CARDIOVASCULAR AGENTS

1. Introduction

Over the last several decades, tremendous advances in basic and clinical research on cardiovascular disease have greatly improved the prevention and treatment of the nation's number one killer of men and women of all races (it is estimated that ~40% of Americans (~60 million between the ages of 40–70, suffer from some degree of this disease) (1–3). During the second half of the twentieth century, the problem of treating heart disease was at the forefront of the international medical communities' agenda. This was reflected in the World Health Organizations (WHO) 1967 classification of cardiovascular disease as the world's most serious epidemic. The problem of cardiovascular disease continues to be the leading cause of death in the United States and other industrialized countries as we progress into the new millennium. According to the American Heart Association, heart disease and stroke cost an estimated $329.2 billion in medical expenses and lost productivity in the United States in 2002– more than double the economic cost of cancer.

Cardiovascular disease encompasses a wide range of disorders, and the methods of its treatment are both vast and diverse. As such, this article covers a range of key therapeutic agents including antiarrhythmic agents, antianginal agents, antilipemic agents, thrombolytic agents, agents used in the treatment of congestive heart failure, antiathersclerotic agents, and antihypertensive agents. The cardiac physiology, pathophysiology, and the causes of common cardiac diseases are reviewed before considering the drugs used in their treatment.

2. The Circulatory System and Cardiac Physiology

The cardiovascular system consists of the heart and a complex network of blood vessels—arteries, veins, and capillaries. The blood vessels provide nutrients to the body's cells and remove waste products. The heart functions as the pump that maintains the constant movement of blood through the blood vessels, ensuring that nutrient access and waste removal are constantly in homeostasis. During cardiac disease, this homeostasis is compromised by a malfunction in any one or several of the components of the cardiovascular system. Such disorders or diseases can lead to irreversible damage, and if untreated, death. Over the past several decades, great scientific strides have been made to provide therapeutic agents that restore normal function to malfunctioning components of the cardiovascular system.

The human heart and physiological processes that are altered during cardiovascular diseases are reviewed as background to the mechanisms of action of therapeutic agents. However, for in-depth details about heart anatomy, physiology, and electrophysiology, the reader is referred to textbooks and reviews (4).

2.1. Heart Anatomy. The human heart consists of four chambers: the right and left atria, and the right and left ventricles. Blood returning from the body collects in the right atrium, passes into the right ventricle, and is pumped to the lungs. Blood returning from the lungs enters the left atrium, passes into the left ventricle, and is pumped into the aorta. Valves in the heart prevent the backflow of blood from the aorta to the ventricle, the atrium, and the veins.

Heart muscle (the myocardium) is composed of three types of fibers or cells. The first type of muscle cell, found in the sinus and atrioventricular node, is weakly contractile, autorhythmic, and exhibits slow intercellular conduction. The second type of cell, located in the ventricles, is specialized for fast impulse conduction. The third type of myocardial cell is highly contractile, and composes the bulk of the heart.

Muscle cells in the heart abut tightly from end to end and form fused junctions known as intercalated disks. These tight junctions serve two functions. First, when one muscle cell contracts, it pulls on cells attached to its ends. Second, the close contacts facilitate excitation wave propagation. In addition, large channels, referred to as gap-junctions, pass through intercalated disks, and connect adjacent cells. These connections play an important role in transmitting and excitation wave from one cell to another.

Myocardial cells receive nutrients from coronary arteries that branch from the base of the aorta. Blockage of sections of these coronary arteries occurs during coronary artery disease (CAD). This leads to myocardial ischemia, which is the cause of myocardial infarction (heart attack) and angina pectoris.

2.2. Electrophysiology. With the exception of differences in calcium ion uptake and release, the mechanisms of contraction of human skeletal and cardiac muscle are comparable. However, unlike skeletal muscle, which requires neuronal stimulation, heart muscle contracts automatically. A heartbeat is composed of a contraction and relaxation of the heart muscle mass, and is associated with an action potential in each cell. The constant pumping action of the heart depends on the precise integration of electrical impulse generation, transmission, and myocardial tissue response.

A single heartbeat involves three principal electrical events: (*1*) an electrical signal to contract is initiated; (*2*) the impulse signal propagates from its point of origin over the rest of the heart; and (*3*) the signal abates or fades away. Cardiac arrhythmias develop when any of these three events are disrupted or impaired.

Figure 1 shows the principle components of the heart involved in cardiac impulse generation and conduction. In a healthy heart, the electrical impulse signal to contract is initiated in the sinoatrial (SA) node, which is located at the top of the right atrium (Fig. 1). Following depolarization of the SA node, the impulse spreads from cell to cell into the atria membrane. The atria contract first. Following, the impulse is focused through specialized automatic fibers in the atria known as the atrioventricular (AV) node (Fig. 1). At this node, the impulse is slowed so that the atria finish contracting before the impulse is propagated to myocardial tissue of the ventricles, which allows for the rhythmic pumping action that allows blood to pass from the atria to the ventricles.

After the electrical impulse emerges from the AV node, it is propagated by tissue known as the bundle of His, which passes the signal onto fast-conducting myocytes known as Purkinje fibers. These fibers conduct the impulse to surrounding, myocardial cells. The transmission of the impulse results in a characteristic electrocardiographic pattern.

Following contraction, heart muscle fibers enter a refractory period during which they will not contract or accept a signal to contract. Without this resting period, the initial contraction impulse originating in the SA node would not fade away, but would continue to propagate over the heart, leading to disorganized contraction (known as fibrillation).

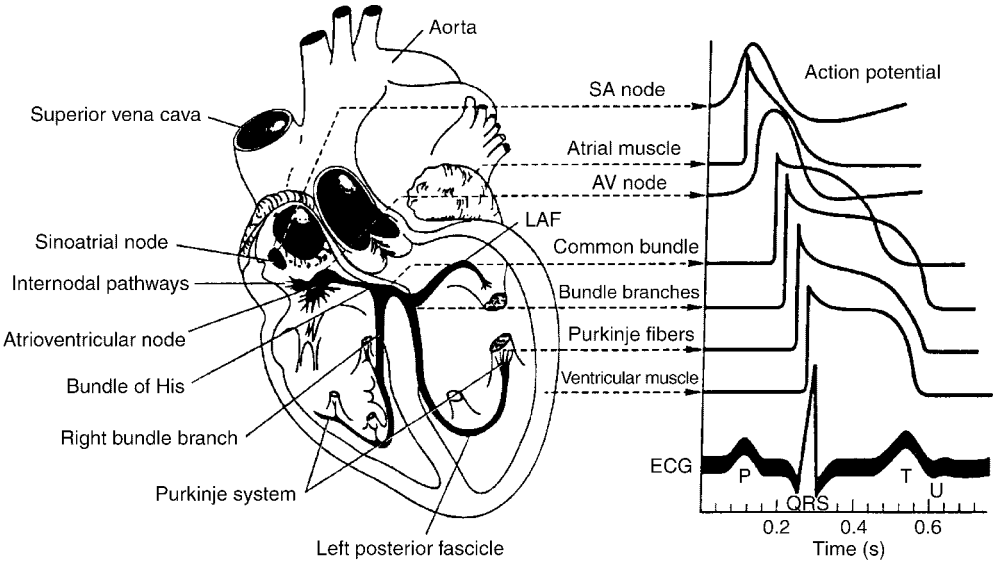


Fig. 1. Action potentials and the conducting system of the heart. Shown are typical transmembrane action potentials of the SA and AV nodes, specialized conducting myocardial cells, and nonspecialized myocardial cells. Also shown is the ECG plotted on the same time scale. Courtesy of Appleton & Lange.

2.3. Excitation and Contraction Coupling. Myocardial pacemaker cells, usually in the SA node, initiate an action potential that travels from cell to cell through the intercalated disks. This opens calcium channels and leads to a small influx of extracellular calcium ions, which triggers events leading to muscle contraction.

The biophysical property that connects excitation impulse and muscle contraction is based on the electrical potential differences that exist across cell membranes. These potentials arise due to several factors: (*1*) intracellular fluid is rich in potassium (K^+) and low in sodium (Na^+) (the reverse is true of extracellular fluid); (*2*) the cell membrane is more permeable to K^+ than it is to Na^+; (*3*) anions in the intracellular fluid are mostly organic and fixed, and do not diffuse out through the membrane; and (*4*) cells use active transport to maintain gradients of Na^+ and K^+.

Stimulation, either electrical or chemical, can depolarize the cell membranes by causing conformational changes that open membrane ion channels. This allows Na^+ to flow into the cell, which produces an action potential that is transmitted in an all-or-none fashion along the cellular membrane. As the action potential travels along the cell membrane, it induces a rise in the levels of free, or activator, calcium (Ca^{2+}) within the cell. This, in turn, initiates the interaction between actin and myosin, which leads to muscle contraction.

The action potential of a nonautomatic ventricular myocyte is shown in Figure 2. It is divided into phases 0–4. Phase 0, rapid membrane depolarization, results from the opening of fast sodium channels, and is augmented by Ca^{2+} entering via calcium channels. Phase 1 follows depolarization where there is a brief initial repolarization due to the closing of the sodium channels, and a brief outward movement of K^+ ions (ie, decrease in potassium conductance by inward rectifying current). Phase 2, is a plateau period, during which the slow influx of Ca^{2+} via an opening of the L-type calcium channel occurs (Fig. 2). During this phase, a prolonged refractory period exists during which the muscle cannot be reexcited. Phase 3, the repolarization period, is due primarily to the opening of and outward-rectifying K^+ channel and the closure of the calcium channels. The repolarization that occurs during this phase involves the interplay of several different types of potassium channels. Following phase 3, the transmembrane potential is restored to its resting value (phase 4, Fig. 2).

Cells of the nodal tissue and specialized conducting myocytes, such as Purkinje fibers, can spontaneously depolarize and generate action potentials that propagate over myocardial tissue. This is referred to as automaticity, and hence, all of these cells have pacemaker potential. In automatic cells, the outward leak of K^+ slows after repolarization; however, Na^+ continues to leach into the cell, which results in a steady increase in intracellular cations, and leads to depolarization. The action potential phase 4 of such cells is not flat, as observed in Figure 2, but becomes less negative until it reaches a threshold that triggers the opening of an L-type calcium channel in nodal tissue, or the sodium channel in conducting tissue. Thus, phase 0 in nodal tissue is due to the influx of Ca^{2+} and not Na^+. Figure 1 displays the action potentials for several cardiac cells having spontaneous and nonspontaneous depolarizability. The electrical activity of myocardial cells produces a current that can be recorded as an electrocardiogram (ECG).

