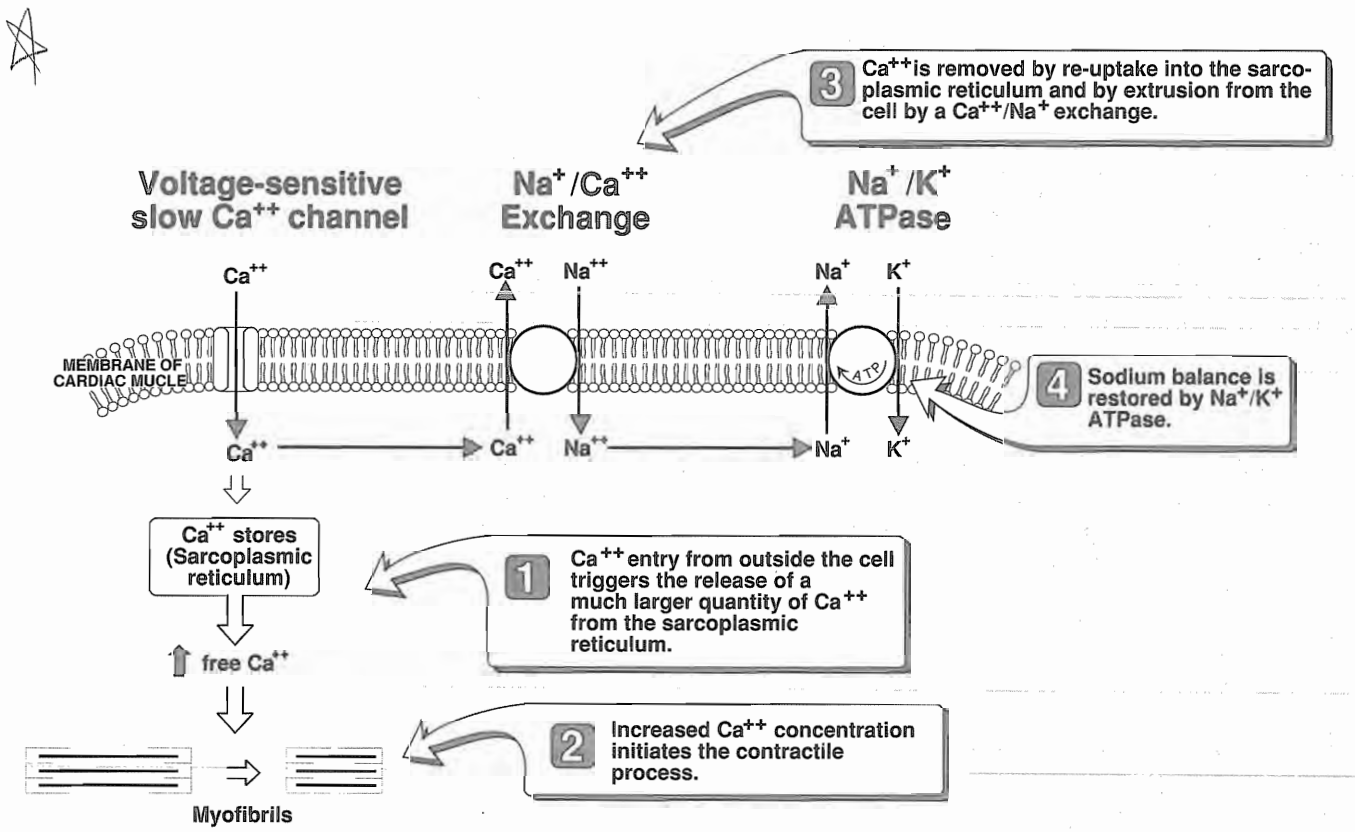


Figure 16.3
Ion movements during the contraction of cardiac muscle.

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

b. Uptake of calcium by the sarcoplasmic reticulum and mitochondria: Calcium is also recaptured by the sarcoplasmic reticulum and the mitochondria. More than 99% 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 CHF

The failing heart evokes three major compensatory mechanisms to enhance cardiac output (Figure 16.4).

1. **Increased sympathetic activity:** Baroreceptors sense a decrease in blood pressure, and trigger activation of β-adrenergic receptors in the heart. This results in an increase in heart rate and a greater force of contraction of the heart muscle (Figure 16.4). In addition, vasoconstriction (α_1-mediated) enhances venous return and increases cardiac preload. These compensatory responses increase the work of the heart and, therefore, can contribute to the further decline in cardiac function.

2. **Fluid retention:** A fall in cardiac output decreases blood flow to the kidney, prompting the release of renin, with a resulting increase in the synthesis of angiotensin II and aldosterone (see p. 181). 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 (Figure 16.4). These compensatory responses increase the work of the heart and, therefore, can contribute to the further decline in cardiac function.

3. **Myocardial hypertrophy:** The heart increases in size, and the chambers dilate. Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive elongation of the fibers results in weaker contractions. This type of failure is termed systolic failure and is a result of a ventricle unable to pump effectively. Less commonly, patients with CHF may have diastolic dysfunction—a term applied when the ventricles' ability 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 decreases 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 heart failure.

D. Decompensated heart failure

If the mechanisms listed above adequately restore cardiac output, then the heart failure 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 heart failure is termed decompensated.

E. Therapeutic strategies in CHF

Chronic heart failure is typically managed by reduction in physical activity, low dietary intake of sodium (less than 1500 mg sodium per day), and treatment with vasodilators, diuretics and inotropic agents. Drugs that may precipitate or exacerbate CHF—nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, β-blockers, calcium channel-blockers and some antiarrhythmic drugs—should be avoided if possible. Patients with CHF complain of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and dependent edema.

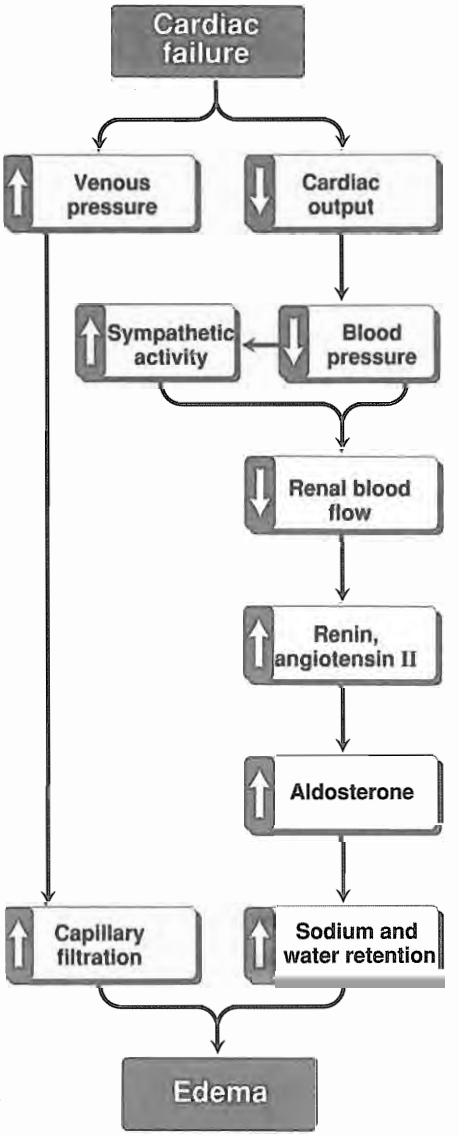


Figure 16.4
Cardiovascular consequences of heart failure.

III. VASODILATORS

In CHF, the impaired contractile function of the heart is exacerbated by compensatory increases in both preload and afterload. Preload is the volume of blood that fills the ventricle during diastole. Elevated preload causes overfilling of the heart, which increases the workload. Afterload is the pressure that must be overcome for the heart to pump blood into the arterial system. Elevated afterload causes the heart to work harder to pump blood into the arterial system. Vasodilators are useful in reducing excessive preload and afterload. Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance; arterial dilators reduce systemic arteriolar resistance and decrease afterload.

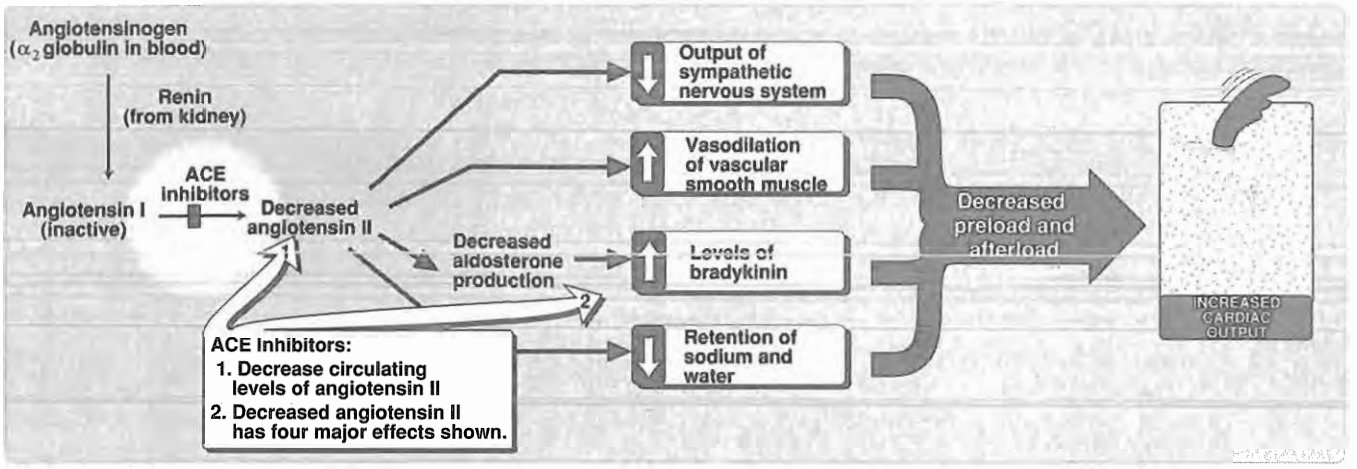


Figure 16.5
Effects of ACE inhibitors.

A. Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors are the agents of choice in CHF and are superior to other vasodilators.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 heart:** ACE inhibitors decrease vascular resistance, venous tone, and blood pressure, resulting in an increased cardiac output (Figure 16.5). ACE inhibitors also blunt the usual angiotensin II-mediated increase in epinephrine and aldosterone seen in CHF. ACE inhibitors improve clinical signs and symptoms in patients also receiving a diuretic and/or *digoxin* (see p. 157). The use of ACE inhibitors in the treatment of CHF 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 heart failure. [Note: Reduction in mortality is due primarily to a decrease in deaths caused by progressive heart failure.] Treatment with *enalapril* also reduced 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 who do not show signs or symptoms of volume overload. ACE inhibitors are useful in decreasing CHF in asymptomatic patients with ejection fraction less than 35% (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 treating patients with all stages of left ventricular failure, with and without symptoms, and therapy should be initiated immediately after myocardial infarction. See p. 186 for the use of ACE inhibitors in the treatment of hypertension.

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

B. Direct smooth muscle relaxants

Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance; arterial dilators reduce systemic arteriolar resistance and decrease afterload. Nitrates (see p. 175) are commonly employed venous dilators for patients with congestive heart failure. If the patient is intolerant of ACE inhibitors, the combination of *hydralazine* and *isosorbide dinitrate* is most commonly used. *Amlodipine* and *felodipine* (see p. 188) have less negative inotropic effect than other calcium channel blockers, and seem to decrease sympathetic nervous activity.

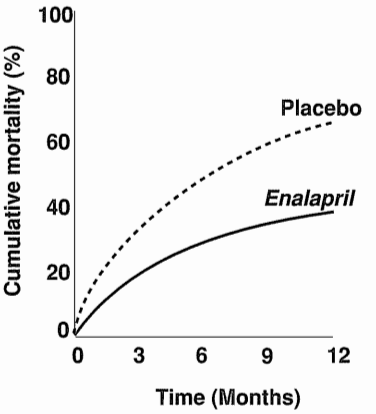


Figure 16.6
Effect of *enalapril* on mortality of patients with congestive heart failure.

IV. DIURETICS

Diuretics relieve pulmonary congestion and peripheral edema. These agents are 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 oxygen demand. Diuretics also decrease afterload by reducing plasma volume, thus decreasing blood pressure. Thiazide diuretics (see p. 229) are relatively mild diuretics and lose efficacy if patient creatinine clearance is less than 50 ml/min. Loop diuretics (see p. 227) are used in patients with renal insufficiency. [Note: Overdoses of loop diuretics can lead to profound hypovolemia.]

V. 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 are therefore widely used in treating heart failure. Like the antiarrhythmic drugs described in Chapter 17, the cardiac glycosides influence the

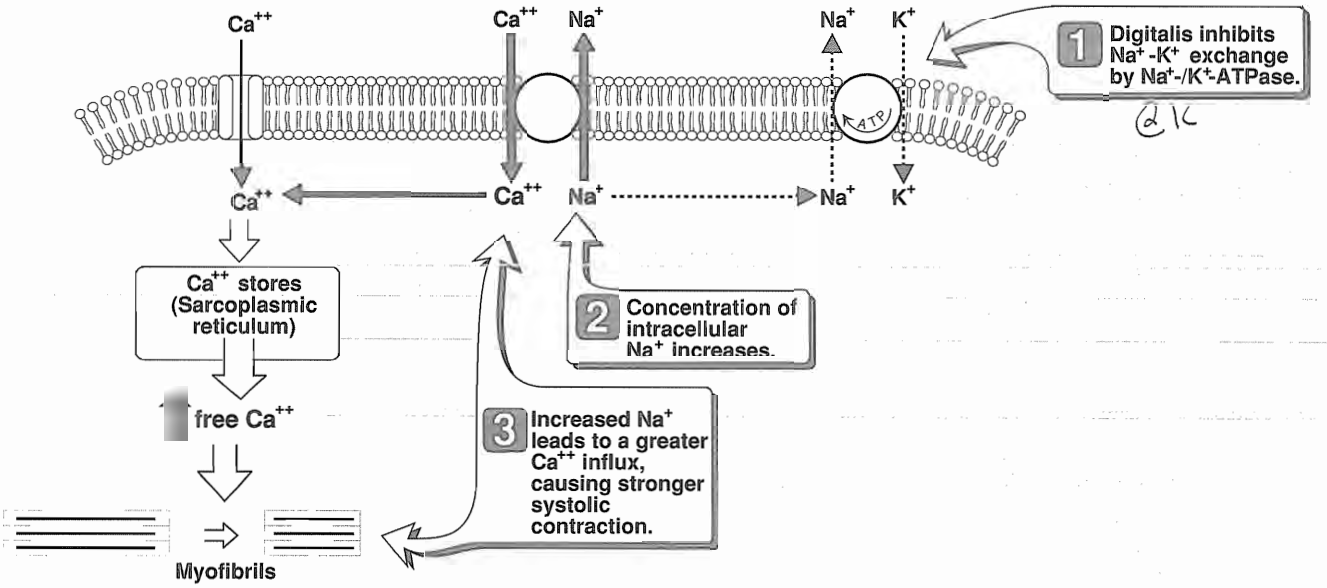
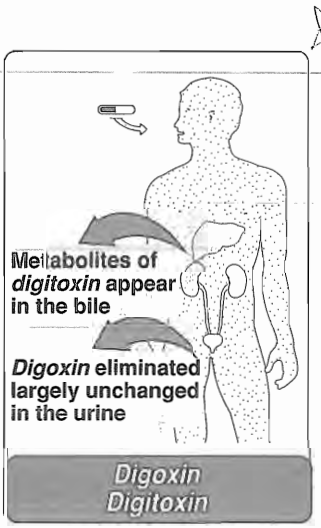


Figure 16.7
Mechanism of action of cardiac glycosides, or digitalis.

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 (see p. 23). The digitalis glycosides include *digitoxin* [di ji TOX in], and the most widely used agent, *digoxin* [di JOX in].

1. Mode of action:

a. Regulation of cytosolic calcium concentration: Cardiac glycosides combine reversibly with the sodium-potassium ATPase of the cardiac cell membrane (Figure 16.7), resulting in an inhibition of pump activity. This causes an increase in the intracellular sodium concentration, which favors the transport of calcium into the cell via the sodium-calcium exchange mechanism (Figure 16.7). The elevated intracellular calcium levels result in an increase in the systolic force of contraction.



b. Increased contractility of the cardiac muscle: Administration of digitalis glycosides increases the force of cardiac contractility causing the cardiac output to more closely resemble that of the normal heart (Figure 16.8). An 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 is diminished. [Note: In the normal heart, the positive inotropic effect of digitalis is counteracted by compensatory autonomic reflexes.]

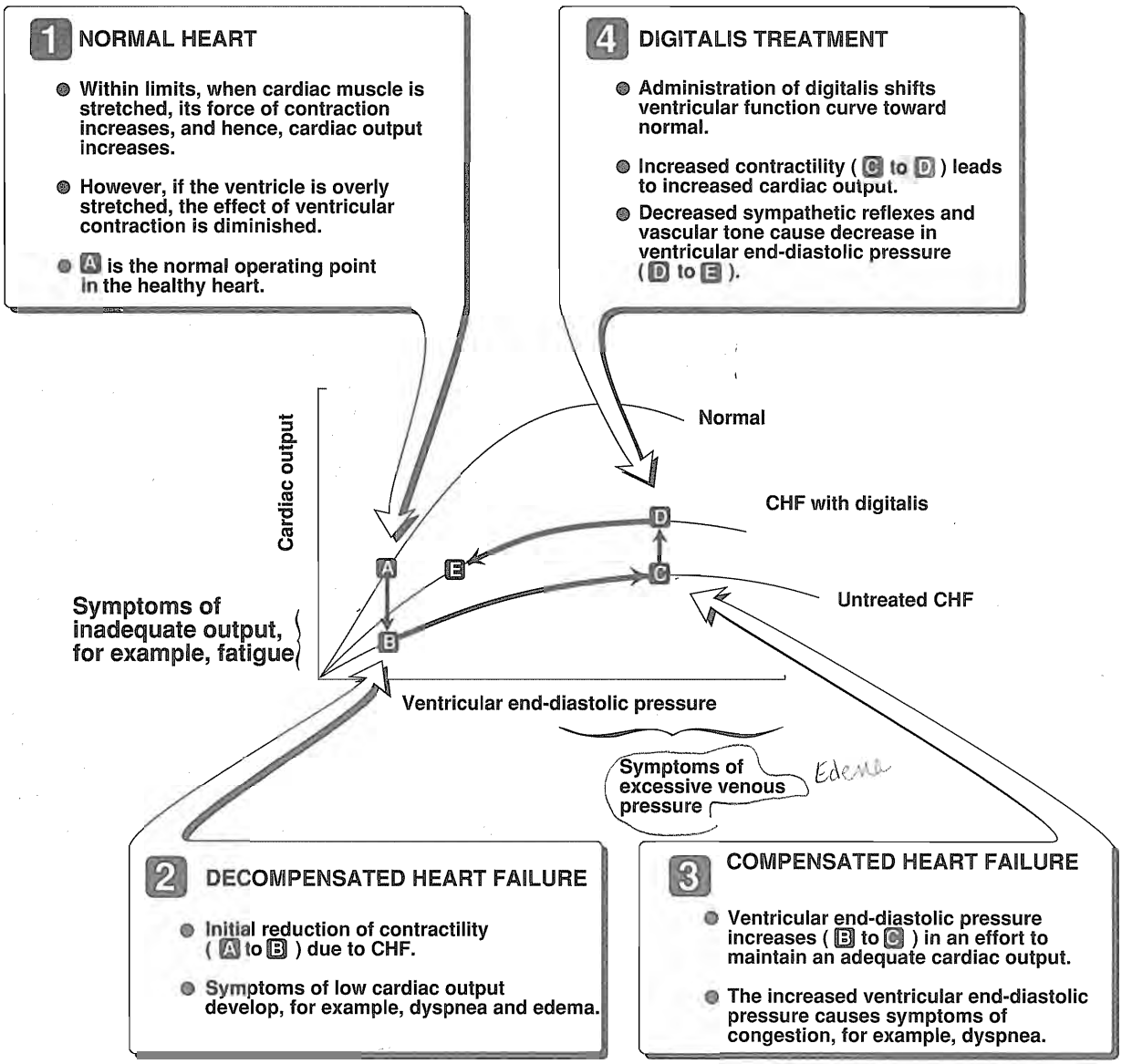


Figure 16.8
Ventricular function curves in the normal heart, in congestive heart failure (CHF), and in CHF treated with digitalis.

2. **Therapeutic uses:** *Digoxin* therapy is indicated in patients with severe left ventricular systolic dysfunction after initiation of diuretic and vasodilation therapy. *Digoxin* is not indicated in patients with diastolic or right-sided heart failure. *Dobutamine*, another inotropic agent, can be given intravenously in the hospital, but at present no good oral inotropic agents exist other than *digoxin*. Patients with mild to moderate heart failure will often respond to treatment with ACE inhibitors and diuretics and do not require *digoxin*.

3. **Pharmacokinetics:** All digitalis glycosides possess the same pharmacologic actions, but they vary in potency and pharmacokinetics

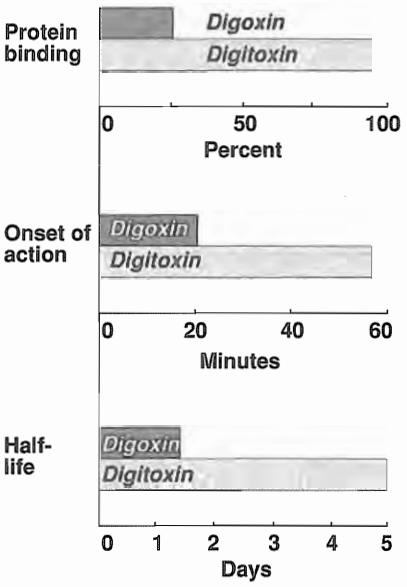


Figure 16.9
A comparison of the properties of *digoxin* and *digitoxin*.

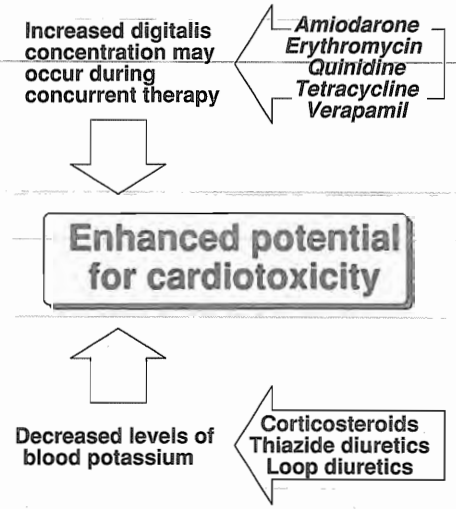


Figure 16.10
Drugs interacting with *digoxin* and other digitalis glycosides.

(Figure 16.9). These drugs are absorbed after oral administration. Note that *digitoxin* binds strongly to proteins in the extravascular space, resulting in a large volume of distribution. *Digoxin* has the advantage of a relatively short half-life, which allows better treatment of toxic reactions. *Digoxin* also has a more rapid onset of action, making it useful in emergency situations. *Digoxin* is eliminated largely unchanged in the urine. *Digitoxin* is extensively metabolized by the liver before excretion in the feces, and hepatic disease may require decreased doses.

4. Adverse effects

Digitalis toxicity is one of the most commonly encountered adverse drug reactions. Side effects can often be managed by discontinuing cardiac glycoside therapy, determining serum potassium levels, and if indicated, by 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 (FAB fragments) to *digoxin,* which bind and inactivate the drug. Types of adverse effects include:

a. Cardiac effects: The major effect is progressively more severe dysrhythmia, moving from decreased or blocked atrioventricular nodal conduction, paroxysmal supraventricular tachycardia, to the conversion of atrial flutter to atrial fibrillation, premature ventricular depolarization, ventricular fibrillation, and finally, to complete heart block. 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. CNS effects: These include headache, fatigue, confusion, blurred vision, alteration of color perception, and haloes 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 can usually 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* can cause *digitalis* intoxication both by displacing *digitalis* from plasma protein binding sites, and by competing with *digitalis* for renal excretion. *Verapamil* also displaces *digitalis* from plasma protein binding sites and can increase *digoxin* levels by 50 to 75%; this may require a reduction in the dose of *digoxin*. Potassium-depleting diuretics, corticosteroids, and a variety of other drugs can also increase digitalis toxicity (Figure 16.10). Hypothyroidism, hypoxia, renal

failure, and myocarditis are also predisposing factors to *digitalis* toxicity.

B. β-Adrenergic agonists

β-Adrenergic stimulation improves cardiac performance by positive inotropic effects and vasodilation. *Dobutamine* (see p. 66) is the most commonly used inotropic agent other than digitalis. *Dobutamine* leads to an increase in intracellular 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 16.11). *Dobutamine* must be given by intravenous infusion, and is primarily used in the treatment of acute heart failure 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 (Figure 16.11). This results in an increase in intracellular calcium, and therefore cardiac contractility, as discussed above for the β-adrenergic agonists. [Note: Recent clinical trials have shown that *amiodarone* did not reduce the incidence of sudden death or prolong survival in patients with CHF (see p. 172). *Milrinone* showed increased mortality and no beneficial effects.]

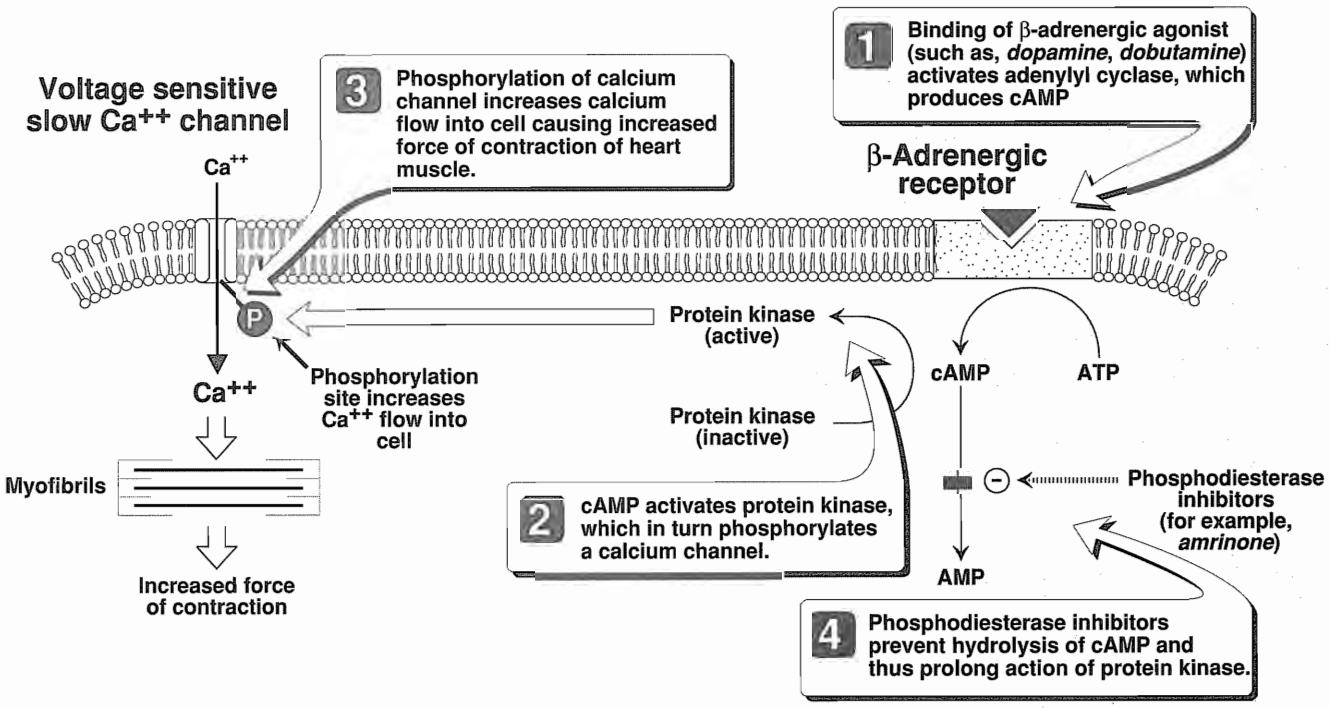


Figure 16.11
Sites of action of β-adrenergic agonists on heart muscle.

Choose the ONE best answer.

16.1 Which of the following most directly describes the mechanism of action of digitalis?

A. Inhibits sodium-potassium ATPase.
B. Decreases intracellular sodium concentration.
C. Increases the intracellular level of ATP.
D. Stimulates production of cAMP.
E. Decreases release of calcium from the sarcoplasmic reticulum.

Correct answer = A. The cardiac glycosides bind to and block the action of the sodium-potassium ATPase. The cardiac glycosides inhibit the extrusion of sodium from the cell, leading to an increase in sodium levels within the cell. The production of ATP is not significantly changed in the treated heart. Stimulation of the production of cAMP is the mechanism of action of the β-adrenergic agonists. By increasing intracellular calcium, digitalis stimulates the SR to release additional calcium.

16.2 Which one of the following drugs would be the most appropriate single drug therapy for mild congestive heart failure?

A. A vasodilator such as hydralazine.
B. A cardiac glycoside such as digoxin.
C. A β-adrenergic agonist such as norepinephrine.
D. A diuretic such as hydrochlorothiazide.
E. An ACE inhibitor, such as captopril.

Correct answer = E. ACE inhibitors may be considered sole therapy in patients who present with mild dyspnea on exertion and who do not show signs or symptoms of volume overload.

16.3 All of the following are useful in the treatment of digitalis overdose EXCEPT:

A. anti-digoxin FAB fragments.
B. dietary potassium supplements for patients being treated concomitantly with diuretics.
C. lidocaine.
D. phenytoin.
E. quinidine.

Correct choice = E. Quinidine may increase digitalis concentration by reducing renal clearance. Purified fragments of antibodies specific for digoxin are used to treat potentially lethal toxicities. Hypokalemia is frequently encountered in individuals taking loop or thiazide diuretics and can predispose the patient to digitalis toxicity. Antiarrhythmic drugs, such as lidocaine and phenytoin, are used for ventricular tachycardia.

16.4 Which one of the following statements concerning congestive heart failure is correct?

A. Digitoxin is more widely used than digoxin because it has a shorter half-life.
B. Serum levels of digoxin can be decreased by quinidine.
C. Loop diuretics are used in patients with renal insufficiency.
D. Digoxin is eliminated primarily in the bile.
E. Congenital heart defects are the most common cause of congestive heart failure.

Correct answer = C.

16.5 Which one of the following aggravates a digitalis-induced arrhythmia?

A. Decreased serum calcium.
B. Decreasing heart rate with propranolol.
C. Decreased serum sodium.
D. Decreased serum potassium.
E. Decreased serum angiotensin II.

Correct answer = D. Low serum potassium further decreases the efflux of sodium from the cardiac cell, leading to an enhanced toxicity. Low levels of circulating calcium diminish the digitalis-stimulated calcium uptake into the cardiac cell. Agents that decrease the heart rate tend to diminish the toxicity of digitalis. Low serum sodium enhances the efflux of sodium from the cardiac cell, leading to a diminished sodium-calcium exchange.

Antiarrhythmic Drugs

17

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 "pacemaker" 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 currents (see p. 152). This depolarization is fastest in the sinoatrial (SA) node (the normal initiation site of the action potential) and 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 simple—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 (1) to beat too slowly (sinus bradycardia); (2) to beat too rapidly (sinus or ventricular tachycardia, atrial or ventricular premature depolarization, atrial flutter); (3) to respond to impulses originating from sites other than the SA node; or (4) to respond to impulses traveling along accessory (extra) pathways that lead to deviant depolarizations (A-V reentry, Wolff-Parkinson White syndrome). In order 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 the abnormality—the atria, 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 (ECG) findings.

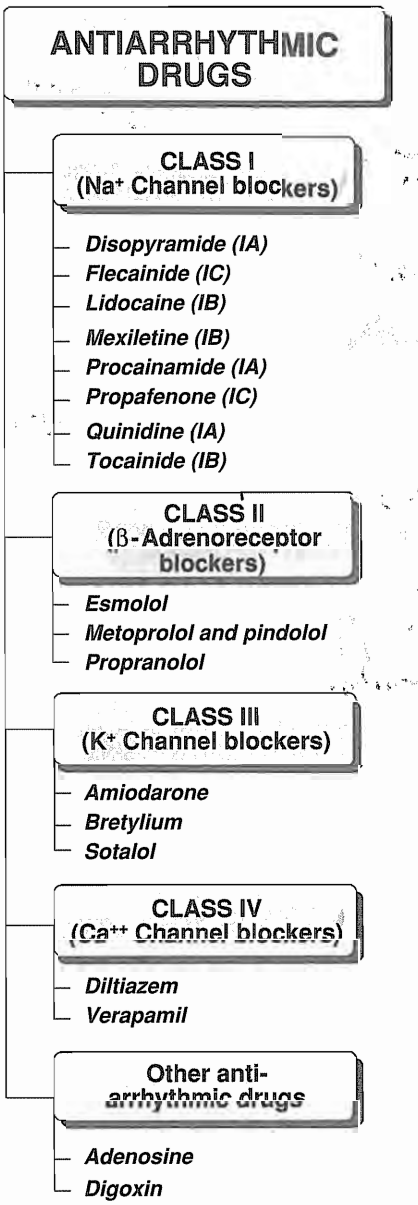


Figure 17.1
Summary of antiarrhythmic drugs.

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by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
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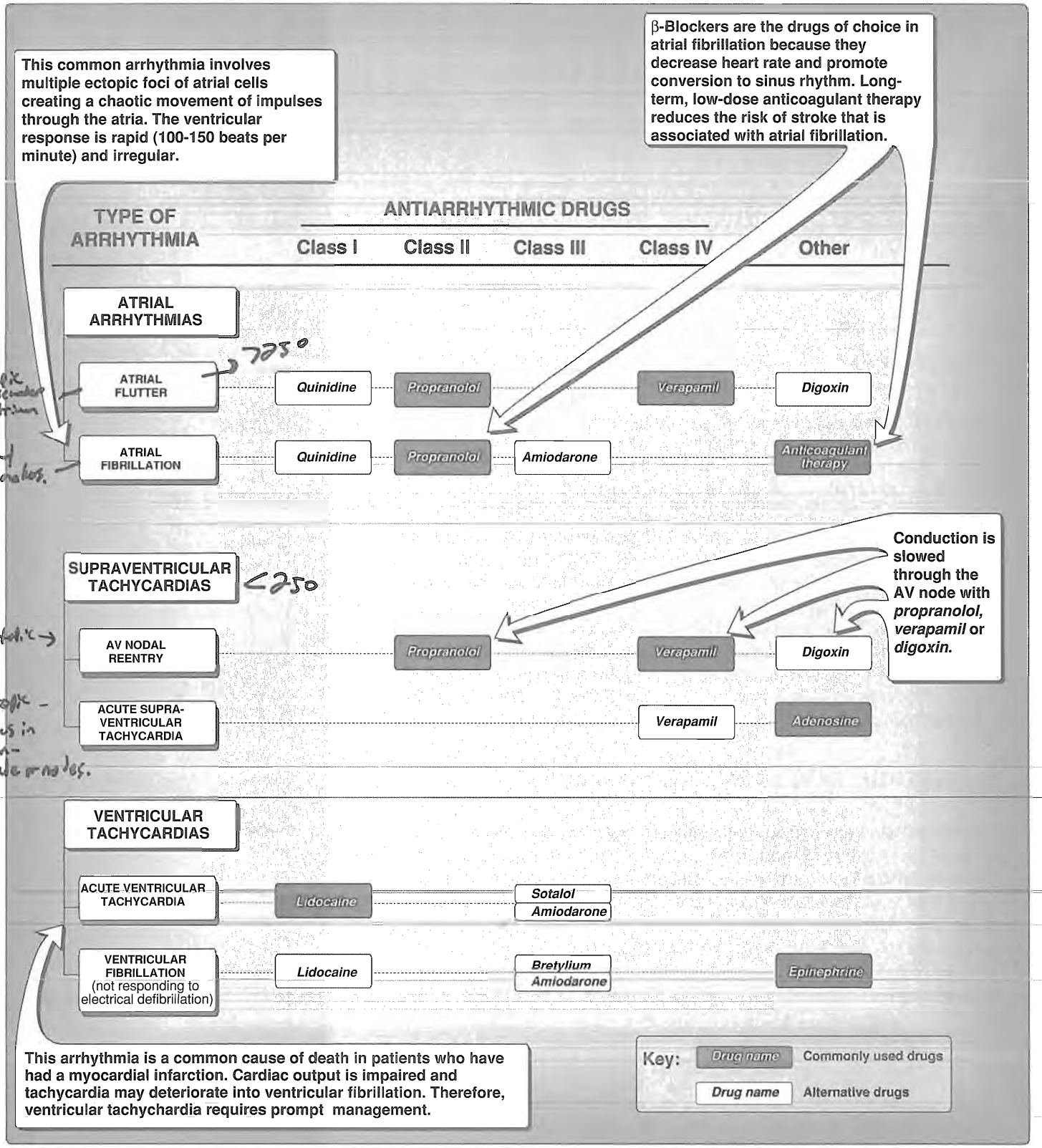


Figure 17.2
Therapeutic indications for some commonly encountered arrhythmias.

A. Causes of arrhythmias

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

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. The SA node thus 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 (1) by decreasing the slope of Phase 4 (diastolic) depolarization and/or (2) by raising the threshold of discharge to a less negative voltage. Such drugs cause the frequency of discharge to decrease, 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 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 required to convert a unidirectional block into a bidirectional block.

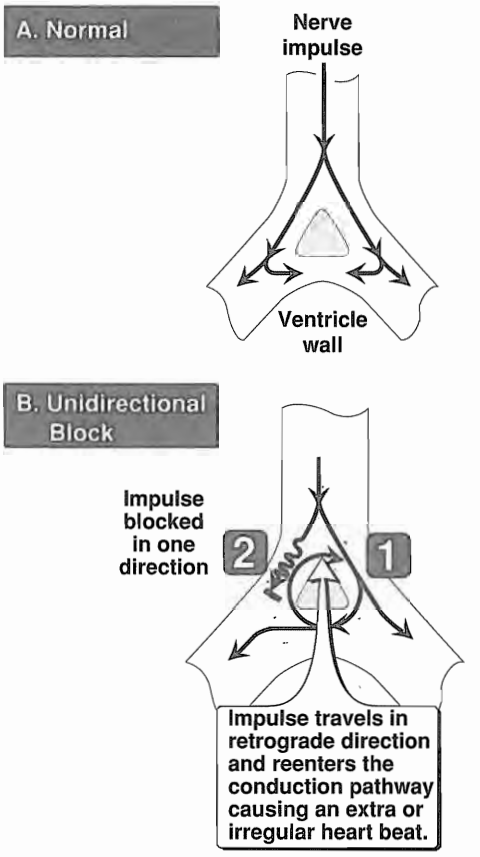


Figure 17.3
Schematic representation of reentry.

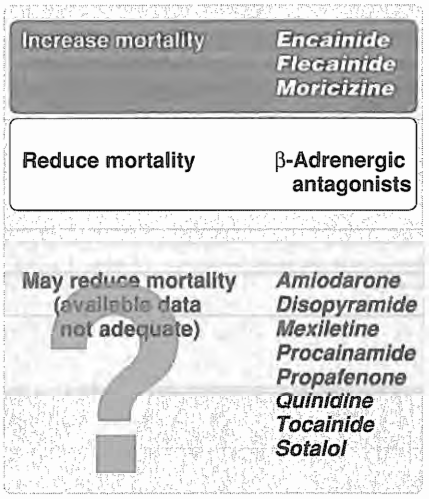


Figure 17.4
Effect of long-term antiarrhythmic therapy on mortality based on placebo-controlled, randomized trials.

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 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 lethal proarrhythmic actions, that is, to cause arrhythmias.

1. **Proarrhythmic effects of antiarrhythmic drugs:** In the Cardiac Arrhythmia Suppression Trial (CAST) treatment with *encainide* and *flecainide*, two class IC antiarrhythmic agents, successfully prevented ventricular ectopic beats in patients who had myocardial infarction. However, continued therapy with either drug was associated with a two- to three-fold increase in death due to cardiac arrhythmias. Similar results were reported for *moricizine*. Increased death was probably due to drug-induced fatal arrhythmias triggered by recurrent myocardial ischemia.

2. **The unexpected conclusion:** The results of CAST challenged the assumption that treating postmyocardial arrhythmia—and perhaps arrhythmias in general—was in fact beneficial. CAST accentuated the fact that the efficacy of many antiarrhythmic agents remains unproven in placebo-controlled, random trials (Figure 17.4). This has caused many clinicians to review current drug recommendations, particularly as new data from clinical trials become available.

III. CLASS I ANTIARRHYTHMIC DRUGS

The antiarrhythmic drugs can be classified according to their predominant effects on the action potential. 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 they may have active metabolites with a different class of action. Class I antiarrhythmic drugs act by blocking voltage-sensitive sodium channels by the same mechanism as local anesthetics (see p. 117). 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.] Class I antiarrhythmic drugs therefore generally cause a decrease in excitability and conduction velocity.

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 fre-

Classification of Drug	Mechanism of Action	Comment
IA	Na^+ channel blocker	Slows Phase 0 depolarization
IB	Na^+ channel blocker	Shortens Phase 3 repolarization
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization
II	β Adrenoreceptor blocker	Suppresses Phase 4 depolarization
III	K^+channel blocker	Prolongs Phase 3 repolarization
IV	Ca^{++}channel blocker	Shortens action potential

Figure 17.5
Actions of antiarrhythmic drugs.

quently depolarizing (for example, during tachycardia when the sodium channels open often). This property is called use-dependence (or state-dependence) and 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, and 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. Class IB drugs have little effect on the rate of depolarization, but 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, and therefore they cause marked conduction slowing but have little effect on the duration of the membrane action potential or the ventricular effective refractory period. They bind slowly to sodium channels. [See Figure 17.5 for a summary of the actions of the antiarrhythmic drugs.]