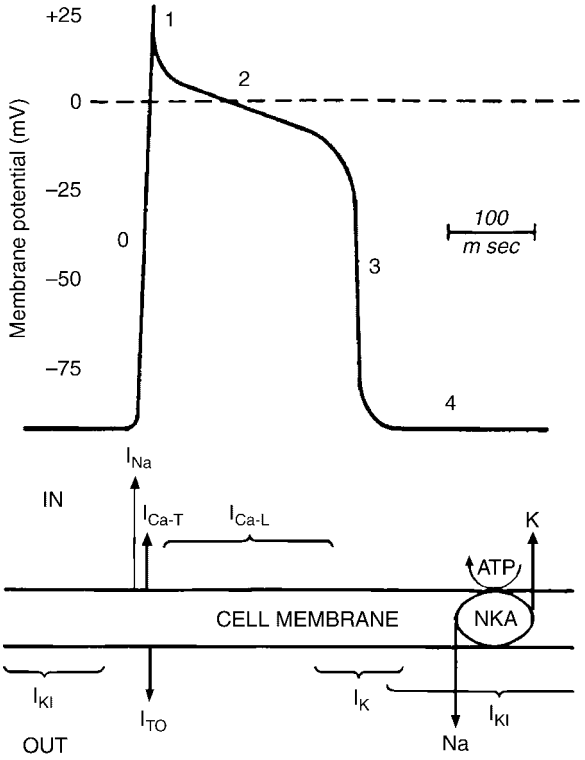


Fig. 2. Diagrammatic representation of an action potential of a nonautomatic ventricular cell, showing the principal ion fluxes involved in membrane depolarization and repolarization. The membrane potential in millivolts is given on the vertical axis. This denotes the electrical potential of the inner-face of the membrane relative to the outer-face. Phases of the potential are numbered 0,1,2,3,4, and are described in detail in the text.

Under normal physiological conditions, the SA node is the pacemaker for the rest of the heart. However, if the impulse from the SA node is slowed or blocked, or if the process of depolarization is accelerated in other automatic cells, non-SA node cells may initiate a wave of depolarization that either replaces the SA node impulse, or interferes with it. Heartbeats that originate from non-SA pacemaker activity are referred to as ectopic beats. However, not all ectopic beats result from altered pacemaker activity. Reentrant rhythms also are a major cause of ectopic beats. It is also possible to alter pacemaker activity without inducing an ectopic beat (ie, accelerated pacemaker in the atria).

The spontaneous impulse rate of automatic cells depends on the slope of action potential phase 4, the magnitude of the maximum diastolic potential, and the threshold potential. Changes in any of these values can occur during disease states, or from the effects of small "drug" molecules. B_1-Adrenergic receptor agonists increase heart rate by increasing phase 4 of the pacemaker cell action potential. Cholinergic drugs, which are agonists of muscarinic receptors, not only slow the heart by decreasing the phase 4 slope, but also hyperpolarize the cells.

Thus, compounds that block muscarinic receptors (atropine-like) increase heart rate, while compounds that block β-receptors slow the heart.

2.4. Ion Channels. The basic ion channel transmembrane protein consists of subunits designated as α, β, γ, and δ. The α subunit is the major component of Na^+, K^+, and Ca^{2+} channels and is tetrameric in nature. Each unit of this tetramer is designated as a domain, and each domain is made up of six segments designated: S1, S2, S3, S4, S5, and S6. The S5 and S6 segments are linked to each other in a specific arrangement so as to form the lining of the ion channels. The S4 segment of each domain contains many lysine and arginine residues that act in response to changes in the membrane potential, and are thus involved in the opening (voltage gating) of the channel. It is believed that the S4 segment constitutes the "*m*" gate (5–11). While a polypeptide chain that links the S6 segment of domain III to the S1 segment of domain IV constitutes the "*h*" gate (12,13).

Many of the drugs used to treat heart disease exert their therapeutic effects by blocking Na^+, K^+, and Ca^{2+} ion channels. In the case of sodium channel blockers, this results in a decrease in the slope of phase 0 of the action potential, and thereby decreases the V_{max}, or rate of conduction of the impulse. Sodium channel blockade can also prolong the refractory period by increasing the time that the channel is in the inactivated state, before returning to the resting state. Potassium channel blockers increase the duration of the action potential, as potassium currents are responsible for repolarizing the membrane during the action potential. Calcium channel blockers slow impulse conduction through the SA and AV nodes.

2.5. Channel Gates. The term gating refers to the process during which external stimuli cause conformational changes in membrane proteins, leading to the opening and closing of ion channels. It has been theorized that ion channels have at least two gates, referred to as *m* and *h*, and that both gates must be open for ions to pass through the channel (14). According to this model, channel gates cycle through three states: (*1*) closed resting (R), (*2*) open active (A), and (*3*) closed inactive (I).

The gating model shown in Figure 3, is a basic outline of the channel gating mechanism, and is useful for describing drug action (15,16). In the closed resting state, the *h* gate is open and the *m* gate is shut. During depolarization the *m* gate switches to the open position and the channel is activated, allowing the fast passage of ions through the channel. Depolarization also initiates the channel inactivation so that the channel begins to move from the open to the closed inactive state. In the closed inactive state both the *m* and *h* gates are shut, and the channel does not respond to further repolarization until it has moved back to the closed resting state, during which the *h* gate is again open and the *m* gate is shut.

2.6. Sodium Channels. There is strong evidence indicating that the amino acid sequence of sodium channels has been conserved over a long period. As indicated earlier, the inward voltage dependent Na^+channel consists of four protein subunits designated as α, β, γ, and δ. The α subunit, the major component of Na^+ channel made up of 200 amino acids, is subdivided into four covalently bound domains and contains binding sites for a number of antiarrhythmic compounds and other drugs. The Na^+ channels are found in neurons, vertebrate

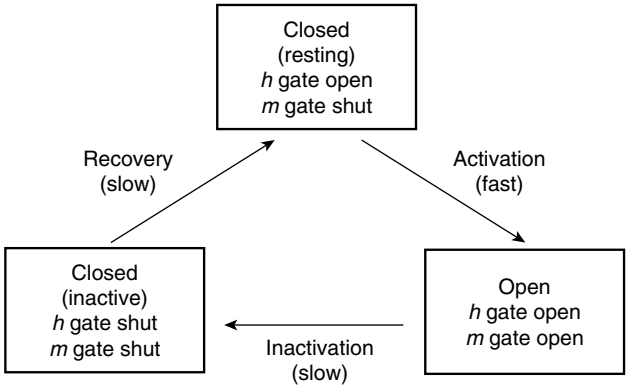


Fig. 3. Simplified representation of the gating mechanism in voltage-activated sodium, potassium, and calcium channels. The model hypothesizes three states: closed resting, open active, and closed inactive; and two gates h and m. The figure depicts what are generally considered to be the essential features of gating, which include a closed "resting" state that is capable of rapidly opening in response to changes in membrane potential followed by a refractory period in which the channel slowly returns to the resting state.

skeletal muscle, and cardiac muscle. Electrophysiological studies indicating that Na^+ channels favor the passage of Na^+ over K^+, point to the fact that Na^+ channels must be narrow and ion conductance depends on the ions size (ionic radius of Na^+ is 0.95 in. as compared to that of K^+ being 1.33 in.) and possibly steric factors (7). There is also some evidence indicating that voltage dependent cardiac Na^+ channels exist in two isoforms: fast and slow (17). Activation of the fast Na^+ channels in cardiac cells produces the rapid influx of Na^+ and depolarizes the membrane in all cardiac myocytes, except nodal tissue, where Na^+ channels are either absent or relatively few in number (18). The Na^+ channels are almost all voltage-gated, and gates open in response to changes in membrane potential.

2.7. Potassium Channels. Potassium channels are outward voltage-dependent channels. Similar to Na^+ channels, the major K^+ channel subunit consists of four domains, but unlike the α subunit of Na^+ channels, the domains of the K^+ channels are not covalently linked. At least 10 genes code for the K^+ channel domains, which means that hundreds of combinations of four-domain channels can be constructed. Recently, it has been reported that some of the K^+ channels contain only two transmembrane segments (9,10). Many K^+ channels are classified as rectifying, which means that they are unidirectional (or transport ions in one direction only), and that their ability to pass current varies with membrane potential.

The inward-rectifying K^+ current (usually designated I_K) allows K^+ to move out of the cell during phase 4 of the action potential, but is closed by depolarization; the outward-rectifying K^+ current (usually designated I_K) is opened by depolarization. Hence, the I_{KI} makes a substantial contribution to the value of the resting (phase 4) membrane potential; the I_K is the major outward current contributing to repolarization (19). Adenosine Triphosphate (ATP) sensitive K^+ channels are activated if the ATP level in the heart decreases as observed in myocardial ischemia (20). This leads to the inward flow of Ca^{2+} ions, thereby

reducing myocardial contractility and conserving energy for basic cell survival processes.

The K^+ channels are highly selective and are 100-fold more permeable to K^+ than to Na^+ (21). Certain types of molecules bind extracellularly and block the voltage gated K^+ channels (16). These include several peptide toxins, as well as small charged organic molecules such as tetraethylammonium, 4-aminopyridine, and quinine. Other molecules have been found to be K^+ channel openers. These compounds act on the ATP sensitive K^+ current, and provide cardioprotection during ischemia. The K^+ channel opener molecules also relax smooth muscle cells, and may increase the coronary blood flow during angina (22–28). The activation of ATP-sensitive K^+ channels does result in an increase inward flow of Ca^{2+} and outward flow of K^+ resulting in reduction of action potential duration and net Ca^{2+} entry.