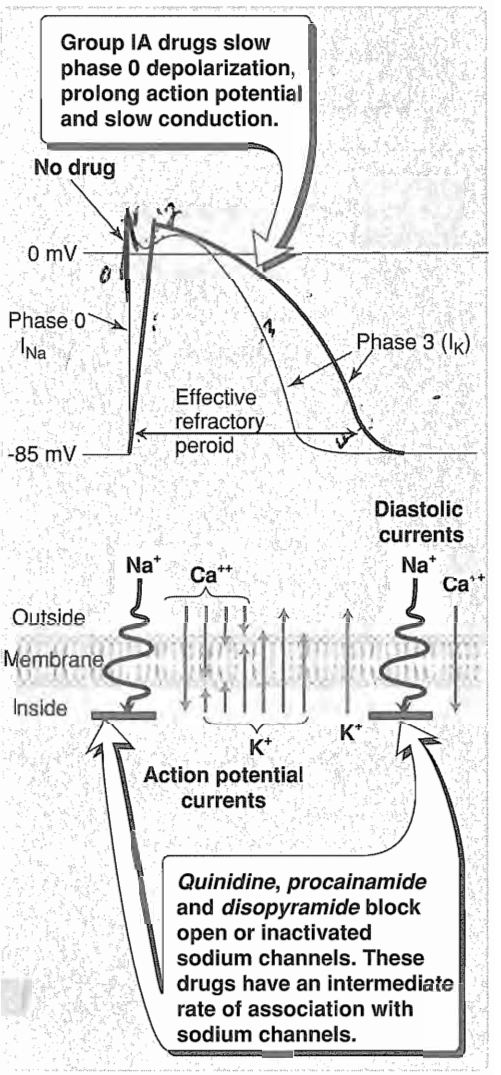


Figure 17.6
Schematic diagram of the effects of Group IA agents.

B. Quinidine

Quinidine [KWIN i deen] is the prototype Class IA drug. At high doses, it can actually precipitate arrhythmias, which can lead to fatal ventricular fibrillation. Because of *quinidine's* toxic potential, calcium antagonists, such as *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 17.6). It also decreases the slope of Phase 4 spontaneous depolarization.

2. **Actions:** *Quinidine* inhibits ectopic arrhythmias and ventricular arrhythmias caused by increased normal automaticity. *Quinidine* also prevents reentry arrhythmias by producing bidirectional block through decreasing membrane responsiveness and pro-

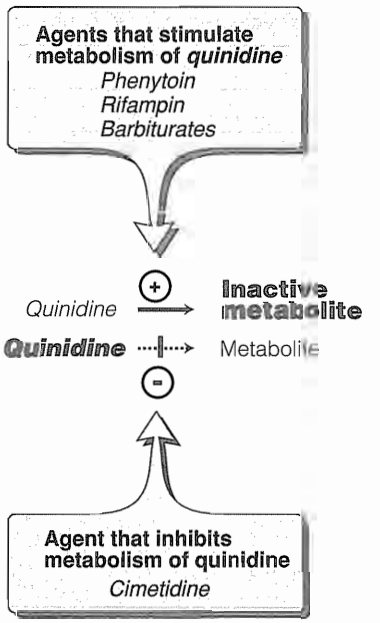


Figure 17.7
Drugs affecting the metabolism of *quinidine*.

longing the effective refractory period. The drug has little effect on normal automaticity. [Note: *Quinidine* can induce a tachycardia in normal individuals because of its atropine-like (anticholinergic) effect.]

3. **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.

4. **Pharmacokinetics:** *Quinidine sulfate* is rapidly and almost completely absorbed after oral administration.

5. **Adverse effects:** A potential adverse effect of *quinidine* (or any antiarrhythmic drug) is exacerbation of the arrhythmia. *Quinidine* may cause SA and AV block or asystole. At toxic levels, the drug may induce ventricular tachycardia. Cardiotoxic effects are exacerbated by hyperkalemia. *Quinidine* can increase the steady state concentration of *digoxin* by displacement of *digoxin* from tissue binding sites. Nausea, vomiting, and diarrhea are commonly observed. Large doses may induce the symptoms of cinchonism, for example, blurred vision, tinnitus, headache, disorientation, and psychosis. The drug has a mild α-adrenergic blocking action as well as an *atropine*-like effect. Drugs interacting with *quinidine* are shown in Figure 17.7

C. Procainamide

1. **Actions:** This Class IA drug, a derivative of the local anesthetic *procaine* (see p. 117), shows actions similar to those of *quinidine*.

2. **Pharmacokinetics** *Procainamide* [pro kane A mide] is absorbed following oral administration. [Note: The intravenous route is rarely used because hypotension occurs if the drug is too rapidly infused.] *Procainamide* has a relatively short half-life of 2-3 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 erythematosus-like syndrome that develops in 25 to 30% 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*.

D. Disopyramide

1. **Actions:** This Class IA drug shows actions similar to those of *quinidine*. *Disopyramide* [dye so 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 for treatment of ventricular arrhythmias as an alternative to *procainamide* or *quinidine*.

2. **Pharmacokinetics** Approximately one half of the orally ingested drug is excreted unchanged by the kidneys. About 30% 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.

E. Lidocaine

Lidocaine [LYE doe kane] is a Class IB drug. The 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* is 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 17.8). Unlike *quinidine*, which suppresses arrhythmias caused by increased normal automaticity, *lidocaine* suppresses arrhythmias caused by abnormal automaticity. *Lidocaine*, like *quinidine*, abolishes ventricular reentry.

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.

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. The CNS effects include drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions; cardiac arrhythmias may also occur.

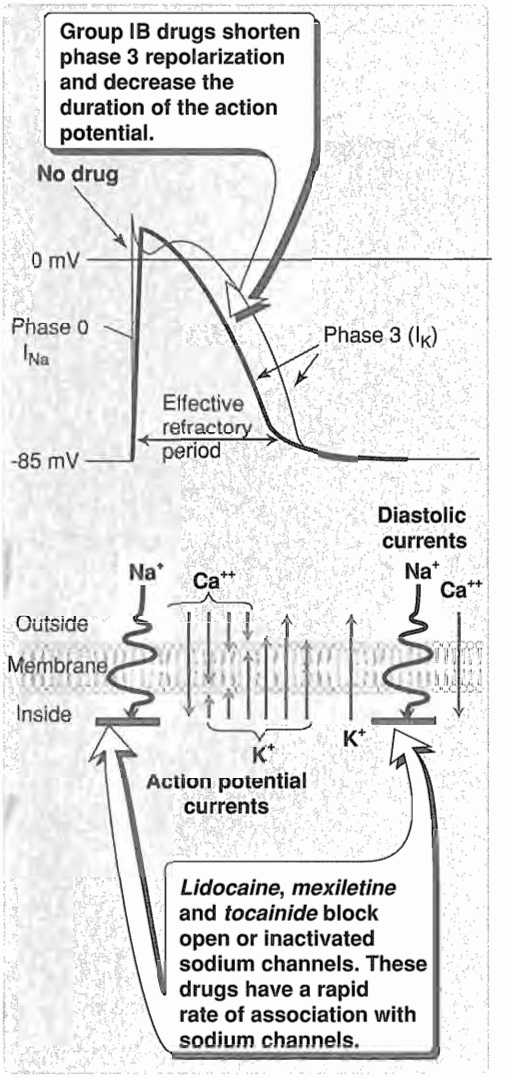


Figure 17.8
Schematic diagram of the effects of Group IB agents.

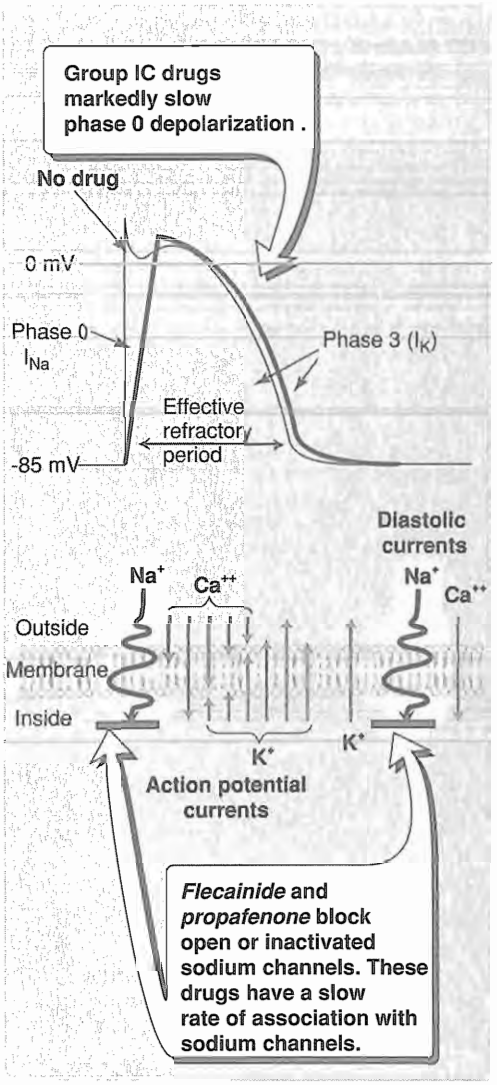


Figure 17.9
Schematic diagram of the effects of Group IC agents.

F. Mexiletine and tocainide

These are Class IB drugs with actions similar to those of *lidocaine*. These agents can be administered orally. *Mexiletine* [mex IL e 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.

G. Flecainide

Flecainide [fle KAY nide] is a Class IC drug. These drugs slowly dissociate from resting sodium channels and show prominent effects, even at normal heart rates. These drugs are approved only for refractory ventricular arrhythmias. However, recent data have cast serious doubts on the safety of the Class IC drugs.

1. **Actions:** *Flecainide* suppresses Phase 0 upstroke in Purkinje and myocardial fibers (Figure 17.9). 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 (see p. 166).

H. Propafenone

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

IV. CLASS II ANTIARRHYTHMIC DRUGS

The Class II agents include the β-adrenergic antagonists (see p. 73). 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.

A. Propranolol

Propranolol 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. (*Propranolol* is described in detail on p. 74)

B. Metoprolol and pindolol

Propranolol is the β-adrenergic antagonist most widely used in the treatment of cardiac arrhythmias. However, β_1-specific drugs, such as *metoprolol* (see p. 77) reduce the risk of bronchospasm, and drugs with partial agonist activity, such as *pindolol* (see p. 77), may decrease the frequency of cardiac failure.

C. Esmolol

Esmolol [ESS moe lol] is a very short-acting β blocker used for intravenous administration in acute arrhythmias occurring during surgery or emergency situations.

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 17.10). Instead, they prolong the effective refractory period. All Class III drugs have the potential to induce arrhythmias.

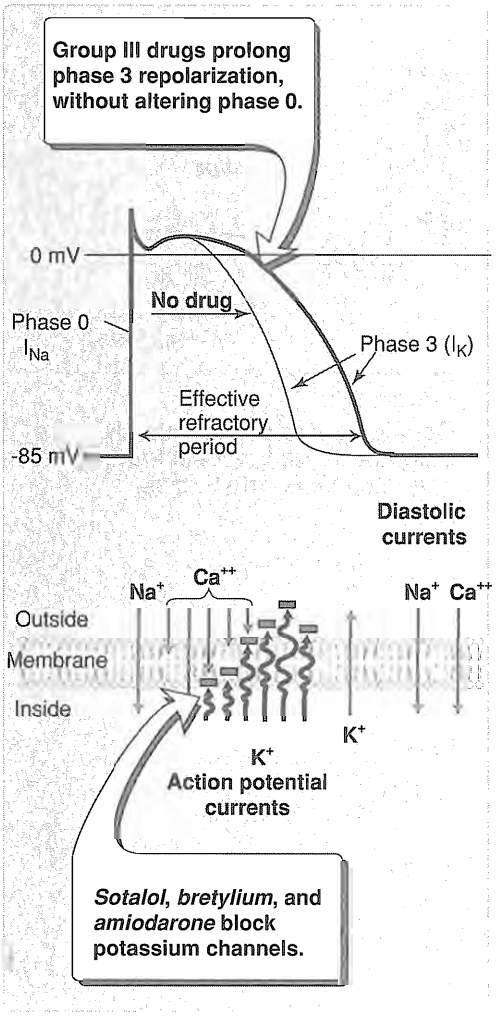


Figure 17.10
Schematic diagram of the effects of Group III agents.

A. Sotalol

Sotalol [SOE ta lol], although a class III antiarrhythmic agent, also has potent β-blocker activity. It is well established that β-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 the duration of the action potential, thus lengthening the effective refractory period.

2. **Therapeutic uses:** β-Blockers are used for long-term therapy to decrease the rate of sudden death following an acute myocardial infarction. β-Blockers have modest ability to suppress ectopic beats and reduce myocardial oxygen demand. They have strong antifibrillary effects, particularly in the ischemic myocardium. *Sotalol* was more effective in preventing arrhythmia recurrence and in decreasing mortality than *imipramine*, *mexiletine*, *procainamide*, *propafenone* and *quinidine* in patients with sustained ventricular tachycardia (Figure 17.11).

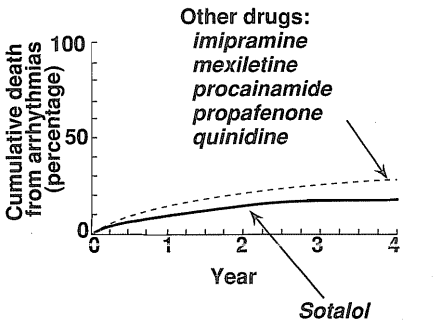


Figure 17.11
Comparison of *sotalol* with six other drugs with respect to deaths due to cardiac arrhythmias.

3. **Adverse effects:** This drug also had 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 3 to 4% of patients.

B. Bretylium

1. **Actions:** *Bretylium* has a number of direct and indirect electrophysiological actions, the most prominent of which are prolongation of the refractory period and raising of the intensity of the electrical current necessary to induce ventricular fibrillation in the His-Purkinje system.

2. **Therapeutic uses:** *Bretylium* is reserved for life-threatening ventricular arrhythmias, especially recurrent ventricular fibrillation or tachycardia.

3. **Pharmacokinetics:** *Bretylium* is poorly absorbed from the gastrointestinal tract and therefore is usually administered parenterally. The drug is excreted unchanged in the urine, and dosage may have to be adjusted in patients with kidney dysfunctions.

4. **Adverse effects:** *Bretylium* can cause severe postural hypotension.

C. 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 tachyarrhythmia. Its clinical usefulness is limited by its toxicity.

3. **Pharmacokinetics:** *Amiodarone* is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks. 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 one half of the patients receiving the drug show side effects sufficiently severe to prompt its discontinuation. 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 (see p. 166) recent clinical trials have shown that *amiodarone* did not reduce incidence of sudden death or prolong survival in patient with congestive heart failure (CHF).

VI. CLASS IV ANTIARRHYTHMIC DRUGS

The Class IV drugs are calcium channel blockers. They decrease the inward current carried by calcium, resulting in a decrease in the rate of Phase 4 spontaneous depolarization and slowed conduction in tissues dependent on calcium currents, such as the AV node (Figure 17.12). 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 mill] shows greater action on the heart than on vascular smooth muscle, whereas *nifedipine*, a calcium channel-blocker used to treat hypertension (see p. 187) exerts a stronger effect on 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 (see p. 152). *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 (see p. 166), that is, they block most effectively when the heart is beating rapidly, since 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 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 ventricular dysrhythmias. They are useful in treating reentrant supraventricular tachycardia and reducing ventricular rate in atrial flutter and fibrillation. In addition, these drugs are used to treat hypertension (see p. 187) and angina (see p. 177).

3. **Pharmacokinetics:** *Verapamil* and *diltiazem* are absorbed after oral administration. *Verapamil* is extensively metabolized by the liver; thus, care should be taken in administration of 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 cause a decrease in blood pressure caused by peripheral vasodilation.

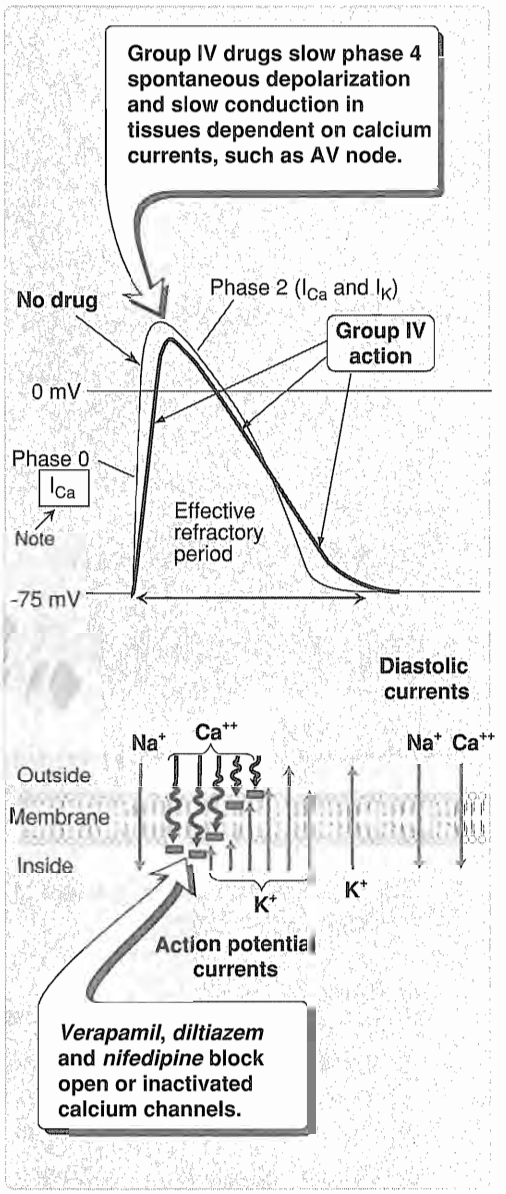


Figure 17.12
Schematic diagram of the effects of Group IV agents.

VII. OTHER ANTIARRHYTHMIC DRUGS

A. Digoxin

Digoxin (see p. 158) shortens the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in Purkinje fibers. *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 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 (about 15 seconds).

Study Questions

Choose the ONE best answer.

17.1 All of the following mechanisms of action correctly match a drug EXCEPT:

A. Quinidine: Blocks Na^+ channels
B. Bretylium: Blocks K^+ channels
C. Verapamil: Blocks Ca^{++} channels
D. Propranolol: Blocks β adrenoceptors
E. Procainamide: Blocks K^+ channels

Correct answer = E. Procainamide blocks Na^+ channels.

17.2 Which one of the following statements is INCORRECT?

A. Lidocaine must be given parenterally.
B. Lidocaine is used mainly for atrial arrhythmias.
C. Procainamide is associated with a reversible lupus phenomenon.
D. Quinidine is active orally.
E. All antiarrhythmic drugs can suppress cardiac contractions.

Correct answer = B. Lidocaine is useful in treating ventricular arrhythmias. Lidocaine is given intravenously because of extensive first-pass transformation by the liver, which precludes oral administration. All of the antiarrhythmic drugs can exert a negative inotropic effect.

17.3 Which one of the following statements is INCORRECT?

A. Quinidine prolongs repolarization and the effective refractory period.
B. Mexiletine shortens repolarization and decreases the effective refractory period.
C. Propranolol increases Phase 4 depolarization.
D. Verapamil shortens the duration of the action potential.
E. Amiodarone prolongs repolarization.

Correct choice = C. Propranolol decreases Phase 4 depolarization.

17.4 Which one of the following statements about antiarrhythmic drugs is CORRECT?

A. They may act by converting unidirectional block to a bidirectional block.
B. They often cause an increase in cardiac output.
C. As a group they have mild side effects.
D. They all affect Na^+ channels in the cell membrane.
E. They are equally useful in atrial and ventricular arrhythmias.

Correct answer = A. A bidirectional block can decrease arrhythmias caused by reentry. All antiarrhythmic drugs exert some negative inotropic effect and decrease cardiac output. The side effects of this group of drugs are serious and include arrhythmias that can lead to sudden death. Some antiarrhythmic drugs affect K^+ or Ca^{++} channels, or β adrenoreceptors.

Antianginal Drugs

18

I. OVERVIEW

Angina pectoris is a characteristic chest pain caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium. The imbalance between oxygen delivery and utilization may result from a spasm of the vascular smooth muscle or from obstruction of blood vessels caused by atherosclerotic lesions. Angina is characterized by a sudden, severe pressing substernal pain radiating to the left arm. Three classes of drugs are effective, either alone or in combination, in treating patients with stable angina: nitrates, β-blockers, and calcium channel-blockers. Nitrates decrease coronary vasoconstriction or spasm and increase perfusion of the myocardium by relaxing coronary arteries. β-Blockers decrease the oxygen demands of the heart. Variant angina (also called Prinzimetal's angina) caused by spontaneous coronary spasm, either at work or at rest, rather than by increases in myocardial oxygen requirements, is controlled by organic nitrates or calcium channel blockers, but β-blockers are contraindicated. (See Figure 18.1 for a summary of these antianginal agents.)

II. ORGANIC NITRATES

Organic nitrates (and nitrites) are simple nitric and nitrous acid esters of alcohols. They differ in their volatility; for example, *isosorbide dinitrate* is solid at room temperature, *nitroglycerin* is only moderately volatile, whereas *amyl nitrate* 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 Prinzmetal's or variant angina pectoris.

A. Nitroglycerin

Nitrates, β-blockers, and calcium channel blockers are equally effective for relief of anginal symptoms. However, 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.

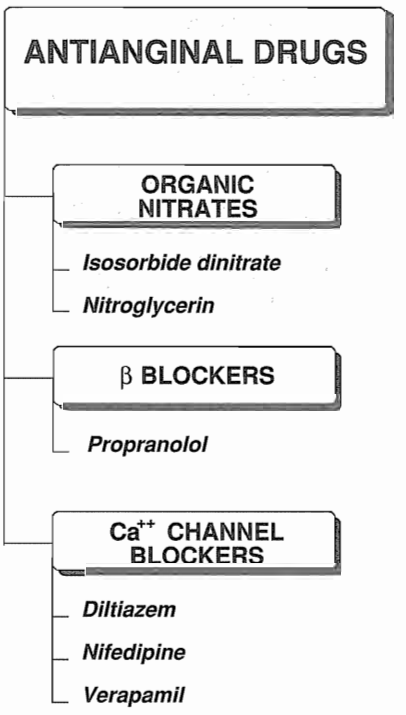


Figure 18.1
Summary of antianginal drugs.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.J.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

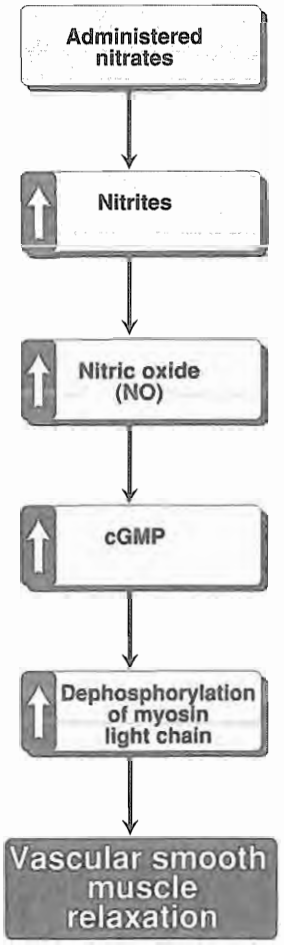


Figure 18.2
Effects of nitrates and nitrites on smooth muscle.

1. **Mechanisms of action:** The organic nitrates, such as *nitroglycerin* [nye troe GLI ser in], are thought to relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide (NO), which in turn activates guanylate cyclase and increases the cells' cyclic GMP. Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation (Figure 18.2).

2. **Effects on cardiovascular system:** 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 increased blood supply to the heart muscle. *Nitroglycerin* causes a decrease in myocardial oxygen consumption because of decreased cardiac work.

3. **Pharmacokinetics:** The time to onset of action varies from one minute for *nitroglycerin* to more than one hour for *isosorbide mononitrate* (Figure 18.3). Significant first-pass metabolism of *nitroglycerin* occurs in the liver. Therefore, it is common to give the drug either sublingually or via a transdermal patch.

4. **Adverse effects:** The most common adverse effect of *nitroglycerin,* as well as the other nitrates, is headache. Thirty to sixty 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.

5. **Tolerance:** Tolerance to the actions of nitrates develops rapidly. It can be overcome by provision of a daily "nitrate-free interval" to restore sensitivity to the drug. This interval is typically 6 to 8 hours, usually at night because there is decreased demand on the heart at that time. *Nitroglycerin* patches are worn for 12 hours and removed for 12 hours. However, Prinzimetal's or variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. These patients' nitrate-free interval should be late afternoon.

B. Isosorbide dinitrate

Isosorbide dinitrate [eye soe SOR bide] is an orally active nitrate (Figure 18.3). The drug is not readily metabolized by the liver or smooth muscle and has a lower potency than *nitroglycerin* in relaxing vascular smooth muscle.

III. β-ADRENERGIC BLOCKERS

The β-adrenergic blocking agents suppress the activation of the heart by blocking β_1 receptors (see p. 73). They also reduce the work of the heart by decreasing cardiac output and causing a slight decrease in blood pressure. *Propranolol* (see p. 74) is the prototype of this class of compounds, but other β-blockers, such as *metoprolol* and *atenolol* are

equally effective. However, agents with intrinsic sympathomimetic activity (for example, *pindolol* and *acebutolol*) are less effective and should be avoided. The β-blockers reduce the frequency and severity of angina attacks. These agents are particularly useful in the treatment of patients with myocardial infarction. The β-blockers can be used with nitrates to increase exercise duration and tolerance. They are, however, contraindicated in patients with diabetes, peripheral vascular disease, or chronic obstructive pulmonary disease.

IV. CALCIUM CHANNEL BLOCKERS

The calcium channel blockers inhibit the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium channel blockers are therefore vasodilators that cause a decrease in smooth muscle tone and vascular resistance. (See p. 187 for a description of the mechanism of action of 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.]

A. Nifedipine:

Nifedipine [nye FED i peen] functions mainly as an arteriolar vasodilator. This drug has minimal effect on cardiac conduction or heart rate. *Nifedipine* is administered orally and has a short half-life (about 4 hours) requiring multiple dosing. 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. The drug may cause reflex tachycardia if peripheral vasodilation is marked resulting in a substantial decrease in blood pressure.

B. Verapamil

Verapamil [ver AP a mill] slows cardiac conduction directly and thus decreases heart rate and oxygen demand. *Verapamil* causes greater negative inotropic effects than does *nifedipine*, but it is a weaker vasodilator. *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 digitalized patients, since it increases *digoxin* levels (see p. 160).

C. Diltiazem

Diltiazem [dil TYE a zem] has cardiovascular effects that are similar to those of *verapamil*. It 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 is therefore particularly useful in patients with variant angina. The incidence of adverse side effects is low. Figure 18.4 shows treatment of angina in patients with concomitant diseases.

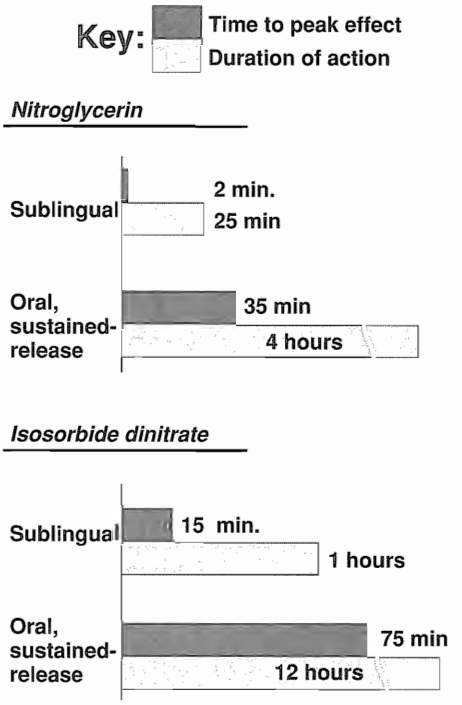


Figure 18.3
Time to peak effect and duration of action for two organic nitrate agents.

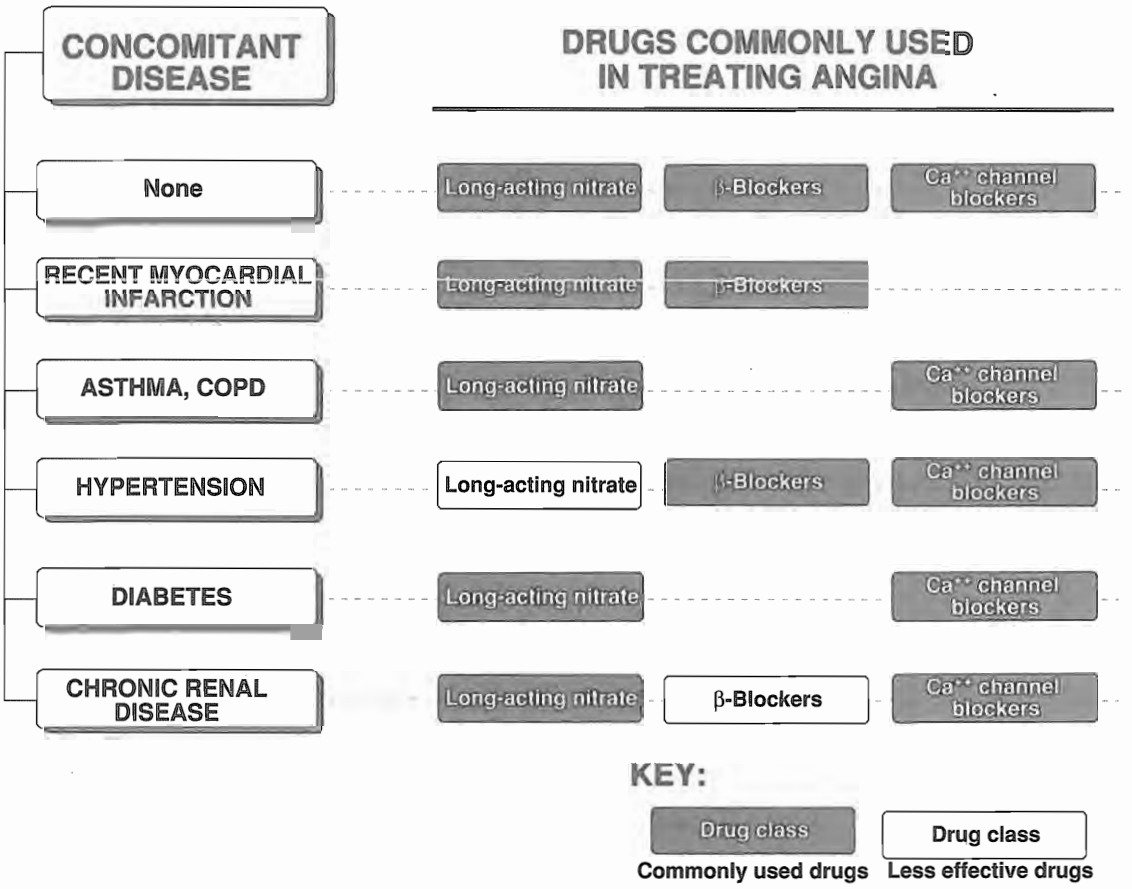


Figure 18.4
Treatment of angina in patients with concomitant diseases. COPD, chronic obstructive pulmonary disease.

Study Questions

Choose the ONE best answer.

18.1 All of the following statements concerning nitroglycerin are correct EXCEPT:

A. It causes an elevation of intracellular cGMP.
B. It undergoes significant first-pass metabolism in the liver.
C. It may cause significant reflex tachycardia.
D. It significantly decreases AV conduction.
E. It can cause postural hypotension.

Correct choice = D. In contrast to other antianginal drugs, such as calcium channel blockers and β-adrenergic blockers, nitroglycerin does not block impulse conduction in the heart. Nitroglycerin causes increased cGMP, leading to vascular smooth muscle relaxation. The drug is commonly administered sublingually or transdermally to avoid hepatic inactivation. Increased heart rate results from the decrease in peripheral resistance and drop in blood pressure induced by nitroglycerin.

18.2 Which one of the following adverse effects is associated with nitroglycerin?

A. Hypertension
B. Throbbing headache
C. Bradycardia
D. Sexual dysfunction
E. Anemia

Correct answer = B. Nitroglycerin causes throbbing headache in 30 to 60% of patients taking the drug. The other choices are incorrect. [Note: Nitroglycerin may cause postural hypotension.]

Antihypertensive Drugs

19

I. OVERVIEW

Hypertension is defined as a sustained diastolic blood pressure greater than 90 mm Hg accompanied by an elevated systolic blood pressure (>140 mm Hg). Hypertension results from increased peripheral vascular smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. Elevated blood pressure is an extremely common disorder, affecting approximately 15% of the population of the United States (60 million people). Although many of these individuals have no symptoms, chronic hypertension—either systolic or diastolic—can lead to congestive heart failure, myocardial infarction, renal damage, and cerebrovascular accidents. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated.

II. ETIOLOGY OF HYPERTENSION

Although hypertension may occur secondary to other disease processes, more than 90% 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. Essential hypertension occurs four times more frequently among blacks than among whites, and it occurs more often among middle-aged males than among middle-aged females. Environmental factors such as a stressful lifestyle, high dietary intake of sodium, obesity, and smoking all further predispose an individual to the occurrence of hypertension. Figure 19.1 summarizes the drugs used to treat hypertension. [Note: Nonsteroidal anti-inflammatory drugs (NSAID) (see p. 403) interfere with the hypotensive action of many antihypertensives.]

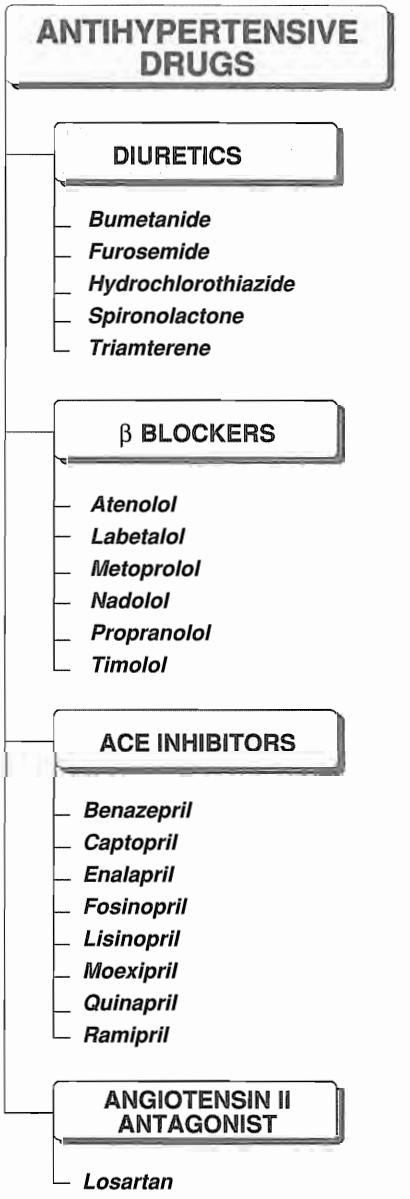


Figure 19.1
Summary of antihypertensive drugs.
(Figure continues on next page.)

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

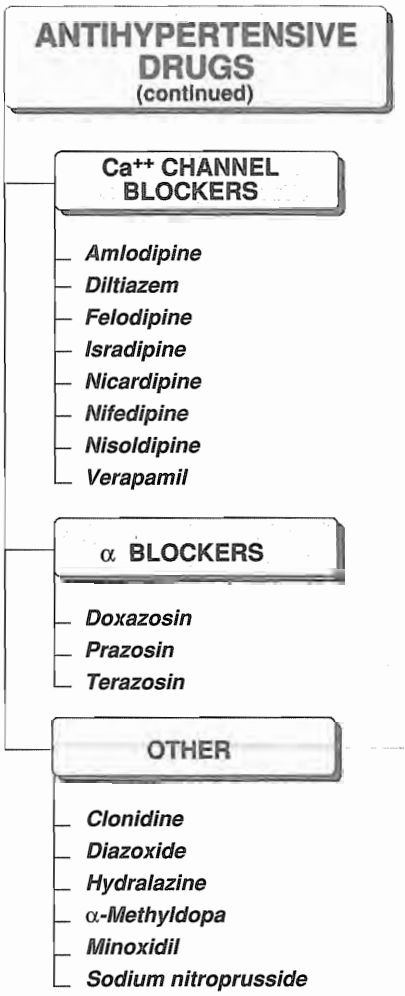


Figure 19.1
Summary of antihypertensive drugs.

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. Arterial blood pressure is directly proportional to the product of the cardiac output and the peripheral vascular resistance (Figure 19.2). In both normal and hypertensive individuals, cardiac output and peripheral resistance are controlled mainly by two overlapping control mechanisms: the baroreflexes 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 (Figure 19.3, and Figure 3.5, see p. 31).

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 β-adrenoceptors) by releasing the enzyme renin (see Figure 19.3). This peptidase converts angiotensinogen to angiotensin I, which is in turn converted to angiotensin II in the presence of angiotensin converting enzyme (ACE, see p. 186). Angiotensin II is the body's most

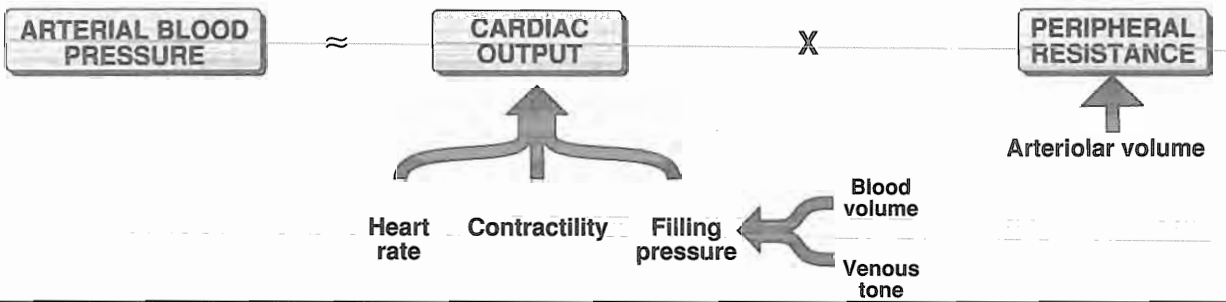


Figure 19.2
Major factors influencing blood pressure.

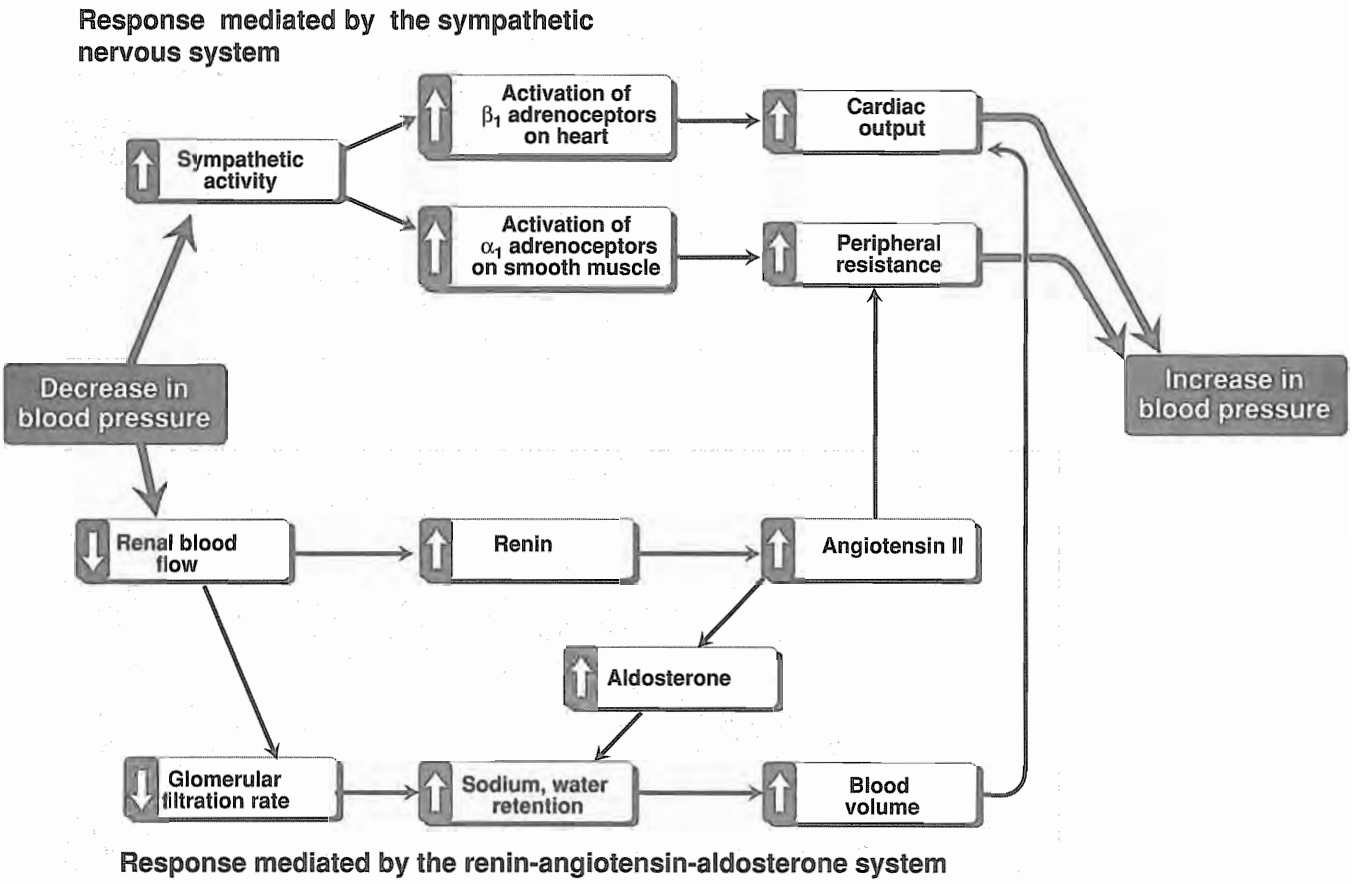


Figure 19.3
Response of the autonomic nervous system and the renin-angiotensin-aldosterone system to a decrease in blood pressure.

potent circulating vasoconstrictor, causing an increase in blood pressure. Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and an increase in blood volume, which contribute to a further increase in blood pressure).