2.8. Calcium Channels. Calcium ions are essential for the chain of events that lead to myocardial contraction. The role of calcium in the cardiac cycle has been studied extensively for years. Four types of voltage-dependent calcium channels with specific function and location have been identified. These include (*1*) the L type (found mainly in skeletal, cardiac and smooth muscle cells); (*2*) the T type (located in pacemaker cells); (*3*) the N type (found in neuronal cells), and (*4*) the P type (located at neuromuscular junctions) (29–31). L-type Ca^{2+} channels are formed by a complex arrangement of five protein subunits designated as the $\alpha 1$, $\alpha 2$, β, γ, and δ subunits, which are comprised of polypeptide chains of different lengths. The arrangement of these subunits is shown in Figure 4. The tetrameric $\alpha 1$ subunit is the most important functional component forming the Ca^{2+} channel, and is responsible for producing the pharmacological effects of calcium channel blockers. The Ca^{2+} channels play an important role in cellular excitability by allowing the rapid influx of Ca^{2+}, which depolarizes the cell. The resulting increase in intracellular Ca^{2+} is essential for the regulation

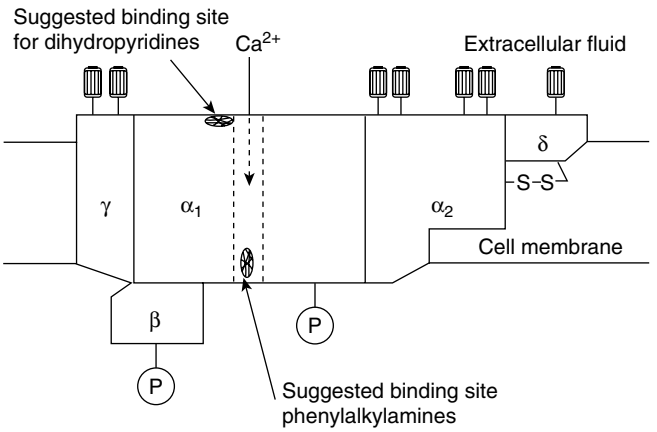


Fig. 4. Suggested structure of an L-type calcium channel from skeletal muscle, showing the five protein subunits that comprise the channel. Phosphorylation sites are indicated by P. Binding sites for phenylalkylamine and dihydropyridine calcium channel blockers. Courtesy of *Trend. Pharmacol. Sci.*

of Ca^{2+} dependent processes including excitation–contraction coupling, excitation–secretion coupling, and gene regulation. It has been suggested that dihydropyridine calcium channel blockers exert their effects by binding at the top of the channel near the cytoplasmic entrance, while arylalkylamines bind at the bottom of the channel between domains III and IV of the $\alpha 1$ subunit. The other hydrophobic $\alpha 2$, β, γ, and δ subunits may play a role in positioning the $\alpha 1$ subunit in the membrane. L-type channels are activated slowly by partial depolarization of the cell membrane, and inactivated by full depolarization and by increasing Ca^{2+} concentration. In nodal tissues, where fast sodium channels are absent or sparse, L- and T-type Ca^{2+} channels are responsible for depolarization.

3. Antiarrhythmic Agents

3.1. Mechanisms of Cardiac Arrhythmias. The pumping action of the heart involves three principle electrical events: the generation, the conduction or propagation, and the fading away of the signal. When one or more of these events is disrupted, cardiac arrhythmias may arise.

In a healthy heart, cells located in the right atrium, referred to as the SA node or pacemaker cells, initiate a cardiac impulse. The spontaneous electrical depolarization of the SA pacemaker cells is independent of the nervous system; however, these cells are innervated by both sympathetic and parasympathetic fibers, which can cause increases or decreases in heart rate as a result of nervous system stimulation. Other special cells in the heart also possess the ability to generate an impulse, and may influence cardiac rhythm, but are normally surpassed by the dominant signal generation of SA pacemaker cells. When normal pacemaker function is suppressed due to pathological changes occurring from infarction, digitalis toxicity, or excessive vagal tone or when excessive release of catecholamines from sympathomimetic nerve fibers occurs, these other automatic cells (including special atrial cells, certain AV node cells, the bundle of His, and Purkinje fibers) have the potential to become ectopic pacemakers, which can dominate cardiac rhythm, and consequently lead to arrhythmias.

Disorders in the transmission of the electrical impulse can lead to conduction block and reentry phenomenon. Conduction block may be complete (no impulses pass through the block), partial (some impulses pass through the block), and bidirectional or unidirectional. During bidirectional block, an impulse is blocked regardless of the direction of entry; a unidirectional block occurs when an impulse from one direction is completely blocked, while impulses from the opposite direction are propagated (although usually at a slower than normal rate).

During another condition known as heart block, the impulse signal from the SA node is not transmitted through either the AV node or lower electrical pathways properly. Heart block is classified by degree of severity: (*1*) first degree heart block: all impulses moving through the AV node are conducted, but at a slower than normal rate; (*2*) second degree heart block: some impulses fully transit the AV node, whereas others are blocked (as a result, the ventricles fail to beat at the proper moment); (*3*) third degree heart block: no impulses reach the ventricles (automatic cells in the ventricles initiate impulses, but at a slower rate, and as a result the atria and ventricles beat at somewhat independent rates).

The most serious cause of life-threatening cardiac arrhythmias results from a condition known as reentry, which occurs when an impulse wave circles back through the heart, reenters previously excited tissue, and reactivates the cells. Under normal conditions, reentry does not occur, as cells become unable to accept an excitation impulse for a period of time that is sufficient for the original signal to abate. Hence, the cells will not contract again until a new impulse emerges from the SA node. However, there are certain conditions during which this does not happen, and the impulse continues to circulate. The essential condition for reentry to occur involves the development of a cellular refractory period that is shorter than the conduction velocity. Consequently, any circumstance that either shortens the refractory period, or lengthens the conduction time, can lead to reentry. Various types of alteration in automacity (enhanced and triggered automacity) can trigger cardiac arrhythmias.

Nearly all tachycardias, including fibrillation, are due to reentry. The length of the refractory period depends mainly on the rate of activation of the potassium current; the rate of conduction depends on the rate of activation of the calcium current in nodal tissue, and the sodium current in other myocytes. The channels controlling these currents are the targets for suppressing reentry.

While many conditions can lead to reentry, the most common is shown in Figure 5. The conditions needed for this type of reentry are as follows: first, the existence of an obstacle, around which the impulse wave front can propagate,

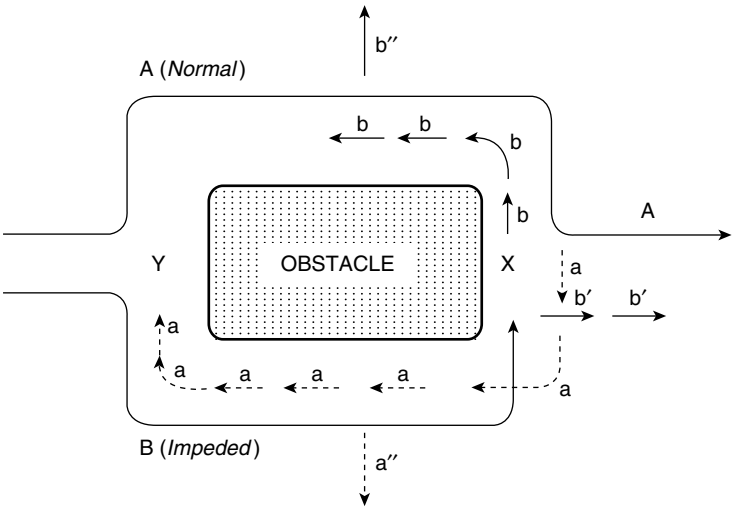


Fig. 5. Model for reentrant activity. A depolarization impulse approaches an obstacle (nonconducting region of the myocardium) and splits into two pathways (A and B) to circumvent the obstacle. If pathway B has impeded ability to conduct the action potential the following may occur. (*1*) If impulse B is slowed and arrives at cross junction X after the absolute refractory period of cells depolarized by A, the impulse may continue around the obstacle as shown by path b and/or follow A along path b′. In both cases, the impulse is said to be reflected. (*2*) If pathway B shows unidirectional block, impulse A may continue around the obstacle as shown by path a. If the obstacle is large enough, so that cells in cross region Y are repolarized before the return of a or b, then a circus movement may be established. Both (*1*) and (*2*) may propagate daughter impulses (a″ and b″) to other parts of the myocardium. These effects can give rise to coupled beats and fibrillation.

is needed. The obstacle may be infarcted or scarred tissue that cannot conduct the impulse. The second condition needed is the existence of a pathway that allows conduction at the normal rate around one side of the obstacle, while the other side of the pathway is impaired. The impairment may be such that it allows conduction in only one direction (unidirectional block) or it may allow conduction to proceed at a greatly reduced rate, such that when the impulse emerges from the impaired tissue, the normal tissue is no longer refractory. These pathways are usually localized, eg, within the AV node or the end branches of part of the Purkinje system. Alternatively, they can be more extensive and may give rise to daughter impulses capable of spreading to the rest of the myocardium.

Unidirectional block occurs in tissue that has been impaired, such that its ability to conduct an impulse is completely blocked in one direction but only slowed in the other. As a result of unidirectional block, the impulse cannot proceed forward along path B (Fig. 5), and the cells on this path remain in a polarized state. However, when the impulse traveling along path A reaches a suitable cross-junction (point X in Fig. 5), the impulse proceeds back along path a (Fig. 5), although at a slower rate than normal (indicated by the dotted path line, Fig. 5). When this impulse reaches another cross-junction (Y), it is picked up by path A and conducted around the circle. If the obstacle is large enough, the cells in path A will have repolarized and the path will again be followed, giving rise to a continuous circular movement. When reentry occurs randomly in the myocardium, it results in random impulses that lead to cardiac fibrillation. Thus, the reentry is critically dependent on two factors: unidirectional conduction block and decremental conduction.

3.2. Types of Cardiac Arrhythmias. Arrhythmias can be divided into two categories: ventricular and supraventricular arrhythmias. Within these two categories, arrhythmias are further defined by the pace of the heartbeats. Bradycardia indicates a very slow heart rate of <60 beats/min; tachycardia refers to a very fast heart rate of >100 beats/min. Fibrillation refers to fast, uncoordinated heartbeats.

Listed below are common forms of arrhythmias grouped according to their origin in the heart. Supraventricular arrhythmias include (*1*) sinus arrhythmia (cyclic changes in heart rate during breathing); (*2*) sinus tachycardia (the SA node emits impulses faster than normal); (*3*) sick sinus syndrome (the SA node fires improperly, resulting in either slowed or increased heart rate); (*4*) premature supraventricular contractions (a premature impulse initiation in the atria causes the heart to beat prior to the time of the next normal heartbeat); (*5*) supraventricular tachycardia (early impulse generation in the atria speed up the heart rate); (*6*) atrial flutter (rapid firing of signals in the atria cause atrial myocardial cells to contract quickly, leading to a fast and steady heartbeat); (*7*) atrial fibrillation (electrical impulses in the atria are fired in a fast and uncontrolled manner, and arrive in the ventricles in an irregular fashion); and (*8*) Wolff-Parkinson-White syndrome (abnormal conduction paths between the atria and ventricles cause electrical signals to arrive in the ventricles too early, and subsequently reenter the atria).