IV. TREATMENT STRATEGIES

Mild hypertension can often be controlled with a single drug. More severe hypertension may require treatment with several drugs that are selected to minimize adverse effects of the combined regimen. Treatment is initiated with any of four drugs depending on the individual patient: a diuretic, a β-blocker, an ACE inhibitor, or a calcium channel blocker. If blood pressure is inadequately controlled, a second drug is added. A β-blocker is usually added if the initial drug was a diuretic, or a diuretic is added if the first drug was a β-blocker. A vasodilator can be added as a third step for those patients who still fail to respond.

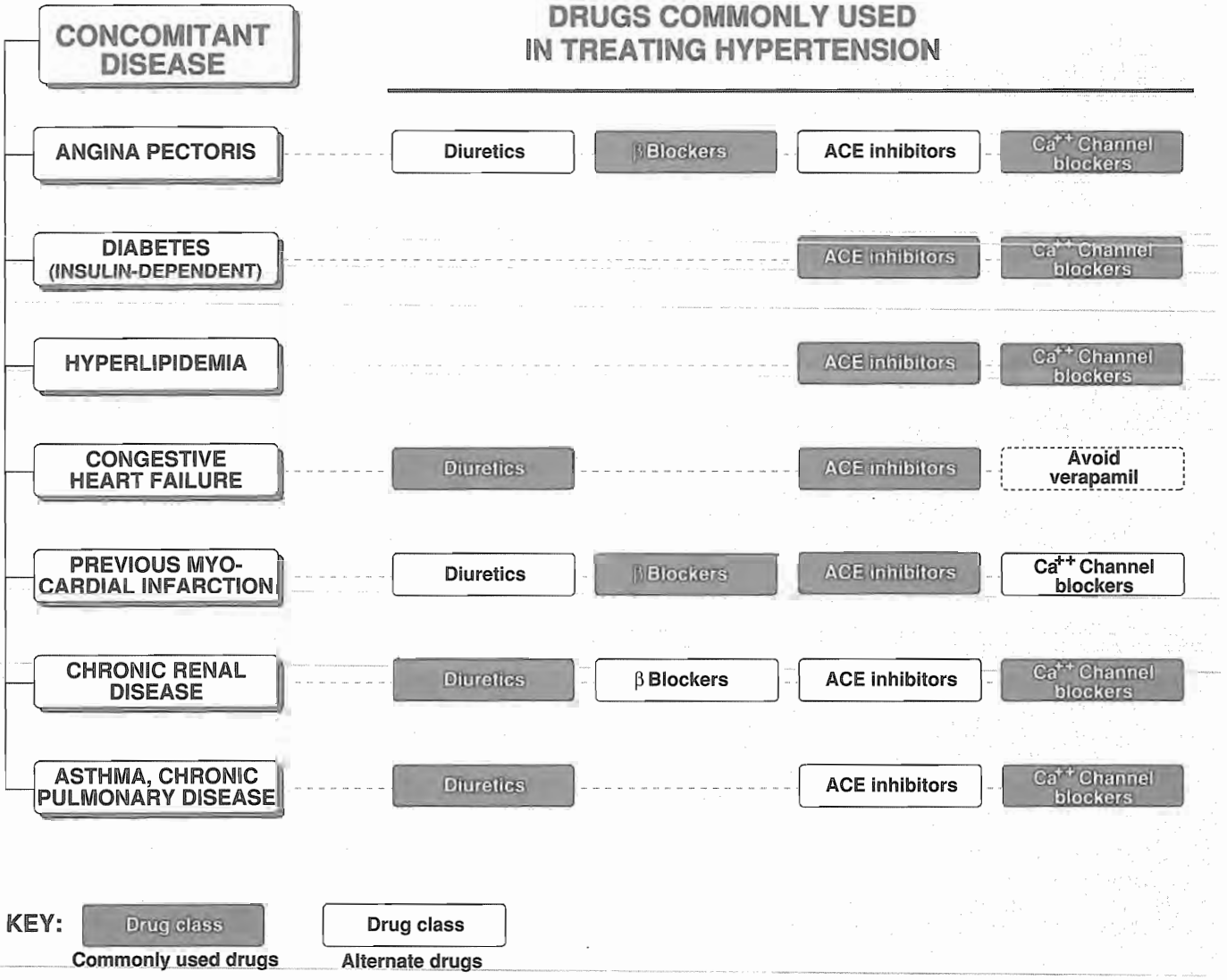


Figure 19.4
Treatment of hypertension in patients with concomitant diseases.

A. Individualized care

Certain subsets of the hypertensive population respond better to one class of drug than another. For example, black patients respond well to diuretics and calcium channel blockers, but therapy with β-blockers or ACE inhibitors is often less effective. Similarly, calcium channel blockers, ACE inhbibitors, and diuretics are favored for treatment of hypertension in the elderly, whereas β-blockers and α-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.

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 directed at preventing disease sequelae (that occur in the future), rather than in relieving present discomfort of the patient. The adverse effects associated with the hypertensive therapy may influence the patient more than future benefits. For example, β-blockers can decrease libido and induce impotence in males, particulary 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.

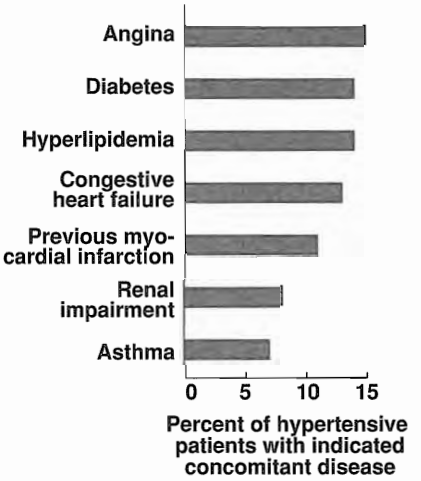


Figure 19.5
Frequency of occurrence of concomitant disease among the hypertensive patient population.

V. DIURETICS

Diuretics and/or β-blockers are currently recommended as the first-line drug therapy for hypertension. Low-dose diuretic therapy is safe and effective in preventing stroke, myocardial infarction, congestive heart failure and total mortality. Recent data suggest that diuretics are superior to β-blockers 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. *Spironolactone* [spye row no LAK tone], a potassium-sparing diuretic, is often used with thiazides. (A complete discussion of diuretics is found on p. 223.)

2. **Therapeutic uses:** Thiazide diuretics decrease blood pressure in both the supine and standing positions; 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 β-blockers and ACE inhibitors. Thiazide diuretics are particularly useful in the treatment of black or elderly patients, and in those with chronic renal disease. Thiazide diuretics are not effective in patients with inadequate kidney function (creatinine clearance less than 50 mls/min). Loop diuretics may be required in these patients.

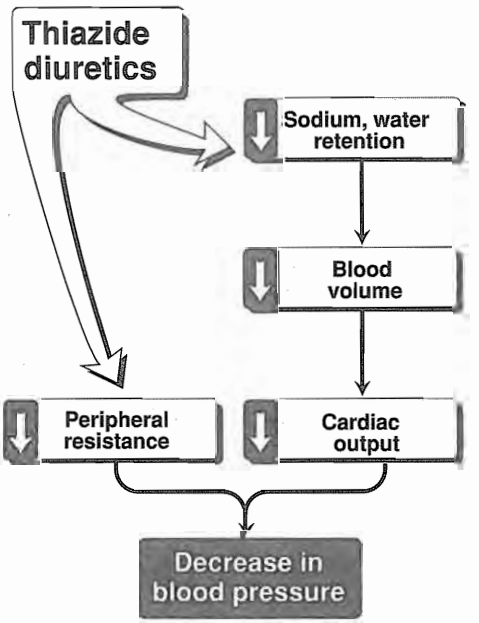


Figure 19.6
Actions of thiazide diuretics.

3. **Pharmacokinetics:** Thiazide diuretics can be administered orally. They induce considerable disturbances in electrolyte balance. For example, blood levels of K^+ and Mg^{++} are reduced, and Ca^{++} is retained by the body (see p. 229).

4. **Adverse effects:** Thiazide diuretics induce hypokalemia and hyperuricemia in 70% of patients, and hyperglycemia in 10% of patients. 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 congestive heart failure) and who are concurrently being treated with both thiazide diuretics and *digitalis* glycosides (see p. 160). Diuretics should be avoided in the treatment of hypertensive diabetics or patients with hyperlipidemia.

B. Loop diuretics

The loop diuretics act promptly, even in patients who have poor renal function or who have not responded to thiazides or other diuretics. The loop diuretics cause decreased renal vascular resistance and increased renal blood flow. [Note: Loop diuretics increase the Ca^{++} content of urine (see p. 227), whereas thiazide diuretics decrease the Ca^{++} concentration of the urine.]

VI. β-ADRENOCEPTOR BLOCKING AGENTS

β-Blockers and/or diuretics are currently recommended as first-line drug therapy for hypertension. These drugs are efficacious but have some contraindications.

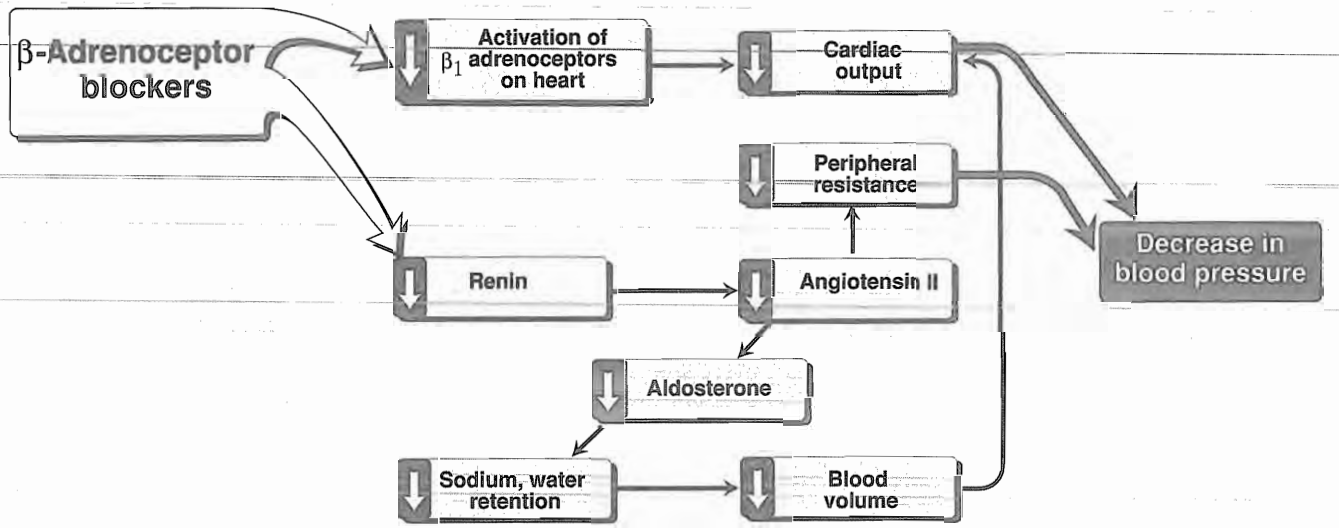


Figure 19.7
Actions of β-adrenoceptor blocking agents.

A. Actions

The β-blockers reduce blood pressure primarily by decreasing cardiac output (Figure 19.7). They may also decrease sympathetic outflow from the CNS and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and secretion of aldosterone. The prototype β-blocker is *propranolol*, which acts at both β_1 and β_2 receptors. Newer agents, such as *atenolol* and *metoprolol*, are selective for β_1 receptors. These agents are commonly used in disease states such as asthma, in which *propanolol* is contraindicated due to its β_2-mediated bronchoconstriction. (See p. 73 for a complete discussion of β-blockers.)

B. Therapeutic uses

1. **Subsets of the hypertensive population:** The β-blockers are more effective for treating hypertension in white than in black patients, and in young patients compared to the elderly. [Note: Conditions that discourage the use of β-blockers (for example, severe chronic obstructive lung disease, chronic congestive heart failure, severe symptomatic occlusive peripheral vascular disease) are more commonly found in the elderly and in diabetics.]

2. **Hypertensive patients with concomitant diseases:** The β-blockers are useful in treating conditions that may coexist with hypertension, such as supraventricular tachyarrhythmia, previous myocardial infarction, angina pectoris, glaucoma (applied topically), and migraine headache.

C. Pharmacokinetics

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

D. Adverse effects

1. **Common effects:** The β-blockers may cause CNS side effects such as fatigue, lethargy, insomnia, and hallucinations; these drugs can also cause hypotension. The β-blockers may decrease libido and cause impotence; drug-induced sexual dysfunction can severely reduce patient compliance (Figure 19.8).

2. **Alterations in serum lipid patterns:** The β-blockers may disturb lipid metabolism, decreasing high-density lipoproteins (HDL) and increasing plasma triacylglycerol.

3. **Drug withdrawal:** Abrupt withdrawal may cause rebound hypertension, probably as a result of up-regulation of β-receptors. Patients should be tapered off of β-blocker therapy in order to avoid precipitation of arrhythmias.The β-blockers should be avoided in treating patients with asthma, congestive heart failure, and peripheral vascular disease.

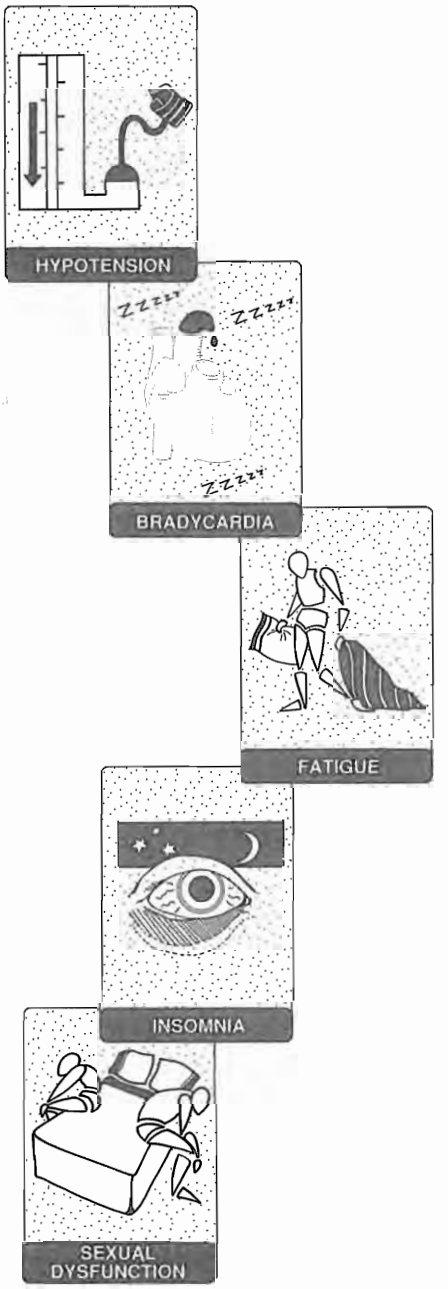


Figure 19.8
Some adverse effects of β blockers.

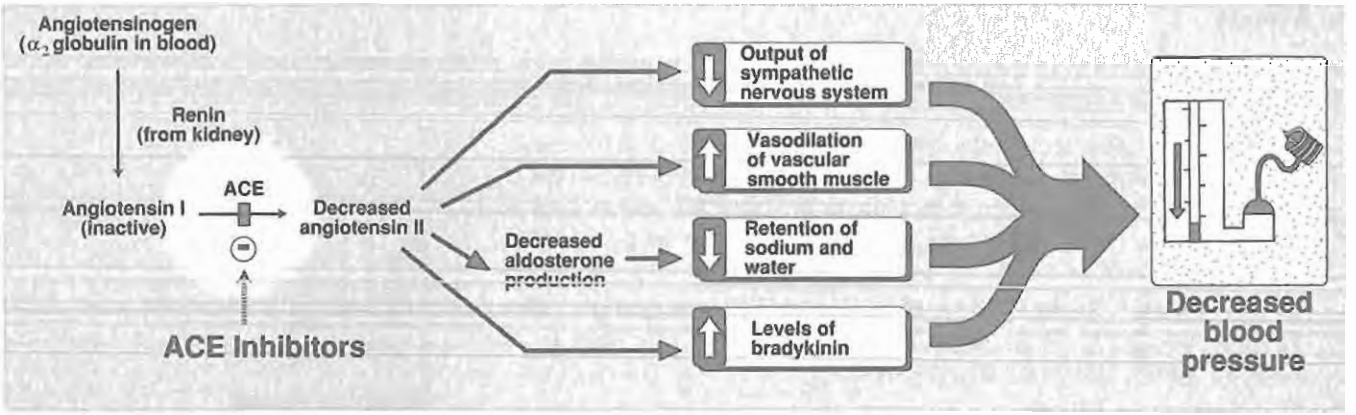


Figure 19.9
Effects of ACE inhibitors.

VII. ACE INHIBITORS

The angiotensin-converting enzyme (ACE) inhibitors are recommended when the preferred first-line agents (diuretics or β-blockers) are contraindicated or ineffective. Despite their wide-spread 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 reflexly increasing cardiac output, rate, or contractility. These drugs block the angiotensin converting enzyme that cleaves angiotensin I to form the potent vasoconstrictor, angiotensin II (Figure 19.9). These inhibitors also diminish the rate of bradykinin inactivation. 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.

B. Therapeutic uses

Like β-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 hypertensive patients. Unlike β-blockers, ACE inhibitors are effective in the management of patients with chronic congestive heart failure (see p. 156). ACE inhibitors are now 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, rashes, fever, altered taste, hypotension (in hypovolemic states), and hyperkalemia (Figure 19.10). Potassium levels must be monitored, and potassium supple-

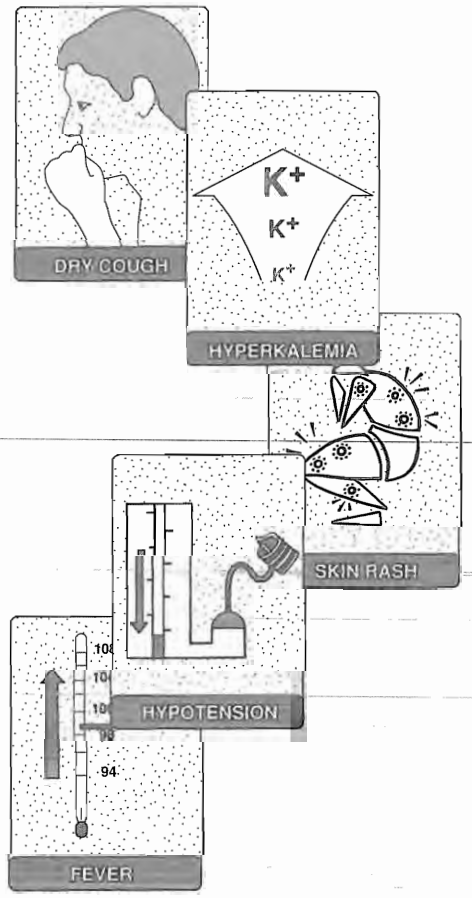


Figure 19.10
Some common adverse effects of the ACE inhibitors.

ments or *spironolactone* (see p. 232) are contraindicated. Angioedema is a rare but potentially life-threatening reaction. Because of the risk of angioedema and first dose syncope, ACE inhibitors are first administered in the physician's office with close observation. Reversible renal failure can occur in patients with severe renal artery stenosis. ACE inhibitors are fetotoxic and should not be used in pregnant women.

VIII. ANGIOTENSIN II ANTAGONISTS

The nanopeptide *losartan* [LOW sar tan], a highly selective angiotensin II receptor blocker, has recently been approved for antihypertensive therapy. Its pharmacologic effects are similar to ACE inhibitors in that it produces vasodilation and blocks aldosterone secretion. Its adverse effects profile is improved over the ACE inhibitors, although it is fetotoxic.