Arrhythmias originating in the ventricles include (*1*) premature ventricular complexes (electrical signals from the ventricles cause an early heartbeat, after which the heart seems to pause before the next normal contraction of the

ventricles occurs); (*2*) ventricular tachycardia (increased heart rate due to ectopic signals from the ventricles); and (*3*) ventricular fibrillation (electrical impulses in the ventricles are fired in a fast and uncontrolled manner, causing the heart to quiver).

3.3. Classification of Antiarrhythmic Drugs. The classification of antiarrhythmic agents is important for clinical application; however, there is no single classification system that has gained universal endorsement. At this time, the method proposed by Singh and Vaughan Williams (32) continues to be the most widespread classification scheme. Since its initial conception, this classification method has undergone several modifications—calcium channel blockers have been added as a fourth class of compounds (33), and class I agents have been subdivided into three groups to account for their sodium channel blocking kinetics (34). Table 1 lists examples of drugs in each of these classes and provides other pertinent information such as CAS registry number, molecular formula, and various trade names. Note that miscellaneous drugs (35) have been added to Table 1 to account for compounds with mechanisms of action that do not fit within the four standard classes (I–IV).

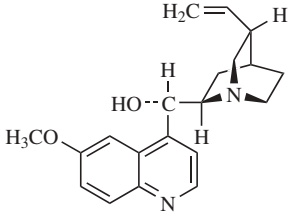
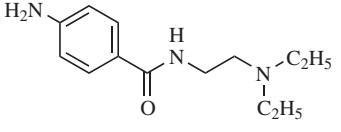
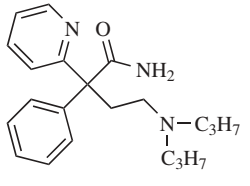
3.4. Perspective: Treatment of Arrhythmias. In recent years, there have been many changes in the way the arrhythmia is treated. New technologies, including radiofrequency ablation and implantable devices for atrial and ventricular arrhythmias, have proven to be remarkably successful mechanical treatments. In addition, cardiac suppression trials (CAST) and numerous other studies have provided evidence indicating drugs that act mainly by blocking sodium ion channels—Class I agents under the Singh and Vaughn Williams system of classification—may have the potential to increase mortality in patients with structural heart disease (36,37). Since the CAST results were released, the use of Class I drugs has decreased, and attention has shifted to developing new Class III agents, which prolong the action potential and refractoriness by acting on potassium channels. Of the Class III antiarrhythmic agents, amiodarone has been studied extensively, and has proven to be a highly effective drug for treating life-threatening arrhythmias.

In addition, new studies have indicated that combination therapies, eg, administration of amiodarone and Class II β-blockers, or concomitant treatment with implantable mechanical devices and drug therapies are effective avenues for treating arrhythmias.

3.5. Class I Agents. Antiarrhythmic agents in this class bind to sodium channels and inhibit or block sodium conductance. This inhibition interferes with charge transfer across the cell membrane. Investigations into the effects of Class I antiarrhythmics on sodium channel activity have resulted in the division of this class into three separate subgroups—referred to as IA, IB, and IC (38).

The basis for dividing the Class I drugs into subclasses resulted from measured differences in the quantitative rates of drug binding to, and dissociation from, sodium ion channels (38). Class IB drugs, which include lidocaine, tocainide, and mexiletine, rapidly dissociate from sodium channels, and consequently have the lowest potencies of the Class I drugs—these molecules produce little to no change in the action potential duration, and shorten repolarization. Class IC drugs, which include encainide and lorcainide, are the most potent of the Class I antiarrhythmics; drugs in this class display a characteristically slow dissociation

Table 1. **Antiarrhythmic Agents**

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
			Class I Antiarrhythmic Agents	
			Class IA	
quinidine	[56-54-2]	$C_{20}H_{24}N_2O_2$	Cardioquin, Galactoquin, Duraquin, Quinaglute, Quinora, Quincardine, Kinidin, Quiniduran	
procainamide	[614-39-1]	$C_{13}H_{22}ClN_3O_3$	Amisalin, Novocamid, Procamide Procanbid, Procapan, Pronestyl	
disopyramide	[3737-09-5]	$C_{21}H_{29}N_3O$	Dicorantil, Isorythm, lispine, Rythmodan, Ritmodan	

Class IB

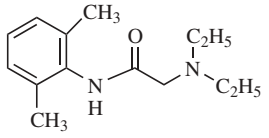
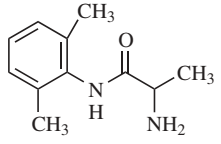
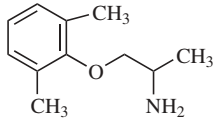
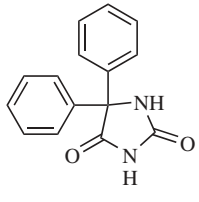
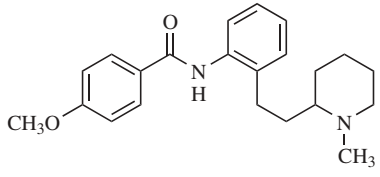
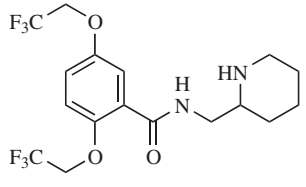
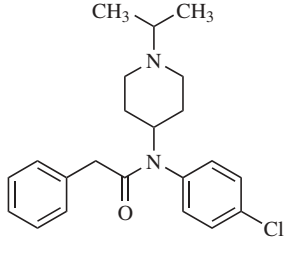
lidocaine	[6108-05-0]	$C_{14}H_{23}ClN_2O$	Lidesthesin, Odontalag, Sedagul, Xylocard, Xyloneural	
tocainide	[71395-14-7]	$C_{11}H_{17}ClN_2O$	Tonocard, Xylotocan, Taquidil	
mexiletine	[5370-01-4]	$C_{11}H_{18}ClNO$	Mexitil, Ritalmex	
phenytoin	[630-93-3]	$C_{15}N_{11}N_2NaO_2$	Aurantin, Epanutin, Phenhydan, Tacosal, Pyoredol	

Table 1 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
			Class IC	
encainide	[66794-74-9]	$C_{22}H_{28}N_2O_2$	Enkaid	
flecainide	[54143-56-5]	$C_{19}H_{24}F_6N_2O_5$	Apocard, Flecaine, Tambocor	
loracainide	[58934-46-6]	$C_{22}H_{28}Cl_2N_2O$	Lopantrol, Lorivox, Remivox	

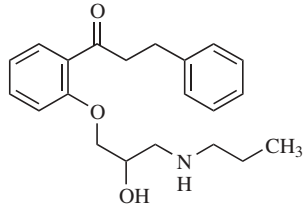
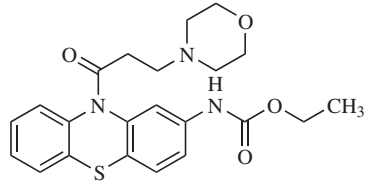
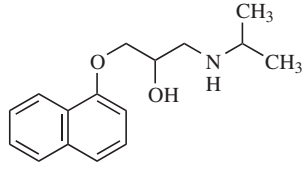
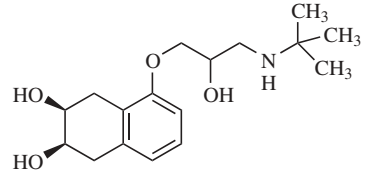
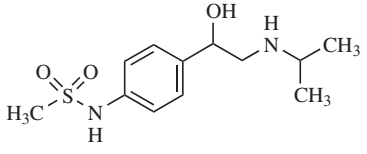
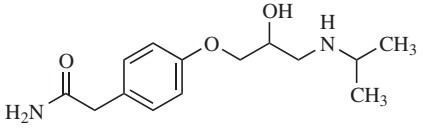
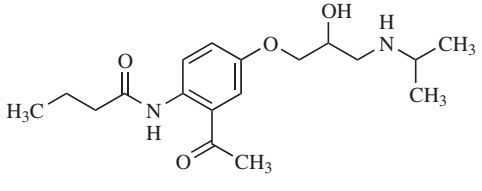
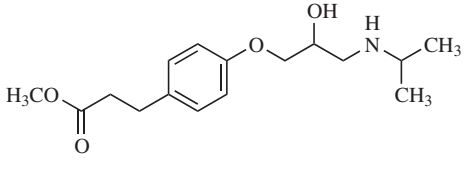
propafenone	[34183-22-7]	$C_{21}H_{28}ClNO_3$	Rythmol, Pronon, Rythmonorm	
moricizine	[29560-58-5]	$C_{22}H_{26}ClN_3O_4S$	Ethmozine	
		Class II Antiarrhythmic Agents		
propranolol HCl	[318-98-9]	$C_{16}H_{22}ClNO_2$	Inderal, Inderide, Angilol, Bedranol, Duranol, Elbrol, Oposim, Tensol	
Nadolol	[42200-33-9]	$C_{17}H_{27}NO_4$	Corgard, Solgol, Corzide, Nadolol	

Table 1 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
l-sotalol	[959-24-0]	$C_{12}H_{21}ClN_2O_3S$	Beta-cardone, Betapace, Darob, Sotacor, Sotalex	
atenolol	[29122-68-7]	$C_{14}H_{22}N_2O_3$	Tenormin, Tenoretic, Atenol, Tenoblock, Basan	
acebutolol	[34381-68-5]	$C_{18}H_{29}ClN_2O_4$	Acecor, Acetanol, Neptal, Prent, Sectral	
esmolol	[81161-17-3]	$C_{16}H_{26}ClNO_4$	Brevibloc	