IX. CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are recommended when the preferred first-line agents are contraindicated or ineffective. Despite their wide-spread use, it is not clear what effects antihypertensive therapy with these drugs has on major disease. In hypertensive patients, one retrospective study suggests that use of short-acting calcium channel blockers, especially in high doses, is associated with an increased risk of myocardial infarction. If confirmed in more rigorous randomized trials, these findings will reinforce the importance of diuretics and β-blockers as first-line agents unless contraindicated.

A. Classes of calcium channel blockers

The calcium channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications (Figures 19.11 and 19.12).

1. **Diphenylalkylamines:** *Verapamil* [ver AP a mill] 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 a 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 than does *verapamil*. *Diltiazem* has a favorable side-effect profile.

3. **Dihydropyridines:** This rapidly expanding class of calcium channel blockers includes the first-generation *nifedipine* [nye FED i peen],

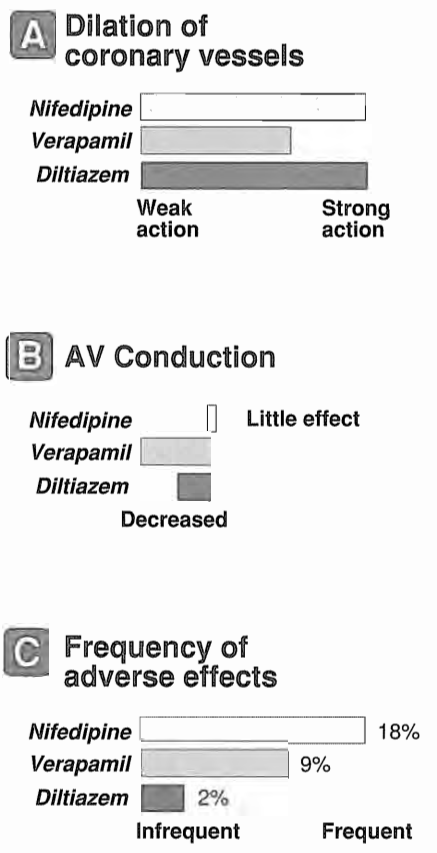


Figure 19.11
Actions of calcium channel blockers.

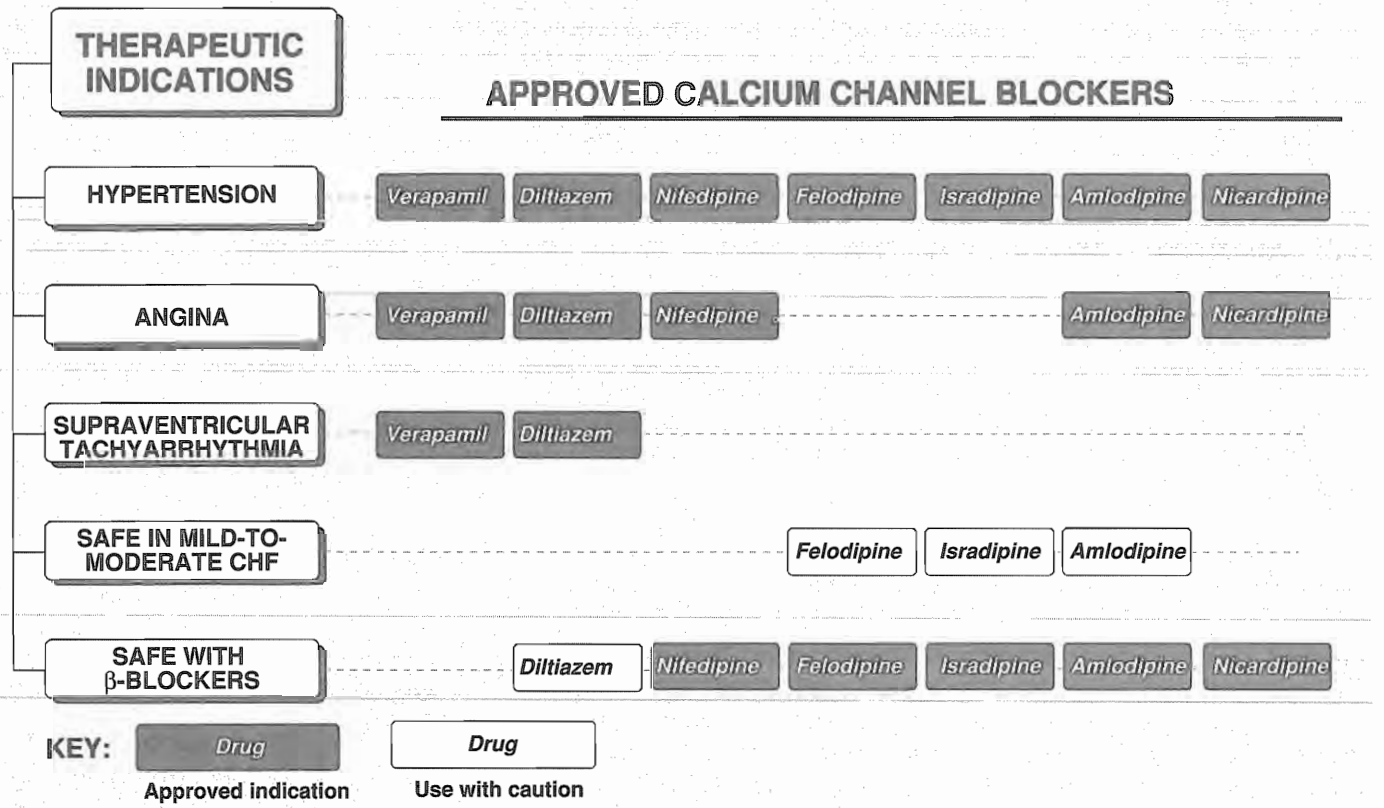


Figure 19.12
Some therapeutic applications of calcium channel blockers. CHF, congestive heart failure.

and five new agents for treating cardiovascular disease: *amlodipine* [am LOE di peen], *felodipine* [fell OH di peen], *isradipine* [eyes RAD i pen], *nicardipine* [nye KAR de peen] and *nisoldipine* [ni SOL de peen]. These second-generation calcium channel blockers differ in pharmacokinetics, approved uses, and drug interactions. All the 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* (see p. 160) or *warfarin* (see p. 199) that are often used concomitantly with calcium channel blocker drugs.

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; therefore, they 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.

D. Pharmacokinetics

Most of these agents have short half-lives ($t_{1/2}$ = 3 to 8 hours) following an oral dose. Treatment is required three times a day to maintain good control of hypertension. Sustained release preparations permit less frequent dosing.

E. Adverse effects

Although infrequent, side effects include constipation in 10% of patients, dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure (Figure 19.13). *Verapamil* should be avoided in treating patients with congestive heart failure due to its negative inotropic effects.

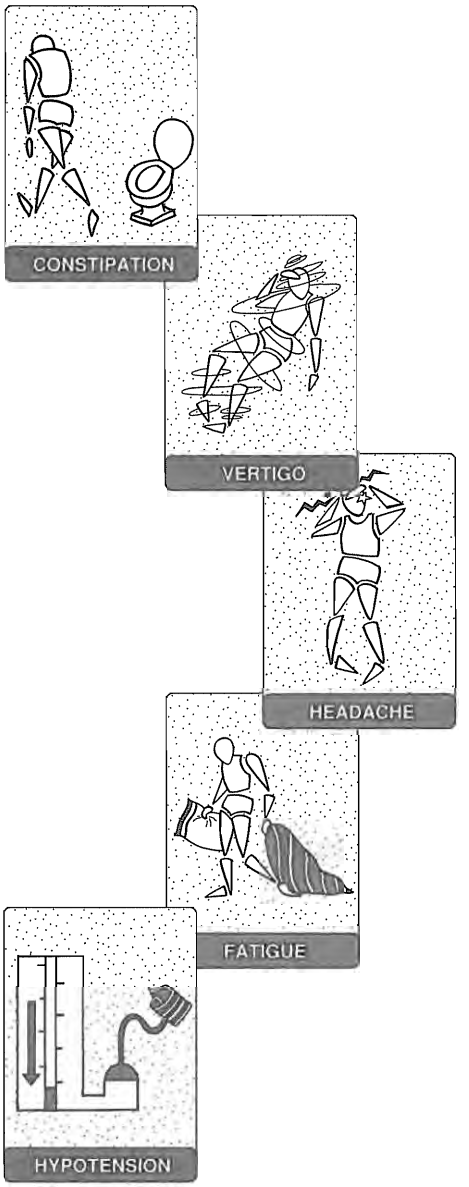


Figure 19.13
Some common adverse effects of the calcium channel blockers.

X. α-ADRENERGIC BLOCKING AGENTS

Prazosin, *oxazosin* and *terazosin* (see p. 73) produce a competitive block of α_1 adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing the 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 and increased renin release do not occur. 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 β-blocker may be necessary to blunt the short-term effect of reflex tachycardia.

XI. CENTRALLY-ACTING ADRENERGIC DRUGS

A. Clonidine

This α_2-agonist diminishes central adrenergic outflow. *Clonidine* [KLOE ni deen] (see p. 67) is used primarily for the treatment of mild to moderate hypertension that has not responded adequately to treatment with diuretics alone. *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 causes sodium and water retention, *clonidine* is usually administered in combination with a diuretic. Adverse effects are generally mild, but the drug can produce sedation and drying of 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. α-Methyldopa

This α-adrenergic agonist diminishes the adrenergic outflow from the CNS, leading 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, *α-methyldopa* [meth ill DOE pa] is especially valuable in treating hypertensive patients with renal insufficiency. The most common side effects of *α-methyldopa* are sedation and drowsiness.

XII. 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 decreases blood pressure. These agents produce reflex stimulation of the heart, resulting in the competing symptoms 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 β-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 a zeen] is used to treat moderately severe hypertension. It is almost always administered in combination with a β-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. Adverse effects of hydralazine therapy include headache, 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 may be severe and may require the concomitant use of a diuretic and a β-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.]

XIII. HYPERTENSIVE EMERGENCY

Hypertensive emergency is a rare, but life-threatening situation in which the diastolic blood pressure is either over 150 mm Hg (with systolic blood pressure greater than 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. 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 ($t_{1/2}$ 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 and can be effectively treated with an infusion of *sodium thiosulfate* to produce thiocyanate, which is less toxic and is eliminated by the kidneys (Figure 19.14). [Note: *Nitroprusside* is poisonous if given orally because of its hydrolysis to cyanide.]

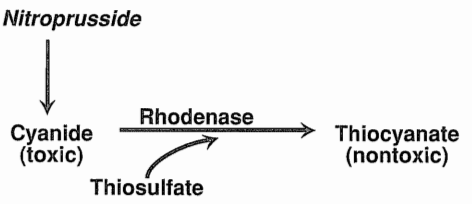


Figure 19.14
Detoxification of cyanide with thiosulfate and rhodenase

B. Diazoxide

Diazoxide [dye az OX ide] is a direct-acting arteriolar vasodilator. It has vascular effects like those of *hydralazine*. For patients with coronary insufficiency, *diazoxide* is administered intravenously with a β-blocker, which diminishes reflex activation of the heart. *Diazoxide* is useful in the treatment of hypertensive emergencies, hypertensive encephalopathy, and eclampsia. Excessive hypotension is the most serious toxicity.

C. Labetalol

Labetalol (see p. 78) is both an α- and β-blocker that has been successfully used in hypertensive emergencies. *Labetalol* does not cause the reflex tachycardia that may be associated with *diazoxide*. *Labetalol* carries the contraindications of a nonselective β-blocker (see p. 78).

Choose the ONE best answer.

19.1 Which of the following patients is most suited for primary therapy with hydrochlorothiazide?

A. Patients with gout
B. Patients with hyperlipidemia
C. Young hypertensive patients with rapid resting heart rates
D. Black patients and elderly patients
E. Patients with impaired renal function

Correct answer = D. Among black patients, diuretic and calcium channel blockers are more effective than ACE inhibitors or β-blockers. Diuretics are effective among the elderly. Thiazide diuretics cause hyperuricemia and can precipitate a gout attack in susceptible individuals. Thiazide diuretics increase LDL cholesterol and may increase the risk of atherosclerosis in patients with hyperlipidemia. Patients with evidence of elevated catecholamines are best treated with β-blockers. Thiazides cannot promote sodium excretion when renal function is severely impaired. The loop diuretics, such as furosemide, are used in patients with impaired renal function.

19.2 All of the following produce a significant decrease in peripheral resistance except:

A. chronic administration of diuretics.
B. hydralazine.
C. β-blockers.
D. ACE inhibitors.
E. clonidine.

Correct choice = C. β-blockers act primarily by decreasing heart rate and cardiac output.

19.3 Which one of the following drugs acts at central presynaptic α_2 receptors?

A. Minoxidil
B. Verapamil
C. Clonidine
D. Enalapril
E. Hydrochlorothiazide

Correct answer = C. Clonidine reduces sympathetic outflow by stimulating α-adrenergic receptors. Minoxidil is a direct-acting vasodilator. Verapamil causes vasodilation by inhibiting calcium ion flow into smooth muscle. Enalapril blocks the enzyme that converts angiotensin I to angiotensin II. Hydrochlorothiazide acts by decreasing blood volume.

19.4 Which one of the following antihypertensives is most likely to cause reflex tachycardia?

A. Propranolol
B. Nifedipine
C. Prazosin
D. Hydralazine
E. Captopril

Correct answer = D. Hydralazine has a significant hypotensive effect that activates baroreceptors.

19.5 From the list of antihypertensive drugs below select the one most likely to lower blood sugar.

A. Prazosin
B. Propranolol
C. Nifedipine
D. Captopril
E. Hydralazine

Correct answer = B. Propranolol blocks glycogenolysis.

19.6 Which one of the following drugs should not be given to a pregnant, hypertensive woman?

A. Hydrochlorothiazide
B. Propranolol
C. α-Methyldopa
D. Lisinopril
E. Verapamil

Correct answer = D. Lisinopril blocks the formation of angiotensin II, which is essential for normal growth and development of fetal kidney and other organs.

Drugs Affecting Blood

20

I. OVERVIEW

This chapter describes drugs useful in treating three important dysfunctions of blood: thrombosis, bleeding, and anemia. Thrombosis—the formation of an unwanted clot within the blood vessels or heart—is the most common abnormality of hemostasis. Bleeding disorders involving failure of hemostasis are less common than thromboembolic diseases and include hemophilia and vitamin K deficiency. Anemias caused by nutritional deficiencies can be treated with either dietary or pharmaceutical supplementation. Recently, *hydroxyurea* has been found to be beneficial in the treatment of sickle cell anemia. See Figure 20.1 for a summary of drugs affecting blood.

II. NORMAL RESPONSE TO VASCULAR TRAUMA

Physical trauma to the vascular system, such as a puncture or 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. The creation of an unwanted thrombus involves many of the same steps, except that the triggering stimulus is a pathologic condition in the vascular system rather than physical trauma.

A. Formation of a clot

Clot formation requires platelet activation and aggregation, followed by formation of thrombin. This serum protease catalyzes the production of fibrin which, when cross-linked, stabilizes the clot.

1. **Role of platelets:** Platelets respond to vascular trauma by "activation" processes, which involve three steps: adhesion to the site of injury, release of intracellular granules, and aggregation of the platelets (Figure 20.2). Normally, platelets circulate in the blood in an inactive form, but in response to various stimuli they become activated. Activated platelets undergo modifications that culminate in morphologic changes and in the expression of proteins and cell receptors. For example, after adhering to exposed collagen in the subendothelial layers of injured blood vessels, the platelets release granules containing chemical mediators. These promote platelet aggregation and the formation of a plug, composed of the viscous contents of lysed platelets, neutrophils and monocytes, that rapidly arrests bleeding.

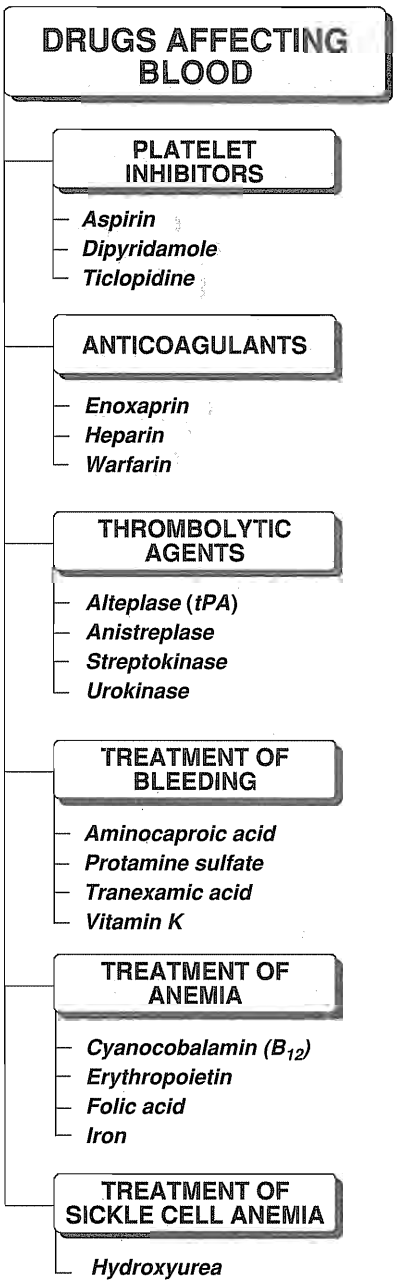


Figure 20.1
Summary of drugs used in treating dysfunctions of blood.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishing, Philadelphia, PA © 1997.

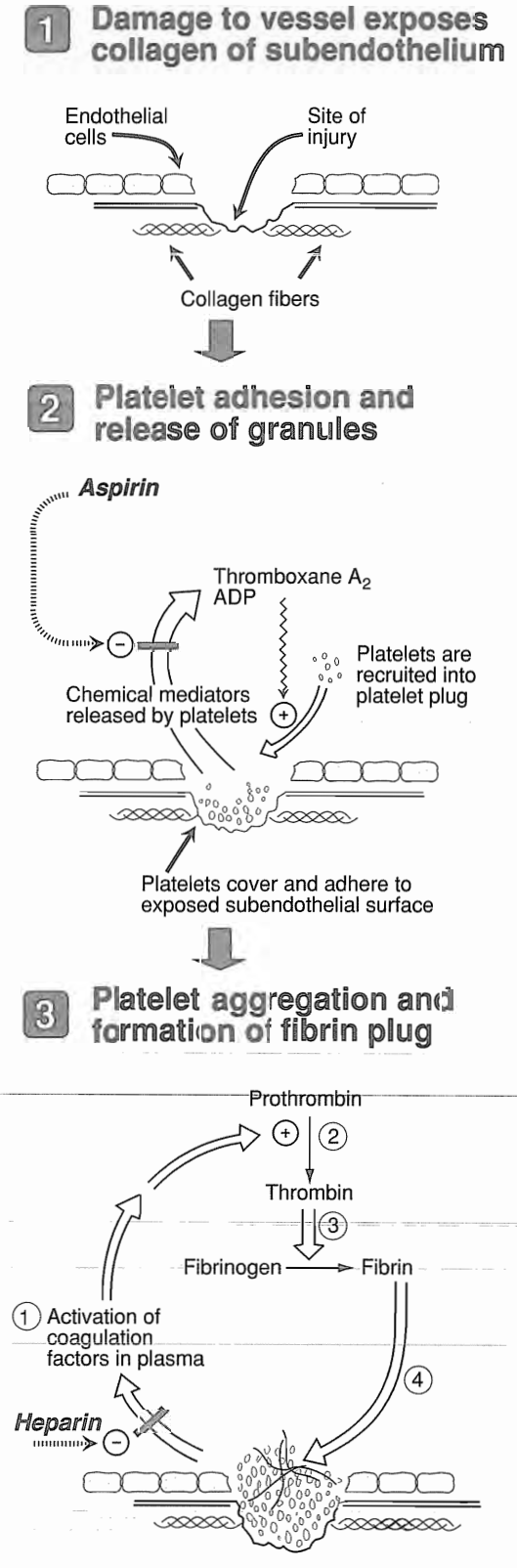


Figure 20.2
Formation of a hemostatic plug.

2. **Role of fibrin:** Local stimulation of the coagulation cascade by factors released from the injured tissue and platelets results in the formation of thrombin (Factor II). In turn, thrombin, a serine protease, catalyzes the conversion of fibrinogen to fibrin, which is incorporated into the plug. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic plug.

3. **Thrombus versus embolus:** A clot that adheres to a vessel wall is called a thrombus, whereas an intravascular clot that floats within 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 involves medium-sized vessels rendered thrombogenic by surface lesions of endothelial cells caused by atherosclerosis. In contrast, venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade, often as a result of a defect in the normal defense hemostatic mechanisms.