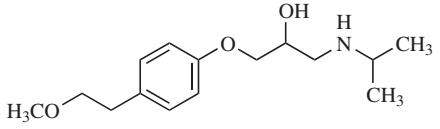
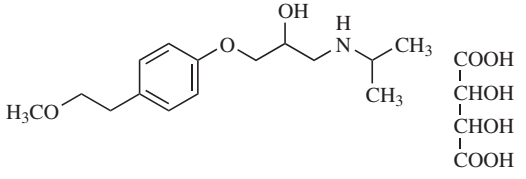
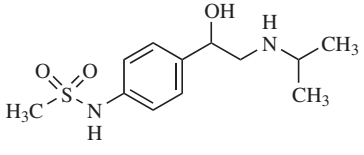
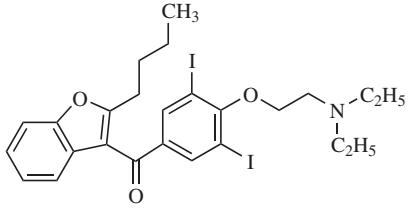
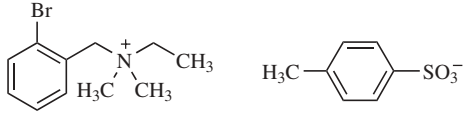
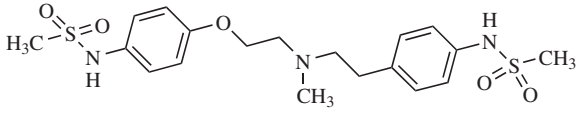
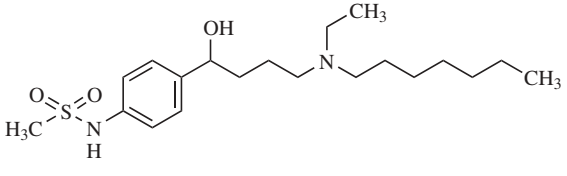
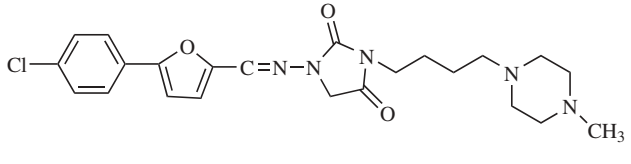
metoprolol succinate	[98418-47-4]	$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$	Toprol-XL	
metoprolol tartarate	[56392-17-7]	$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$	Beloc, Betaloc, Lopressor	
		Class III Antiarrhythmic Agents		
sotalol (*d,l*)	[3930-20-9]	$C_{12}H_{20}N_2O_3S$	Sotalex	
amiodarone	[19774-82-4]	$C_{25}H_{30}ClI_2NO_3$	Amiodar, Anacorn, Cordarex, Cordarone, Ortacrone, Pacerone, Tachydaron, Trangorex	

Table 1 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
bretylium	[61-75-6]	$C_{18}H_{24}BrNO_3S$	Bretylan, Bretylate, Bretylol, Darenthin, Ornid	
ibutilide	[122647-32-9]	$(C_{20}H_{36}N_2O_3S)_2 . C_4H_4O_4$	Corvert	
dofetilide	[115256-11-6]	$C_{19}H_{27}N_3O_5S_2$	Tikosyn	
azimilide	[149888-94-8]	$C_{23}H_{30}Cl_3N_5O_3$	Stedicor	

Class IV Antiarrhythmic Agents

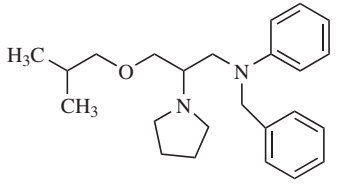
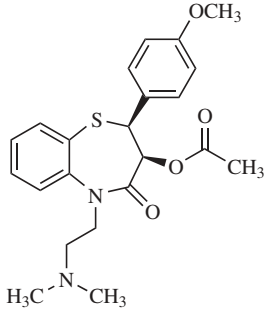
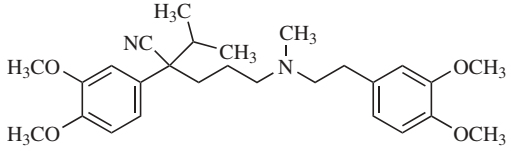
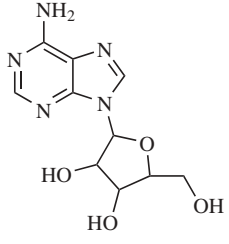
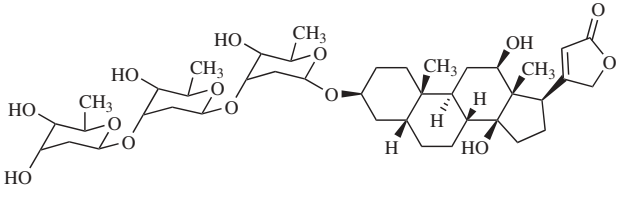
bepridil	[74764-40-2]	$C_{24}H_{35}ClN_2O$	Angopril, Bepadin, Cordium, Vascor	
diltiazem	[33286-22-5]	$C_{22}H_{27}ClN_2O_4S$	Adizem, anginyl, Angizem, Bruzem, Calcicard, Cardizem, Citizem, Deltazen, Diladel, Dilzem, Masdil, Tildiem	
verapamil	[152-11-4]	$C_{27}H_{38}N_2O_4$	Apramyl, Calan, Cordilox, Dignover, Isoptin, Securon, Univer, Vasolan, Veraptin, Verelan, Verexamil, Veramix	

Table 1 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
			Miscellaneous Agents	
adenosine	[58-61-7]	$C_{10}H_{13}N_5O_4$	Adenocard, Adenocor, Adenoscan	
digoxin	[20830-75-5]	$C_{41}H_{64}O_{14}$	Digacin, Dilanacin, Eudigox, Lanacordin, Lanicor, Lanoxicaps, Rougoxin	

rate from sodium ion channels, causing a reduction in impulse conduction time. Agents in this class have been observed to have modest effects on repolarization. Drugs in Class IA—quinidine, procainamide, and disopyramide—have sodium ion channel dissociation rates that are intermediate between Class IB and IC compounds.

The affinities of the Class I antiarrhythmic agents for sodium channels vary with the state of the channel or with the membrane potential (39). As indicated earlier, sodium channels exist in at least three states: R = closed resting, or closed near the resting potential, but able to be opened by stimulation and depolarization; A = open activated, allowing Na^+ ions to pass selectively through the membrane; and I = closed inactivated, and unable to be opened (38). Under normal resting conditions, the sodium channels are predominantly in the resting or R state. When the membrane is depolarized, the sodium channels are active and conduct sodium ions. Next, the inward sodium current rapidly decays as the channels move to the inactivated (I) state. The return of the I state to the R state is referred to as channel reactivation, and is voltage and time dependent. Class I antiarrhythmic drugs have a low affinity for R channels, and a relatively high affinity for both the A or I channels (40).

3.6. Class IA Agents. *Quinidine.* Quinidine is obtained from species of the genus *Cinchona*, and is the *d*-isomer of quinine. This molecule contains two basic nitrogens: one in the quinoline ring and one in the quinuclidine moiety. The nitrogen in the quinuclidine moiety is more basic. Three salt formulations are available: quinidine gluconate, quinidine polygalacturonate (41), and quinidine sulfate (42). Of the three, the gluconate formulation is the most soluble in water.

Quinidine binds to open sodium ion channels, decreasing the entry of sodium into myocardial cells. This depresses phase 4 diastolic depolarization (shifting the intracellular threshold potential toward zero), and decreases transmembrane permeability to the passive influx of sodium (slowing the process of phase 0 depolarization, which decreases impulse velocity), and increases action potential duration (43). Physiologically, this results in a reduction in SA node impulse initiation, and depression of the automaticity of ectopic cells. Quinidine is also thought to act, at least in part, by binding to potassium channels (Table 1), and is used to treat supraventricular and ventricular arrhythmias including atrial flutter and fibrillation, and atrial and ventricular premature beats and tachycardias. It is primarily metabolized to a hydroxylated metabolite—2-hydroxyquinidine—that is equal in potency to the parent compound (44).

Procainamide. Procainamide is an amide derivative of procaine. Replacement of the ether oxygen in procaine, with an amide nitrogen (in procainamide), decreases central nervous system (CNS) side effects, rapid hydrolysis, and instability in aqueous solution that results from the ester moiety in procaine. Procainamide is formulated as a hydrochloride salt of its tertiary amine. The metabtabolite of procainamide is *N*-acetylprocainamide, which possesses 25% of the parent drugs activity (45,46). Mechanistically, procainamide has the same cardiac electrophysiological effects as quinidine. It decreases automaticity and impulse conduction velocity, and increases the duration of the action potential (47). This compound may be used to treat all of the arrhythmias indicated for treatment with quinidine, including atrial flutter and fibrillation, and atrial and ventricular premature beats and tachycardias.

Disopyramide. The electrophysiological effects of this drug are similar to those of quinidine and procainamide—decreased phase 4 depolarization and decreased conduction velocity (48). This molecule contains the ionizable tertiary amine that is characteristic of compounds in this class, is formulated as a phosphate salt, and is administered both orally and intravenously (49). Due to its structural similarity to anticholinergic drugs, disopyramide produces side effects that are similar to those types of therapeutics, including dry mouth, urinary hesitancy, and constipation. Clinically it is used to treat life-threatening ventricular tachyarrhythmias.

3.7. Class IB Agents. *Lidocaine.* Lidocaine is formulated as a hydrochloride salt that is soluble in both water and alcohol. It binds to inactive sodium ion channels, decreasing diastolic depolarization, and prolonging the resting period (50,51). Lidocaine is administered intravenously for suppression of ventricular cardiac arrhythmias. The first pass metabolite of this compound—monoethylglycinexylidide—is generated from deethylation of the tertiary amine, and is equipotent to its parent compound (52,53).

Tocainide. Tocainide is an analogue of lidocaine, but differs structurally in that it possesses as primary, versus a tertiary, terminal side-chain amine. In addition, a methyl substituent on the side chain partially protects the amide moiety against hydrolysis. Tocainide has a mechanism of action that is similar to lidocaine (54,55). It is orally active, and the presence of a primary amine allows for formulation as a hydrochloride salt. Therapeutically it is used to prevent or treat ventricular tachycardias.

Mexiletine. Structurally, mexiletine resembles lidocaine and tocainide in that it contains a xylyl moiety. However, it differs in that it possesses an ether moiety (versus an amide moiety (as found in lidocaine and tocainide) in its side chain. As a result, mexiletine is not vulnerable to hydrolysis, and has a longer half-life than lidocaine (56). Mexiletine possesses a primary amine, and is formulated as a hydrochloride salt that is orally active. Its effects on cardiac electrophysiology are similar to that of lidocaine (57). It is used in the treatment of ventricular arrhythmias, however, due to proarrhythmic side effects; it is generally not used with lesser arrhythmias (58).

Phenytoin. Phenytoin is a hydantoin derivative of the anticonvulsant therapeutics that does not possess sedative properties. It is structurally dissimilar to all other class I antiarrhythmic compounds, and is the only member of this family of compounds that does not contain an ionizable amine. However, its effects on cardiac cells are similar to those of lidocaine. Mechanistically, it decreases the force of contraction, depresses pacemaker action, and improves atrioventricular conduction, especially when administered in conjunction with digitalis (59).