B. Fibrinolysis

During platelet plug formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators present in the tissue. Plasmin interferes in clot propagation and dissolves the fibrin network as wounds heal. At present, a number of fibrinolytic enzymes are available for treatment of myocardial infarctions or pulmonary emboli (see p. 201).

III. PLATELET ACTIVATION

The outer membrane of platelets contains a variety of receptors that function as sensors capable of responding to physiologic signals present in the plasma (Figure 20.3). These chemical stimuli are classified as platelet-activating if they promote platelet aggregation and the subsequent release of granules stored in the platelet. Conversely, other chemical signals are classified as platelet-inhibiting, if they inhibit platelet activation and the release of platelet granules. Whether platelets remain in a quiescent state or become activated is determined by the balance of activating and inhibiting chemical signals.

A. Chemical signals that oppose platelet activation

1. **Elevated prostacyclin levels:** In a normal, undamaged vessel, platelets circulate freely, since the balance of chemical signals indicates that the vascular system is not damaged. For example, prostacyclin (see p. 403), synthesized by the intact endothelial cells and released into plasma, binds to a specific set of platelet membrane receptors that are coupled to the synthesis of cyclic adenosine monophosphate (cAMP) as an intracellular messenger. Elevated levels of intracellular cAMP inhibit platelet activation, and the subsequent release of platelet aggregation agents (Figure 20.3).

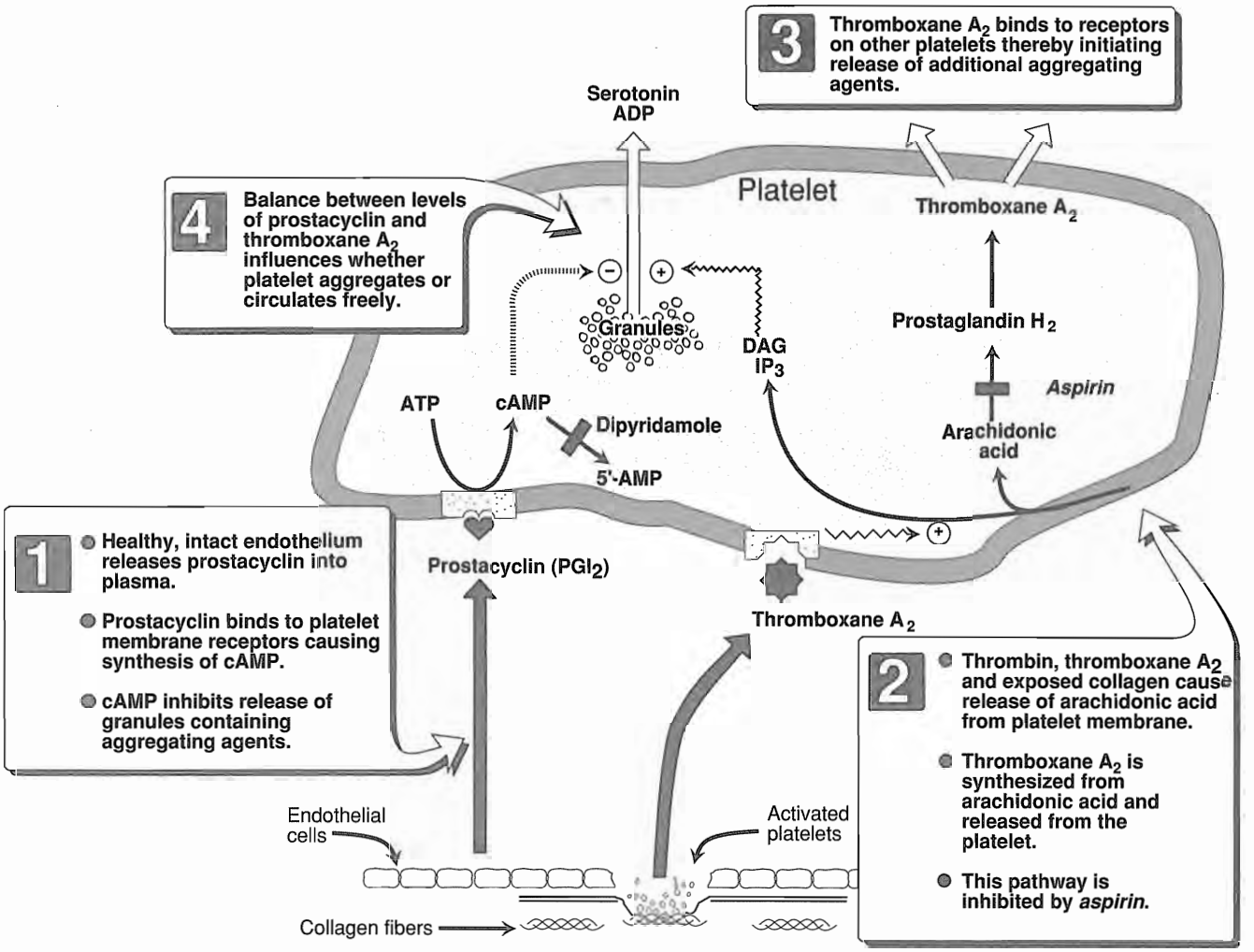


Figure 20.3
Chemical mediators influencing platelet activation and aggregation (relative size of platelets and endothelial cells are not to scale).

2. **Decreased plasma levels of thrombin and thromboxanes:** The platelet membrane also contains receptors that can bind thrombin, thromboxanes, and exposed collagen. When occupied, each of these receptor types triggers a series of reactions leading to the release into the circulation of intracellular granules and ultimately, to platelet aggregation. However, in the intact, normal vessel, circulating levels of thrombin and thromboxanes are low and the intact endothelium covers the collagen present in the subendothelial layers. The corresponding platelet receptors are thus unoccupied, and remain inactive. Consequently, platelet activation and aggregation are not initiated.

B. Chemical signals that promote platelet aggregation

1. **Decreased prostacyclin levels:** Damaged endothelial cells synthesize less prostacyclin, resulting in a localized reduction in

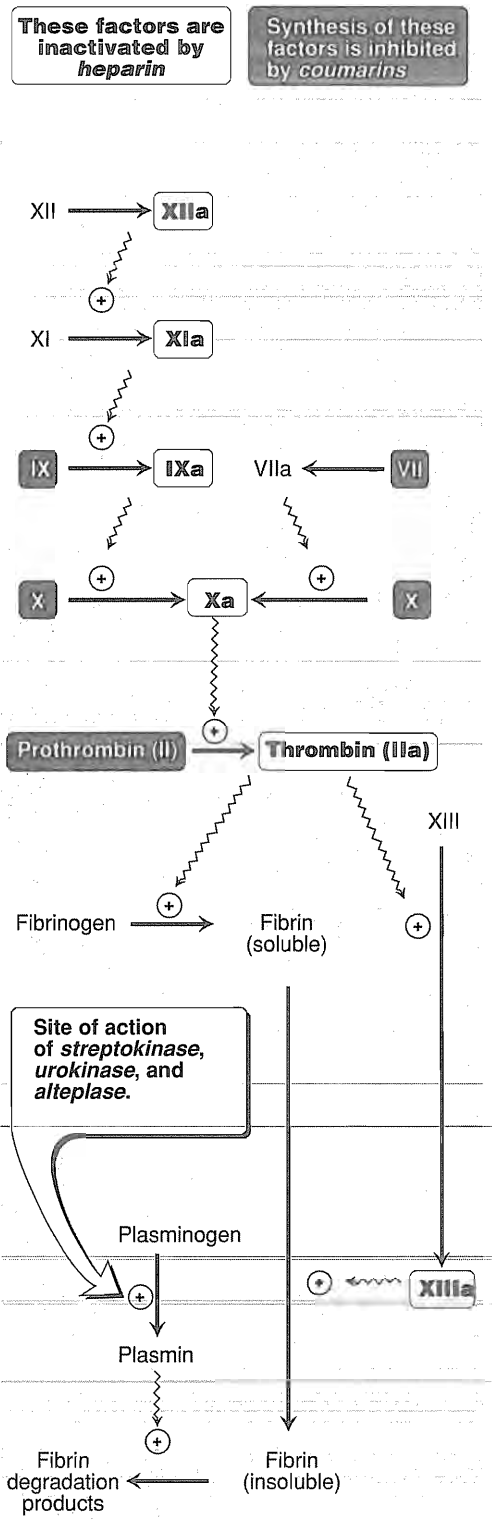


Figure 20.4
Formation of fibrin clot and its ultimate dissolution.

prostacyclin levels. The binding of prostacyclin to platelet receptors is decreased; thus lower levels of intracellular cAMP permit platelet aggregation.

2. **Exposed collagen:** Within seconds of vascular injury, platelets adhere to and virtually cover the exposed collagen of the subendothelium. Receptors on the surface of the platelet are activated by the collagen of this underlying connective tissue, which triggers the release of platelet granules containing adenosine diphosphate (ADP) and serotonin. This process is sometimes referred to as the "platelet release reaction," and the platelet is then said to be activated. Fibrinogen receptors are expressed on the platelet surface and the fibrinogen can then act as a bridge between two platelets.

3. **Increased synthesis of thromboxanes:** Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases, which liberate arachidonic acid from membrane phospholipid. Arachidonic acid is first converted to prostaglandin H_2 by cyclooxygenase, an enzyme that is irreversibly inactivated by *aspirin* (see p. 403). Prostaglandin H_2 is metabolized to thromboxane A_2, which is released into the 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 (see Figure 20.3).

IV. BLOOD COAGULATION

The coagulation process that generates thrombin consists of two interrelated pathways—the extrinsic and the intrinsic systems. The extrinsic system, which is probably the more important in vivo, is initiated by the activation of clotting Factor VII by a tissue factor, thromboplastin—a phospholipid and protein mixture. The intrinsic system is triggered by the activation of clotting Factor XII, following its contact in vitro with glass or highly charged surfaces. Both systems involve a cascade of enzymatic reactions that sequentially transform various plasma factors (proenzymes) to their active (enzymatic) forms, ultimately producing thrombin (Figure 20.4). Thrombin plays a key role in coagulation, since it is responsible for generation of fibrin, a glycoprotein that forms the meshlike matrix of the blood clot. Thrombin also activates clotting Factor XIII (necessary for stabilizing and crosslinking the fibrin molecules into an insoluble clot) as well as activating other blood clotting factors and platelet aggregation. If thrombin is not formed, or its function is impeded, for example, with antithrombin III, coagulation is inhibited.

V. PLATELET AGGREGATION INHIBITORS

Platelet aggregation inhibitors decrease the formation or the action of chemical signals that promote platelet aggregation. These agents have proven beneficial in the prevention and treatment of occlusive cardiovascular diseases, the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombolytic therapy in myocardial infarction.

A. Aspirin

Aspirin [AS pir in] blocks thromboxane A_2 synthesis from arachidonic acid in platelets by irreversible acetylation and inhibition of cyclooxygenase, a key enzyme in prostaglandin and thromboxane A_2 synthesis[1]. (See p. 405 for a discussion of the actions of aspirin on platelets.) 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 platelet—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 postmyocardial infarction patients. Currently, a single loading dose of 200 to 300 mg of *aspirin* followed by a daily dose of 75 to 100 mg is recommended. Bleeding time is prolonged, causing complications that include an increased incidence of hemorrhagic stroke as well as gastrointestinal bleeding, especially at higher doses of the drug.

B. Ticlopidine

Ticlopidine [Tye CLO pih deen] also acts as an inhibitor of platelet aggregation but by a mechanism other than that of *aspirin*. The drug inhibits the ADP pathway involved in the binding of platelets to fibrinogen and to each other. *Ticlopidine* has been shown to decrease the incidence of thrombotic stroke. After oral ingestion it is extensively bound to plasma proteins and undergoes hepatic metabolism. The drug can cause prolonged bleeding; its most serious adverse effect is neutropenia. Therefore, it is reserved for patients who cannot tolerate *aspirin*.

C. Dipyridamole

Dipyridamole [dye peer ID a mole], a coronary vasodilator, is employed to prophylactically treat angina pectoris. It is usually given in combination with *aspirin*. *Dipyridamole* increases intracellular levels of cyclic AMP by inhibiting cyclic nucleotide phosphodiesterase[2]. This inhibits thromboxane A_2 synthesis and may potentiate the effect of prostacyclin (PGI_2) 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 in inhibiting embolization from prosthetic heart valves.

VI. ANTICOAGULANTS

Two types of drugs are employed in preventing blood coagulation, *heparin* and the *vitamin K* antagonists. Their mechanisms of action differ, as do their clinical uses.

A. Heparin

Heparin [HEP a rin] is an injectable, rapidly-acting anticoagulant that is often used acutely to interfere with the formation of thrombi.

[1,2] See p. 206 for Infolink references to other books in this series.

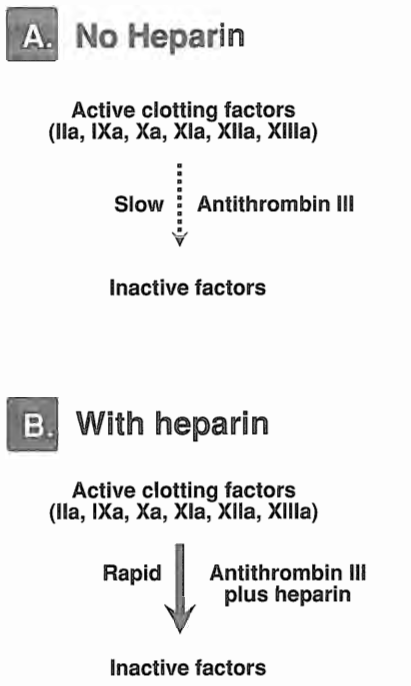


Figure 20.5
Heparin binds to antithrombin III and enhances its proteolytic activity.

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 or bovine lung. *Heparin* is a mixture of straight-chain anionic glycosaminoglycans with a mean molecular weight of 15,000. It is strongly acidic because of the presence of sulfate and carboxylic acid groups[3]. The realization that low molecular weight forms of *heparin* also can act as anticoagulants led to the isolation of *enoxaprin* [e NOX a prin], the first low molecular weight *heparin* (<6000) available in the USA.

1. **Mechanism of action:** *Heparin* acts indirectly by binding to antithrombin III to cause a rapid anticoagulant effect. Maximal anticoagulation occurs within minutes after intravenous *heparin* injection (unlike vitamin K antagonist anticoagulants, such as *warfarin*, whose maximum activity requires 8 to 12 hours). Antithrombin III, sometimes referred to as *heparin* cofactor, is an α-globulin that inhibits serine proteases, including several of the clotting factors, for example, thrombin (Factor II, Figure 20.5). In the absence of *heparin*, antithrombin III interacts with thrombin very slowly. The binding of *heparin* to antithrombin III produces a conformational change allowing the antithrombin to rapidly combine with and inhibit thrombin except that already bound to fibrin. [Note: While the *heparin*-antithrombin III complex readily inactivates thrombin, the complex of low molecular weight *heparin* with antithrombin is more specific against Factor Xa.] Chronic or intermittent administration of *heparin* can lead to a reduction in antithrombin III activity thus, increasing the risk of thrombosis. To minimize this risk, low-dose *heparin* therapy is usually employed.

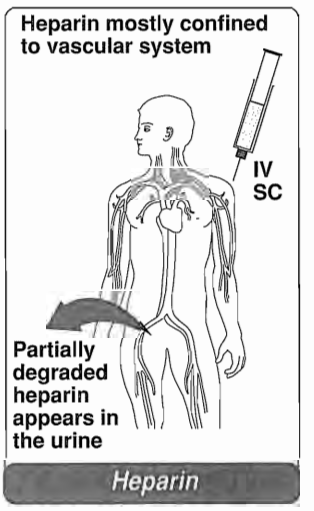
2. **Therapeutic uses:** *Heparin* limits the expansion of thrombi by preventing fibrin formation. *Heparin* is the major antithrombotic drug for the treatment of deep vein thrombosis and pulmonary embolism. It decreases the incidence of recurrent thromboembolic episodes. Clinically, *heparin* is used prophylactically to prevent postoperative venous thrombosis in patients undergoing elective surgery, and in those in the acute phase of myocardial infarction. Coronary artery rethrombosis after thrombolytic treatment is reduced with *heparin.* It is also used in extracorporeal devices (for example, dialysis machines) to prevent thrombosis. It is the anticoagulant of choice for treating pregnant women with prosthetic heart valves or venous thromboembolism, because it does not cross the placenta. *Heparin* has the advantage of speedy onset of action, which is rapidly terminated on suspension of therapy. *Enoxaprin* has been approved for prevention of deep vein thrombosis following hip replacement.

3. **Pharmacokinetics**

   a. **Absorption:** *Heparin* must be given parenterally either in a deep subcutaneous site or intravenously, because the drug does not readily cross membranes. *Enoxaprin* is only given subcutaneously. [Note: Intramuscular administration of either heparin is contraindicated because of hematoma formation.] *Heparin* is often administered intravenously in a bolus to achieve immediate anticoagulation followed by lower doses or

[3]See p. 206 for Infolink references to other books in this series.

continuous infusion. The latter is then maintained for 7 to 10 days, titrating the dose of *heparin* so that the activated partial thromboplastin time (PTT) is 1.5 to 2.5 times the normal control.



b. Fate: In the blood, *heparin* binds to many proteins that neutralize its activity and can cause resistance to the drug. Although generally restricted to the circulation, *heparin* is taken up by the reticuloendothelial system and undergoes depolymerization to inactive products. *Heparin* therefore has a longer half-life in patients with hepatic cirrhosis. Desulfation occurs in mononuclear phagocytes. The inactive metabolites as well as some of the parent *heparin* are excreted into the urine, therefore renal insufficiency also prolongs the half-life. [Note: *Heparin* does not cross the placental barrier.] The $t_{1/2}$ of *heparin* increases with dose; that of the low molecular weight heparins is about double that of the larger species.

4. **Adverse effects:** Despite early hopes of fewer side effects with *enoxaprin*, the complications have proven to be similar to those with *heparin*.

a. Bleeding complications: The chief complication of *heparin* therapy is hemorrhage. Careful monitoring of bleeding time is required to minimize this problem. Excessive bleeding may be managed by suspending the drug or treating with *protamine sulfate*. Infused slowly, the latter combines ionically with *heparin* to form a stable, inactive complex.

b. Hypersensitivity reactions: Chills, fever, urticaria, or anaphylactic shock are possible, since the *heparin* preparations are obtained from animal sources and may therefore be antigenic.

c. Thrombocytopenia: A decrease in the number of circulating platelets may occur after about 8 days of therapy. In some patients, *heparin*-induced platelet aggregation is followed by the formation of antiplatelet antibodies. Discontinuance of the drug then becomes necessary. Should *heparin*-induced thromboembolism occur, therapy with a drug that inhibits platelet aggregation or an oral anticoagulant is instituted in place of the *heparin*.

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

B. Warfarin

The coumarin anticoagulants, which include *warfarin* [WAR far in] and *dicumarol* [dye KOO ma role] (formerly *bishydroxycoumarin*) owe their action to their ability to antagonize the cofactor functions of *vitamin K*. Initially used as a rodenticide, *warfarin* is now widely employed clinically as an oral anticoagulant. Conflicting opinions exist concerning the usefulness of these agents in clinical situations such as myocardial infarction and hip arthroplasty. The potential

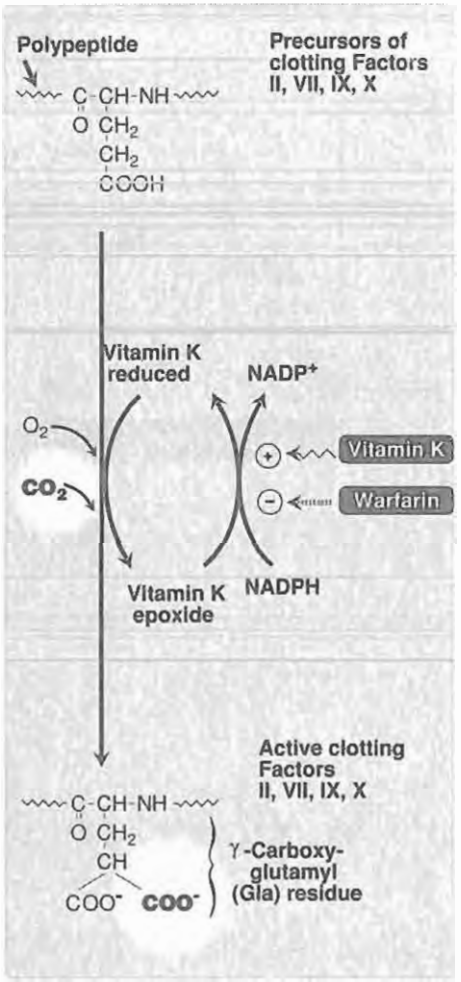


Figure 20.6
Mechanism of action of *warfarin*.

morbidity argues for a way to identify those patients who are truly at risk for thrombosis. Even careful monitoring to keep prothrombin time at 1.5 to 2.5 times longer than normal values does not prevent bleeding complications in about 20% of the patients.