3.8. Class IC Agents. *Encainide.* Encainide is a benzanilide derivative containing a piperidine ring, and like other Class I compounds, blocks sodium channels (60). Encainide contains a terminal tertiary amine, and is formulated as a chloride salt. It is used orally to suppress and prevent recurrence of documented life-threatening ventricular arrhythmias. Use of encainide for less severe arrhythmias is no longer recommended. A metabolite of this compound, ODE, which results from demethylation of the methoxy moiety, is more potent than encainide (61). It has been effective for the management of various

supraventricular tachyarrhythmias, Wolf-Parkinson white syndrome, and AV nodal reentrant tachycardia.

Flecainide. Flecainide is a benzamide–piperidine derivative. However, it is structurally dissimilar from encainide in that it contains one less benzyl group, possesses two lipophilic trifluoroethoxy substituents at the 1 and 4 positions on the benzamide ring (versus a single methoxy substituent at the 4 position of the benzamide in encainide), and lacks a methyl substituent on the piperidine nitrogen. It is formulated as an acetate salt, and like encainide, its metabolites are active. It possesses cardiac physiological effects that are similar to those of encainide, and it is used orally to suppress and prevent the recurrent of documented life-threatening ventricular arrhythmias and supraventricular tachyarrhythmias (62,63). Limited data suggest that flecainide may be effective for conversion of atrial fibrillation to normal sinus rhythm and for the treatment of ectopic or multifocal atrial tachycardias.

Lorcainide. Lorcainide is a benzamide/piperidine derivative with a mechanism of action that is similar to encainide (64,65). Lorcainide is formulated as a hydrochloride salt and is orally active. Metabolism produces an *N*-dealkylated derivative—norlorcainide (66). This metabolite is as potent as the parent compound, but possesses a half-life that is approximately three times longer. Lorcainide is used to treat ventricular arrhythmia, ventricular tachycardia, and Wolff-Parkinson-White Syndrome.

Propafenone. Propafenone is structurally unlike other compounds in this subclass—ie, encainide, flecainide, and lorcainide. Instead, it is an ortho substituted aryloxy propanolamine that is similar in structure to β-blockers. The racemic mixture possesses Na^+ channel blocking activity, while the (*S*) (−) isomer is a potent β-blocker. Mechanistically, propafenone has a stabilizing effect on myocardial membranes, which manifests in a reduction in the upstroke velocity (Phase 0) of the action potential (67). In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone decreases the fast inward current carried by sodium ions, prolongs the refractory period, reduces spontaneous automaticity, and depresses triggered activity (68,69). Propafenone is indicated in the treatment of paroxysmal atrial fibrillation–flutter and paroxysmal supraventricular tachycardia. It is also used to treat ventricular arrhythmias, such as sustained ventricular tachycardias.

Moricizine. Moricizine is a phenothiazine derivative, and is a structurally unique member of the Class IC antiarrhythmic agents. Like other agents in this subclass, it decreases the speed of cardiac conduction by lengthening the refractory period and shortening the length of the action period of cardiac tissue (70). Moricizine is formulated as a hydrochloride salt, and is used to treat ventricular arrhythmias.

3.9. Class II Agents. The inhibitors in this class are all β-adrenergic antagonists that have been found to produce membrane-stabilizing or depressant effects on myocardial tissue. It has been hypothesized that the antiarrhythmic properties of these agents are mainly due to their inhibition of adrenergic stimulation of the heart (71,72) by the endogenous catecholamines, epinephrine and norepinephrine. The principal electrophysiological effects of the β-blocking agents manifest as a reduction in the phase 4 slope potential of sinus or pacemaker cells, which decreases heart rate and slows tachycardias.

With the exception of sotalol (73), the compounds in Class II are all structurally similar to aryloxypropanolamines (Table 1). This name originates from the presence of an $-OCH_2-$ group located between a substituted benzene ring, on one side, and an ethylamino side-chain, on the other side. The aromatic ring and its substituents are the primary determinants of β-antagonist selectivity. Substitution of the para position of the benzene ring, in tandem with the absence of meta-position substitution, appears to confer selectivity for β1 cardiac receptors. Sotalol differs from other members of this class in that it lacks the $-OCH_2-$ group. This results in a shortening of the characteristic ethylamino side chain (Table 1).

Propranolol is the prototype agent for this class of compounds. Due to the substitution pattern on its aromatic ring, it is not a selective β-adrenergic blocking agent. During propranolol-mediated β-receptor block, the chronotropic, ionotropic, and vasodilator responses to β-adrenergic stimulation are decreased. Propranolol exerts its antiarrhythmic effects in concentrations associated with β-adrenergic blockade (74). It has also been shown to possess membrane-stabilizing activity that is similar to quinidine. However, the significance of this membrane action in the treatment of arrhythmias is uncertain, as the concentrations required to produce this effect are greater than required for the observance of its β-blocking effects. Effects of β-adrenergic receptor antagonists to reduce cardiac mortality after MI are well established. The β-adrenergic agents, including amiodarone are the only drugs proven to reduce death in these patients.

Nadolol (75) and *l*-Sotalol (76) are both nonspecific β-blockers (Table 1), while para substitutions on the aromatic rings of atenolol (77), acetobutolol (78), esmolol (79), and metoprolol (80) all confer β_1 antagonist selectivity (Table 1). Each of these agents exerts electrophysiological effects that result in slowed heart rate, decreased AV nodal conduction, and increased AV nodal refractoriness.

3.10. Class III Agents. The drugs in this class—amiodarone, bretylium, dofetilide, ibutilide, and (*d,l*) or racemic sotalol—all generate electrophysical changes in myocardial tissue by blocking ion channels, however, some are selective, while others are multi-channel blockers (this is not surprising, as there is a high degree of sequence homology between the different ion channels). Importantly, all Class III drugs have one common effect—that of prolonging the action potential, which increases the effective refractory period without altering the depolarization or the resting membrane potential (81).

Racemic sotalol, dofetilide, and ibutilide are potassium channel blockers. Sotalol also possesses β-adrenergic blocking properties (as indicated above), while ibutilide is also a sodium channel blocker. The mechanisms of action of amiodarone and bretylium, which also prolong the action potential, remain unclear. However, both have sodium channel-blocking properties.

Of the compounds listed in this class, sotalol, dofetilide, and ibutilide are structurally similar (Table 1). All three drugs contain a central aromatic ring with a sulfonamide moiety, and a para-substituted alkylamine side chain. Dofetilide, unlike sotalol and ibutilide, is nearly symmetrical, with two methanesulfonamides at either end of the molecule.

Amiodarone. Amiodarone is structurally unique in this class, and has received much attention over the past several years for its ability to treat

arrhythmias. Amiodarone is currently the most utilized drug in patients with life-threatening arrhythmias—approximately one-half of the patients currently receiving antiarrhythmic drug therapy are treated with amiodarone (82).

Amiodarone is a benzofuranyl derivative with a central diiodobenzoyl substituent and an alkyl amine side chain. Mechanistically, this agent prolongs the duration of the action potential and effective refractory period, with minimal effect on resting membrane potential (83–85). Amiodarone exhibits mechanisms of activity from each of the four Singh and Vaughan Williams classes. In addition, it also displays noncompetitive α- and β-adrenergic inhibitory properties. It is effective in the treatment of life-threatening recurrent ventricular arrhythmias and atrial fibrillation (86), and is orally available as a chloride salt. Amiodarone contains two iodine substituents, and consequently affects thyroid hormones (87). However, its most serious side effects involve both the exacerbation of arrhythmias and pulmonary toxicity. An experimental noniodinated benzofuranyl derivative of amiodarone, *dronedarone*, has emerged as a potential new member of the Class III antiarrhythmics. It has been found to have similar electrophysiological effects as amiodarone, but with fewer side effects (88).

(d,l) Sotalol. Sotalol is classified as both a Class II and a Class III antiarrhythmic agent. The *l*-isomer is classified as a β-blocker, and is 50 times more active than the *d*-isomer in this capacity; the racemic mixture of this drug is considered to be a Class III agent, as it inhibits the component of the potassium channel involved in the rectifier potassium current. Sotalol is used to treat and prevent life-threatening ventricular arrhythmias (89). Additionally, because of its Class II and III activity, it is also effective against supraventricular arrhythmias (90). The mode of action, pharmacokinetics, and therapeutic uses of sotalol have been reviewed extensively (91).

Sotalol is formulated as a hydrochloride salt and is orally available. In terms of efficacy, clinical trials have indicated that this agent is at least as effective or more effective in the management of life-threatening ventricular arrhythmia than other available drugs (92).

Bretylium Tosylate. Bretylium tosylate is a bromobenzyl quaternary ammonium salt. It is formulated as a tosylate salt and is soluble in water and alcohol. It is administered by intravenous or intramuscular injection, and is used to treat ventricular fibrillation and ventricular arrhythmias that are resistant to other therapy. The mechanism of antiarrhythmic action of this drug has not been determined (93). Research has shown that this agent selectively accumulates in neurons and inhibits norepinephrine release, and it has been suggested that its adrenergic neuronal-blocking properties are responsible for its antiarrhythmic activity (94).

Ibutilide. Ibutilide is formulated as a fumarate salt, and is administered by intravenous injection (95). This agent prolongs repolarization of cardiac tissue by increasing the duration of the action potential and the effective refractory period in cardiac cells. It blocks both sodium and potassium channels (96–98), but unlike sotalol, does not possess β-adrenergic blocking activity. Ibutilide is used in the treatment of supraventricular tachyarrhythmias, such as atrial flutter and atrial fibrillation (99,100). *Trecetilide* is a congener of ibutilide that is currently under investigation for intravenous and oral treatment of atrial flutter and atrial fibrillation.

Dofetilide. Dofetilide is a recent addition to the Class III antiarrhythmic agents. It prolongs repolarization and refractoriness without affecting cardiac conduction velocity, and is a selective blocking agent of the delayed rectifier potassium current (101,102). Unlike ibutilide and sotalol, this agent does not inhibit sodium channels or β-adrenergic receptors. Dofetilide is formulated as a hydrochloride salt, is administered orally, and is used to treat supraventricular tachyarrhythmias, and to restore normal sinus rhythm during atrial fibrillation and atrial flutter (103,104).

Azimilide. Azimilide is a novel Class III antiarrhythmic agent that has been shown to block both the slow activating and rapidly activating components of the delayed rectifier potassium current (105). Structurally, it is unlike other molecules in this class, containing both imidazolidione and piperazine moieties, and is being evaluated in the treatment of atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia (106–108).

3.11. Class IV Agents. All of the calcium channel blockers in this class of agents—verapamil, diltiazem, and bepridil—also possess antianginal activity. With respect to cardiac arrhythmias, these agents affect calcium ion flux, which is required for the propagation of an electrical impulse through the AV node (109). By decreasing this influx, the calcium channel blockers slow conduction. This, in turn, slows the ventricular rate.

Verapamil. Verapamil blocks the influx of calcium ions across cell membranes (110). Structurally, it is not related to other antiarrhythmic drugs. It is formulated as a hydrochloride salt and is readily soluble in water. Verapamil is used to treat supraventricular arrhythmias, including atrial tachycardias and fibrillations (111), and is administered both orally and via intravenous injection. Verapamil is rapidly metabolized to at least 12 dealkylated metabolites. Norverapamil, a major and active metabolite, has 20% of the cardiovascular activity of verapamil, and reaches plasma concentrations that are almost equal to those of verapamil within 4–6 hours after administration.

Diltiazem. Diltiazem is a benzothiazepine derivative, and is formulated as a hydrochloride salt. It may be administered orally or via injection. Similar to verapamil, diltiazem inhibits the influx of Ca^{2+} during the depolarization of cardiac smooth muscle. Therapeutically, this drug reduces the heart rate during tachycardias. Diltiazem has also been shown to decrease the ventricular rate during atrial fibrillation or atrial flutter (112,113).

Bepridil. Bepridil inhibits the transmembrane influx of Ca^{2+} into cardiac and vascular smooth muscle. Like diltiazem it slows the heart rate by prolonging both the effective refractory periods of the atria and ventricles (114). This agent is formulated as a hydrochloride salt, and is orally available. It is used in treating tachyarrhythmias and in the management of high ventricular rates that are secondary to atrial flutter or fibrillation (115,116).

3.12. Miscellaneous Antiarrhythmic Agents. Two antiarrhythmic agents that do not fall within the Singh and Vaughan Williams classification are adenosine and digoxin.

Adenosine. Adenosine is chemically unrelated to other antiarrhythmic drugs. It is soluble in water, but practically insoluble in alcohol. For the treatment of arrhythmias it is administered via intravenous injection.

Adenosine reduces SA node automaticity, slows conduction time through the AV node, and can interrupt reentry pathways. It is used to restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardia, including Wolff-Parkinson-White syndrome (117–120).

Digoxin and Digitoxin. Digoxin and digitoxin belong to the family of compounds known as the cardiac glycosides. The natural glycosides are isolated from various plant species: *digitalis purpurea Linne*, *digitalis lanata Ehrhart*, *strophanthus gratu*, or *acokanthea schimperi*.

Digoxin and digitoxin inhibit sodium–potassium ATPase, which is responsible for regulating the quantity of sodium and potassium inside cells. Inhibition of this enzyme results in an increase in the intracellular concentration of sodium and calcium. However, reduction in the heart rate associated with digitalis results from at least two different mechanisms. Digitalis increases cardiac parasympathetic activity via CNS actions. In addition, the activation of the reverse mode of the sodium–calcium exchanger leads to a net loss of positive charge (3 sodium out to every calcium in) and results in hyperpolarize of the pacemaker cells and decreased heart rate. Digoxin and digitoxin are available both orally and through intravenous injection, and are used to treat and prevent sinus and supraventricular fibrillation, flutter, and tachycardia (121).

3.13. Current and Future Trends in the Treatment of Arrhythmia. Following the discovery that lidocaine was useful for treating cardiac arrhythmias, early drug discovery and development of antiarrhythmic agents focused on compounds that were structurally similar to lidocaine and possessed similar mechanisms of action—that of blocking sodium channels. This led to the initial identification of lidocaine congeners such as tocainide and mexiletine, and later to encainide and flecainide. The long standing hypotheses for treating arrhythmias with sodium ion channel blockers was based on the belief that these molecules could effectively prevent or suppress the onset of arrhythmias and/or terminate this condition when it became persistent (122). However, CAST (123), which evaluated the effects of well-established sodium channel blockers on mortality in postmyocardial patients (with frequent premature ventricular arrhythmias), dispelled this hypothesis. In fact, these studies found that both encainide and flecainide increased mortality. Since the CAST studies, other trials with mexiletine, propafenone, and moricizine (124) (CAST II) (125) have also shown similar results, and a correlation between increased mortality and the use of sodium ion channel blocking agents in post-myocardial infarction patients has been established.

Based on the findings of CAST and related studies, the treatment of antiarrhythmias has shifted away from Class I sodium channel blockers, and now focuses on Class III drugs (126), which act by prolonging the action potential duration and the refractory period. Class III agents lack many of the negative side effects observed in other classes of antiarrhythmics, affect both atrial and ventricular tissue, and can be administered orally or intravenously. Members of this class, such as amiodarone (which has proven to be a clinically efficient therapeutic for the treatment of a wide variety of arrhythmias) and racemic sotalol, have been the center of much attention in recent years, and have led to the search for new Class III drugs with improved safety profiles (127). New and

investigational Class III agents that are more selective for potassium channel subtypes include azimilide (128), dofetilide, dronedarone, ersentilide, ibutilide, tedisamil, and trecetilide (129).

There have also been numerous reports on the synthesis and evaluation of new antiarrhythmic compounds; several of these are briefly described: Matyus and co-workers (130) reported the synthesis and biological evaluation of novel phenoxyalkyl amines that exhibit both Class IB and Class III type electrophysiological properties; Tripathi and co-workers (131) performed synthesis and SAR studies on 1-substituted-*n*-(4-alkoxycarbonylpiperidin-1-yl) alkanes that showed potent antiarrhythmic activity comparable to quinidine; Bodor and co-workers (132) reported a novel tryptamine analogue that was found to selectively bind to the heart (and within the heart to have tissue specificity), and possessed effects on vital signs of the cardiovascular system that indicated antiarrhythmic activity; Morey and co-workers (133) designed a series of amiodarone homologues that resulted in an SAR that will have implications for the future development of amiodarone-like antiarrhythmic agents; Himmel and co-workers (134) synthesized and evaluated the activities of thiadiazinone derivatives that are potent and selective for potassium ion channels, and show Class III antiarrhythmic activity; Thomas and co-workers (135) developed a novel antiarrhythmic agent—BRL-32872—that inhibits both potassium and calcium channels; and Levy and co-workers (136) described novel dibenzoazepine and 11-oxo-dibenzodiazepine derivatives that are effective ventricular defibrillating drug candidates.

Along with advances in the understanding and development of new therapeutic agents, the development of technological devices to treat arrhythmias has also evolved. One of the most important achievements has been the implantable cardioverter defibrillator (ICD) (82). This device has been an option for treating arrhythmias since the early 1980s, and in the treatment of ventricular tachycardia and fibrillation, no other therapy has been as effective in prolonging patient survival (122). However, an important point regarding ICD treatment is that it is often used in combination with antiarrhythmic drug therapy (82). For frequent symptomatic episodes of ventricular tachycardia, administration of an adjuvant drug therapy is often required to provide maximum prevention and treatment of life-threatening arrhythmias. In particular, combination therapy with ICD and both β-blockers and amiodarone have received the most attention (82).

Finally, new evidence suggests that combinations of therapeutics may be more effective at treating and controlling arrhythmias than using any single agent alone (127). In particular, clinical sources have indicated that the pharmacological properties of amiodarone and β-blockers may be additive or even synergistic for treating arrhythmias (127). Details of the analysis of amiodarone interaction with α-blockers in the European myocardial infarct amiodarone trial (EMIAT) and in the Canadian amiodarone myocardial infarction trial (CAMIAT) have recently been reported (137). Data from randomized patients in these trials were analyzed by multivariate proportional hazard models, and indicated that combination therapy consisting of amiodarone and β-blockers led to a significantly better survival rate. Hence, the possibility of administering combination therapies will be an important aspect in the future development of therapeutic techniques for treating arrhythmias.

4. Antianginal Agents

Angina pectoris is the principal symptom of ischemic heart disease, and is caused by an imbalance between myocardial oxygen demand and oxygen supply by coronary vessels. Such an imbalance could be the result of either increased myocardial oxygen demand due to exercise or decreased myocardial oxygen delivery or both. Angina pectoris is always associated with sudden, severe chest pain and discomfort. The location and character of the pain may vary but often radiates from the sternum to the left shoulder and over the flexor surface of the left arm to the tips of the medial fingers. However, some individuals do not experience pain with ischemia. Angina pectoris can be induced by exercise, anxiety, overeating, or stress and is often relieved quickly by rest. Other factors, such as decreased oxygen carrying capacity of the blood, or reduced aortic pressure may be involved. The attack may be transient and damage to the ischemic myocardium may be minimal or it may result in an acute myocardial infarction (MI) and/or death. It is usually accompanied by ST segment changes in the ECG depending on the condition. Angina occurs because the blood supply to the myocardium via coronary vessels is insufficient to meet the metabolic needs of the heart muscle for oxygen (138) either by a decrease in blood supply or an exceedingly large increase in oxygen requirements of the myocardium or both. For a drug to be efficacious in angina it should improve myocardial oxygen supply (increase blood flow) or reduce myocardial oxygen consumption or have both actions.

Several factors affect mycocardial oxygen supply such as (*1*) *Blood oxygenation and oxygen extraction involving tissue ischemia*: A normal and healthy heart extracts about 75% of blood oxygen at rest, however, increased coronary blood flow and extraction results in an increase in oxygen supply. But, ischemic heart disease develops when there is a deficiency in the supply of blood and oxygen to the heart, typically caused by narrowing of the coronary arteries, a condition known as coronary artery disease (CAD) or coronary heart disease (CHD). CAD is a consequence of a complicated pathological process involving the development of atherosclerotic lesions in the coronary arteries, in which cholesterol, triglycerides, and other substances in the blood deposit in the walls of arteries, narrowing them. The narrowing limits the extraction and flow of oxygen rich blood to the heart. (*2*) *Pulmonary conditions*: Sometimes acute and chronic bronchopulmonary disorders such as pneumonia, bronchitis, emphysema, tracheobronchitis, chronic asthmatic bronchitis, tuberculosis, and primary amyloidosis of the lung affect the oxygen extraction and its supply to the heart, causing severe ischemia. Also, if the heart does not work efficiently as it should, it reduces the cardiac output causing congestion of fluid in the tissues leading to swelling (edema). Occasionally, the fluid collects in the lungs and interferes with breathing, causing shortness of breath at rest or during exertion. Edema is also exacerbated by reduced ability of the kidneys to dispose sodium and water. The retained water further increases the edema (swelling). (*3*) *Coronary vascular conditions*: The various conditions such as coronary collateral blood flow, coronary arterial resistance affected by nervous system, accumulation of local metabolites, tissue death, endothelial function, diastolic blood pressure, and endocardial–epicardial blood flow contribute significantly to the pathogenesis of angina.