1. **Mechanism of action:** Several of the protein factors (including Factors II, VII, IX, and X; see Figure 20.4) that are involved in the coagulation reactions depend on *vitamin K* as a cofactor in their complete synthesis by the liver. These factors undergo *vitamin K*-dependent posttranslational modification, whereby a number of their glutamic acid residues are carboxylated to form γ-carboxyglutamic acid residues[4] (Figure 20.6). In this reaction, the *vitamin K*-dependent carboxylase fixes CO_2 to form the new COOH group on glutamic acid, and reduced *vitamin K* co-factor is converted to *vitamin K* epoxide. *Vitamin K* is regenerated from the epoxide by vitamin K epoxide reductase. It is this enzyme that is inhibited by *warfarin*. The γ-carboxyglutamyl residues bind calcium ion and are essential for interaction with cell membranes. *Warfarin* or *dicumarol* treatment results in the production of inactive clotting factors, since they lack the γ-carboxyglutamyl side chains. Unlike *heparin*, the anticoagulant effects of *warfarin* are not observed until 8 to 12 hours after drug administration. The anticoagulant effects of *warfarin* can be overcome by the administration of *vitamin K*. However, reversal by *vitamin K* takes approximately 24 hours.

2. **Pharmacokinetics**

   a. **Absorption:** The sodium salt of *warfarin* is rapidly and completely absorbed after oral administration. Though food may delay absorption, it does not affect the extent of absorption of the drug. *Warfarin* is 99% bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk. However, drugs having a greater affinity for the binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient elevated activity (see p. 12). The drug readily crosses the placental barrier.

   b. **Fate:** The products of *warfarin* metabolism are inactive and, after conjugation to glucuronic acid, are excreted in the urine and stool.

3. **Adverse effects**

   a. **Bleeding disorders:** The principal untoward reaction 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 greater doses of the vitamin given intravenously. Whole blood, frozen plasma, or plasma concentrates of the blood factors may also be employed to arrest hemorrhaging.

   b. **Drug interactions:** A number of drug interactions that potentiate or attenuate the anticoagulant effects of *warfarin* have been identified. A summary of the most important of these interactions is shown in Figure 20.7.

[4]See p. 206 for Infolink references to other books in this series.

c. **Disease states:** These can also influence the hypoprothrombinemic state of the patient and influence the response to the anticoagulants. For example, a *vitamin K* deficiency, hepatic disease that impairs synthesis of the clotting factors, and hypermetabolic states that increase catabolism of the *vitamin K*-dependent clotting factors, can all augment the response to the oral anticoagulants.

d. **Contraindications:** The drug should never be used in pregnancy because it is teratogenic and can cause abortion.

VII. THROMBOLYTIC DRUGS

Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and thus dissolves clots (Figure 20.8). The first such agents to be approved, *streptokinase* and *urokinase*, cause a systemic fibrinolytic state that can lead to bleeding problems. *Alteplase*, also known as *tissue-type plasminogen activator (tPA),* acts more locally on the thrombotic fibrin to produce fibrinolysis, and is a potentially important agent in treating thromboembolic disease. (See Figure 20.9 for a comparison of the commonly used thrombolytic agents.) Clinical experience has shown about equal efficacy between *streptokinase* and *tPA*. Unfortunately, thrombolytic therapy is unsuccessful in about 20% of infarcted arteries and about 15% of those opened, reclose.

A. Common characteristics of thrombolytic agents

1. **Actions:** 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 20.8). In each case, clot dissolution and reperfusion occurs with a higher frequency when therapy is initiated early after clot formation, since clots become more resistant to lysis as they age. Unfortunately, increased local thrombin 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*.

2. **Administration:** 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 "therapeutic window," beyond which significant myocardial salvage becomes less likely. Thus thrombolytic agents are usually administered intravenously, since this route is rapid, inexpensive, and does not have the risks of catheterization.

3. **Therapeutic uses:** Originally used for the treatment of deep-vein thrombosis and serious pulmonary embolism, thrombolytic drugs are now being used with increasing frequency to treat acute myocardial infarction and peripheral arterial thrombosis and emboli, and for unclotting catheters and shunts.

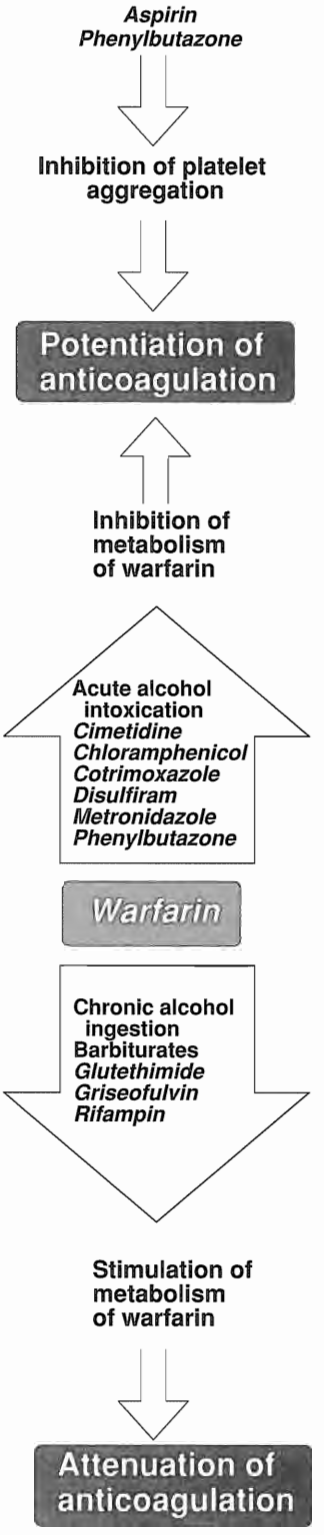


Figure 20.7
Drugs affecting the anticoagulant effect of warfarin.

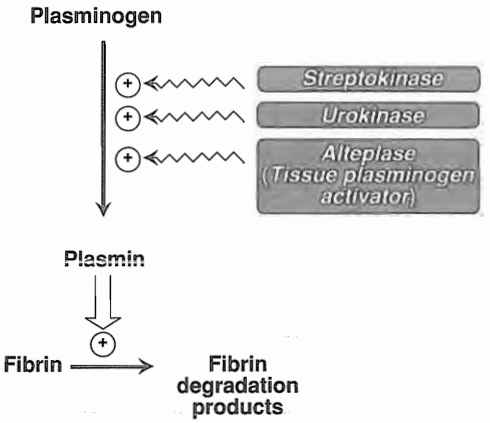


Figure 20.8
Activation of plasminogen by fibrinolytic agents.

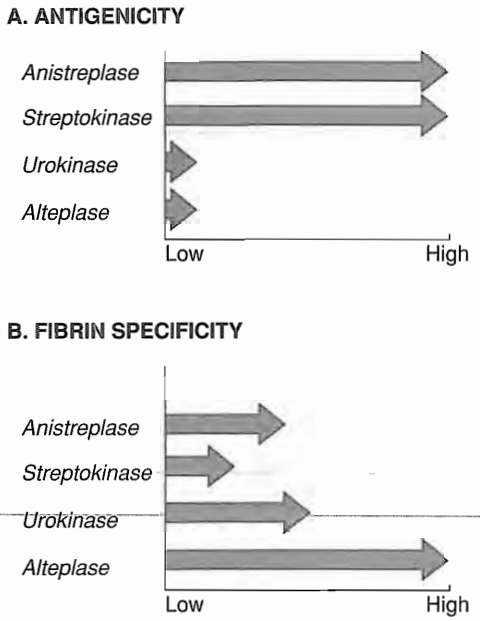


Figure 20.9
A comparison of commonly used thrombolytic agents.

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 20.10). They are contraindicated in patients with a healing wound, pregnancy, history of cerebrovascular accident, or metastatic cancer. Continued presence of thrombogenic stimuli may cause rethrombosis after lysis of the initial clot.

B. Alteplase (tPA)

Alteplase [AL te place] previously known as *tissue-type plasminogen activator (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, but it rapidly activates plasminogen bound to fibrin in a thrombus or a hemostatic plug. Thus, *alteplase* is said to be "fibrin selective" and at low doses, has the advantage of lysing only fibrin, without unwanted degradation of other proteins, notably fibrinogen. This contrasts with *urokinase* and *streptokinase*, which act on free plasminogen and induce a thrombolytic state. [Note: At dose levels of *alteplase* currently in use clinically, circulating plasminogen may be activated, resulting in hemorrhage.]

2. **Therapeutic uses:** Currently *alteplase* is approved for the treatment of myocardial infarction, massive pulmonary embolism, and acute ischemic stroke. *Alteplase* seems to be superior to *streptokinase* and *urokinase* in dissolving older clots, and may ultimately be approved for other applications. *Alteplase* administered within 3 hours of the onset of ischemic stroke significantly improves clinical outcome, that is, the patients' ability to perform activites of daily living.

3. **Pharmacokinetics:** The agent has a very short $t_{1/2}$ (about 5 minutes) and therefore is administered as a 100-mg dose with 10 mg injected intravenously as a bolus and the rest over 90 minutes.

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 β-hemolytic streptococci.

1. **Mechanism of action:** *Streptokinase* has no enzymic activity; instead it forms an active 1:1 complex with plasminogen, which then converts uncomplexed plasminogen to the active enzyme plasmin (Figure 20.11). In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen as well as clotting Factors V and VII.

2. **Therapeutic uses:** *Streptokinase* is approved for use in acute pulmonary embolism, deep venous 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 $t_{1/2}$ is less than a half-hour. Thromboplastin time is monitored and maintained at two to five times control value. On discontinuation of treatment, either *heparin* or oral anticoagulants may be administered.

4. **Adverse effects**

   a. **Bleeding disorders:** Activation of circulating plasminogen leads to elevated levels of plasmin, which may precipitate bleeding by dissolving hemostatic plugs (Figure 20.12). In the rare instance of life-threatening hemorrhage, *aminocaproic acid* (see p. 204) may be administered.

   b. **Hypersensitivity:** *Streptokinase* is a foreign protein and is antigenic. Rashes, fever, and rarely, anaphylaxis occur. Since 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%.

D. Anistreplase

Anistreplase [annie STREP lase] (*anisoylated plasminogen streptokinase activator complex; APSAC*) was synthesized in vitro to improve the kinetics of the *streptokinase-plasminogen* complex. Acylation blocks the lysine at the active site of plasminogen so that the complex is inactive until it binds to fibrin, a property that is retained. On binding, the anisoyl group is removed and fibrinolysis proceeds; thus the complex is semiselective for lysis at the clot site. The plasma half-life of *anistreplase* is long (about 90 minutes) compared to *streptokinase*. It is injected intravenously from 2 to 5 minutes. Reperfusion of the tissue compares favorably with *streptokinase*. Like other thrombolytic agents, bleeding is a complication, as well as are arrhythmias and hypotension.

E. Urokinase

Urokinase [yoor oh KINE ase] is an enzyme capable of directly degrading both fibrin and fibrinogen (see Figure 20.12). *Urokinase* was originally isolated from human urine, but it is now obtained from cultures of human fetal renal cells. *Urokinase* is more expensive than *streptokinase* and is usually employed in patients who are sensitive to *streptokinase*. [Note: *Urokinase* is not a foreign protein and is therefore nonantigenic.] Like *streptokinase, urokinase* is effective in treating severe pulmonary emboli and deep vein thrombosis. Bleeding complications are the most important side effects of this drug therapy.

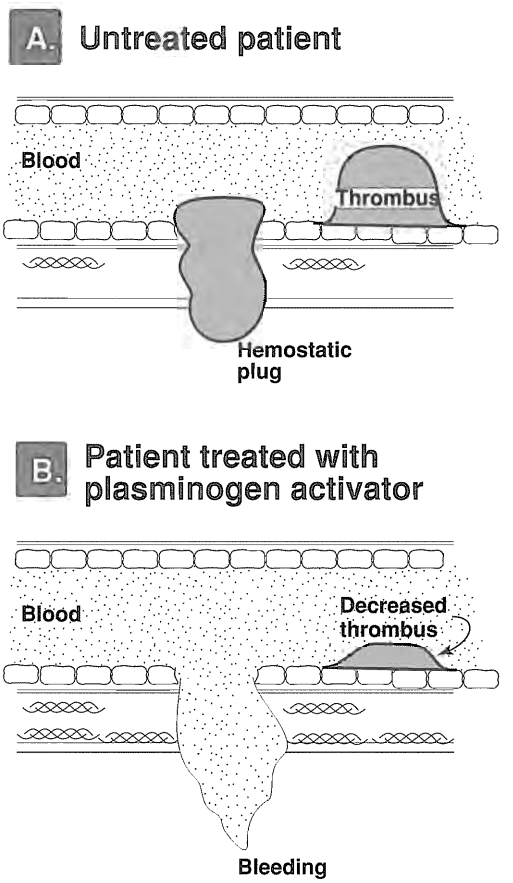


Figure 20.10
Degradation of an unwanted thrombus and a beneficial hemostatic plug by plasminogen activators.

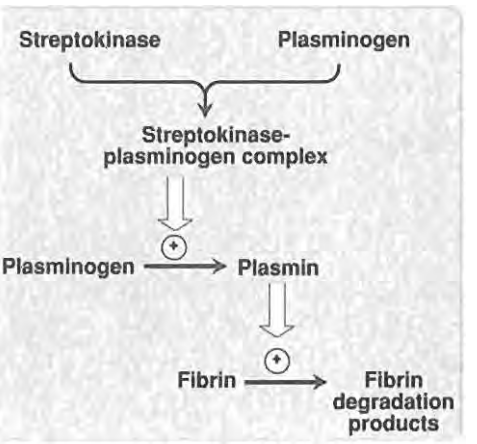


Figure 20.11
Mechanism of action of streptokinase.

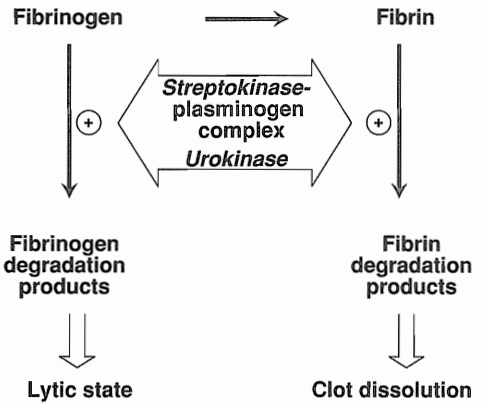


Figure 20.12
Streptokinase and *urokinase* degrade both fibrin and fibrinogen.

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 hemorrhaging. 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, they hold the risk of transferring viral infections.

A. Aminocaproic acid and tranexamic acid

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

B. Protamine sulfate

Protamine sulfate [PROE ta meen] 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 protein interacts with the negatively charged *heparin* to form a stable complex without anticoagulant activity. *Protamine sulfate* itself can interfere in coagulation when it is given in the absence of *heparin*, since the basic protein interacts with platelets and fibrinogen. Adverse effects include hypersensitivity, as well as dyspnea, flushing, bradycardia, and hypotension when rapidly injected.

C. Vitamin K

That *vitamin K1* (*phytonadione*) administration can stem bleeding problems due to the oral anticoagulants is not surprising, since those substances act by interfering in the action of the vitamin (see Figure 20.6). The response to *vitamin K* is slow, requiring about 24 hours; thus if immediate hemostasis is required, fresh frozen plasma should be infused. [Note: *Vitamin K* supplementation is required for patients receiving the cephalosporins, *cefamandole*, *cefoperazone*, and *moxalactam* (see p. 306).]

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, and a number of other disease states. These conditions can be 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 [for example, *iron*, *folic acid*, *vitamin B_{12}* (*cyanocobalamin*)] 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. Therefore it essentially results from a negative iron balance due to depletion of iron stores and inadequate intake, culminating in hypochromic microcytic anemia. Supplementation with *ferrous sulfate* is required to correct the deficiency. Gastrointestinal disturbances caused by local irritation are the most common adverse effects caused by 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* and *trimethoprim*, see p. 293). A primary result of *folic acid* deficiency is megaloblastic anemia, caused by diminished synthesis of purines and pyrimidines. This leads to an inability of erythropoietic tissue to make DNA and proliferate (Figure 20.13). [Note: It is important to evaluate the basis of the megaloblastic anemia prior to instituting therapy, because *vitamin B_{12}* deficiency indirectly causes symptoms of this disorder (see following paragraph).] *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. *Folic acid* administered orally has no known toxicity.

C. Cyanocobalamin (vitamin B_{12})

Deficiencies of *vitamin B_{12}* can result from either low dietary levels or, more commonly, from poor absorption of the vitamin due to the failure of gastric parietal cells to produce intrinsic factor (as in pernicious anemia) or to a loss of activity of the receptor needed for intestinal uptake of the vitamin.[5] Nonspecific malabsorption syndromes or gastric resection can also cause *vitamin B_{12}* deficiency. The vitamin may be administered orally (for dietary deficiencies), or 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.

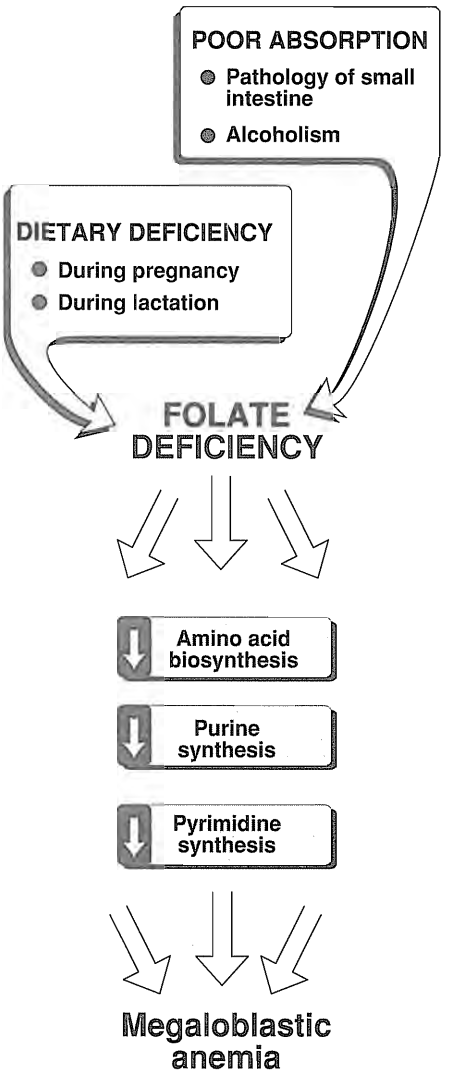


Figure 20.13
Causes and consequences of folic acid depletion.

[5]See p. 206 for Infolink references to other books in this series.

D. Erythropoietin

Erythropoietin [ery throw PO eetin] is a glycoprotein, normally made by the kidney, that regulates red 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 HIV-infected patients, and anemia in some cancer patients. Supplementation with iron may be required to assure an adequate response. The protein is usually administered intravenously in renal dialysis patients, but in others the subcutaneous route is preferred. Side effects such as iron deficiency and an elevation in blood pressure occur. [Note: The latter may be due to increases in peripheral vascular resistance and/or blood viscosity.]

X. AGENTS USED TO TREAT SICKLE CELL DISEASE

Recent clinical trials have shown that *hydroxyurea* can relieve the painful clinical course of sickle cell disease (anemia). *Hydroxyurea* is currently used to treat chronic myelogenous leukemia and polycythemia vera. In sickle cell disease, the drug apparently increases fetal hemoglobin (HbF) levels, thus diluting the abnormal hemoglobin S (HbS). 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.[6] The optimal dose of *hydroxyurea,* and its safety over the long run remain to be determined.

Study Questions

Choose the ONE best answer.

20.1. The anticoagulant activity of warfarin can be potentiated by all of the following EXCEPT:

A. Rifampin.
B. Aspirin.
C. Phenylbutazone.
D. Cimetidine.
E. Disulfiram.

Correct choice = A. Rifampin induces the hepatic mixed function oxidases that metabolize warfarin. Platelet inhibitors, such as aspirin increase the anticoagulant effect of warfarin. Phenylbutazone can transiently increase the level of free warfarin by displacing it from the plasma albumin binding site. Cimetidine inhibits warfarin metabolism and causes potentiation of the anticoagulant. Disulfiram inhibits warfarin metabolism.

[1]See p. 185 in **Biochemistry** (2nd ed.) for a discussion of prostaglandin synthesis.

[2]See p. 83 in **Biochemistry** (2nd ed.) for a discussion of the hydrolysis of cAMP.

[3]See p. 149 in **Biochemistry** (2nd ed.) for a discussion of the structure of heparin.

[4]See p. 338 in **Biochemistry** (2nd ed.) for a discussion of vitamin K.

[5]See p. 326 in **Biochemistry** (2nd ed.) for a discussion of vitamine B_{12}.

[6]See p. 36 in **Biochemistry** (2nd ed.) for a discussion of sickle cell disease.