The factors that govern myocardial oxygen demand include (*4*) *Heart rate*: A significant change in the regular beat (fast or slow) or rhythm of the heart (arrhythmias) may affect the myocardial oxygen demand. Excessive slowing of heartbeat is called bradycardia and is sometimes associated with fatigue, dizziness, and lightheadedness or fainting. The various types of bradycardia have been categorized as sinus bradycardia, and junctional rhythm and heart block. These symptoms can easily be corrected with an electrical pacemaker that is implanted under the skin and takes over the functioning of the natural pacemaker. Conversely, a rapid heart beat is referred to as tachycardia. Tachycardias are classified into two types: supraventricular and ventricular. Different types of abnormal rapid heart beats have been categorized as sinus tachycardia (normal response to exercise), atrial tachycardia, atrial fibrillation, atrial flutter, AV nodal reentry, AV reciprocating tachycardia, premature atrial contractions, ventricular tachycardia, and premature ventricular contractions. Electrocardiographic monitoring is needed for the correct diagnosis of arrhythmias. Since exercise stimulates the heart to beat faster and more forcefully, more blood, and hence oxygen, is needed by the myocardium to meet this increased workload. Normally, this is accomplished by dilation of coronary blood vessels; however, sometimes atherosclerosis may inhibit the flow of oxygen rich blood, causing ischemia. (*5*) *Cardiac contractility (inotropic state)*: Reduction in the cardiac output causes a reflex activation of the sympathetic nervous system to stimulate heart rate and contractility further leading to greater oxygen demand. If the coronary arteries are occluded and incapable of delivering the needed oxygen an ischemia will occur. (*6*) *Preload-venous pressure and its impact on diastolic ventricular wall tension and ventricular volumes*: It has been suggested that an important strategy in the treatment of cardiac function is reduction of the work load of the heart, by reducing the number of heart beats per minute and the work required per heart beat defined by preload and afterload. Preload is defined as the volume of blood that fills the heart before contraction. Contraction of the great veins increases preload, while dilation of veins reduces preload. (*7*) *Afterload—systolic pressure required to pump blood out*: Afterload is defined as the force that the heart must generate to eject blood from ventricles. It largely depends on the resistance of arterial vessels. Contraction of these vessels increases afterload, while dilation reduces afterload.

There are different types of angina (*1*) *Stable Angina*. Stable angina is also called chronic angina, exertional angina, typical or classic angina, angina of effort or atherosclerotic angina. The main underlying pathophysiology of this most common type of angina is usually atherosclerosis, ie, plaques that occlude the vessels or coronary thrombi that block the arteries. This type of angina usually develops by "exertion", exercise, emotional stress, discomfort, or cold exposure and can be diagnosed using EKG. Therapeutic approaches to treat this type of angina include increasing the myocardial blood flow and decreasing the cardiac preload and afterload. (*2*) *Vasopastic Angina*. It is also called variant angina or Prinzmetal's angina. It is usually caused by a transient vasospasm of coronary blood vessels or atheromas, at the site of plaque. This can easily be seen by EKG changes in ST elevation that tend to occur at rest. Sometimes chest pain develops even at rest. A therapeutic approach to treat this type of angina is to decrease vasospasm of coronary arteries normally provoked by α-adrenergic

activation in coronary vasculature. However, α-adrenergic activation is not the only cause of vasospasm. (*3*) *Unstable Angina*. It is also called preinfarction angina, crescendo angina, or angina at rest. It is usually characterized by recurrent episodes of prolonged attacks at rest resulting from the small platelet clots (platelet aggregation) at the atherosclerotic plaque site that may also induce local vasospasm. This type of angina requires immediate medical intervention such as cardiac bypass surgery or angioplasty since it could ultimately lead to myocardial infarction (MI). Treatment regiments include inhibition of platelet aggregation and thrombus formation, vasodilation of coronary arteries (angioplasty) or decrease in cardiac load.

4.1. Etiology and Causes of Angina and Coronary Heart Disease. The risk factors for the development of CHD and angina pectoris are genetic predisposition, age, male sex, and a series of reversible risk factors. The most important factors include high fat and cholesterol rich diet (138–140), lack of exercise and inability to retain normal cardiac function under increased exercise tolerance (141,142), tobacco and smoking (since nicotine is a vasoconstrictor) (143), excessive alcohol drinking, carbohydrate and fat metabolic disorders, diabetes, hypertension (144,145), obesity (146,147), and use of drugs that produce vasoconstriction or enhanced oxygen demand.

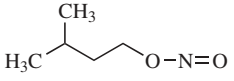
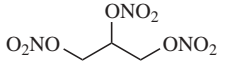
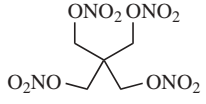
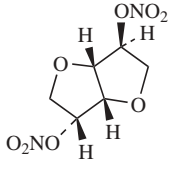
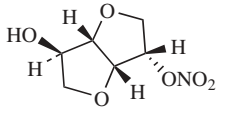
4.2. Treatment. In general, the action of various therapeutic drugs is either by (a) alteration of myocardial contractility or heart rate; (b) modification of conduction of the cardiac action potential; or (c) vasodilatation of coronary and peripheral vessels. Therefore, this article primarily focuses on therapeutics that apply to the treatment of angina, arrhythmia, cardiac heart diasease, thrombolysis, and other cadiac complications.

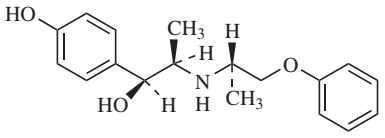
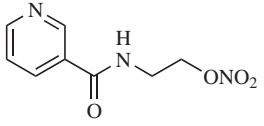
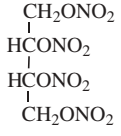
4.3. Treatment of Angina. The various treatment modalities of different kinds of angina include (*1*) prevention of precipitating factors; (*2*) use of nitrates as vasodilators to treat acute symptoms; (*3*) utilization of prophylactic treatment using a choice of drugs among antianginal agents, calcium channel blockers, and β-blockers; (*4*) surgeries such as angioplasty, coronary stenting, and coronary artery bypass surgery; (*5*) anticoagulants and use of antithromobolytic agents.

4.4. Nitrates as Vasodilators. Some of the simple organic nitrates and nitrites find applications for both short- and long-term prophylactic treatment of angina pectoris, myocardial infarction, and hypertension. Most of these nitrates and nitrites are formulated by mixing inert suitable excipients such as lactose, dextrose, mannitol, alcohol, propylene glycol for safe handling, since some of these compounds are heat sensitive, very flammable and powerful explosives, if used alone. The onset, duration of action and potency of organic nitrates could be attributed to structural differences. However, there is no relationship between the number of nitrate groups and activity (Table 2).

4.5. Mechanism of Action. The nitrates and nitrites are simple organic compounds that metabolize to a free radical nitric oxide (NO) at or near the plasma membrane of vascular smooth muscle cells. The basic pharmacological action of nitrates is a relaxation of most vascular smooth muscle cell. It is a direct effect that is not mediated by adrenergic receptors or endothelium. In 1980, Furchgott and Zawadski first discovered that NO is the most potent endogenous vasodilator (148). Nitric oxide is a highly reactive species with a very short

Table 2. **Antianginal Agents: Nitrates as Vasodilators**

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Side effects	Structure
amyl nitrate	[628-05-7]	$C_5H_{11}NO_2$	Inhalant	angina pectoris	tachycardia, CNS	
glyceryl trinitrate or nitroglycerin	[55-63-0]	$C_3H_5N_3O_9$	Nitrogard, Nitrolyn, Nitostat, Nitrol	angina pectoris, hypertension, acute MI	CNS	
pentaerythritol tetranitrate	[78-11-5]	$C_5H_8N_4O_{12}$		prophylactic anginal attacks	CNS	
isosorbide dinitrate	[87-33-2]	$C_6H_8N_2O_8$	Sorbitrate, Isordil, Isordil Titradose	angina pectoris, congestive heart failure, dysphasia	reflex tachycardia, CNS	
isosorbide mononitrate	[16051-77-7]	$C_6H_9NO_6$	Monoket, Ismo, Imdur, Isotrate ER	angina pectoris, congestive heart failure	CNS, GI intolerance	

isoxsuprine	[579-56-6]	$C_{18}H_{23}NO_3$	Dilavase, Duvadilan, Isolait, Navilox, Suprilent, Vadosilan, Vasodilan, Vasoplex, Vasotran	peripheral vascular diseases, Burger's and Raynaud's diseases, arteriosclerosis obliterans	tachycardia, CNS	
nicorandil	[65141-46-01]	$C_8H_9N_3O_4$		antianginal, hypotension		
erythrityl tetranitrate	[7297-25-8]	$C_4H_6N_4O_{12}$	Tetranitrol, Tetranitrin, Cardilate, Cardiloid	coronary vasodilator		

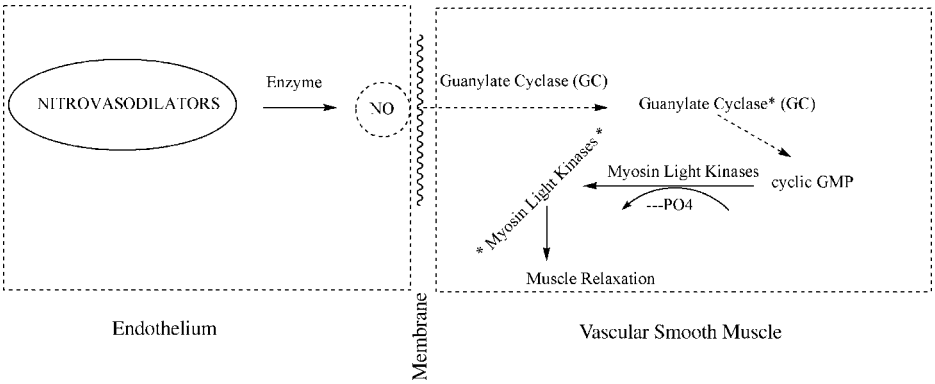


Fig. 6. Suggested mechanism of action of nitrate and nitrites used as vasodilators to generate NO, the most potent (endogenous) vasodilator that induces a cascade of reactions resulting in smooth muscle relaxation and vasodilation.

half-life of a few seconds. It is an endothelium derived relaxing factor (EDRF) that influences vascular tone. Nitric oxide induces vasodilation by stimulating soluble guanylate cyclase to produce cyclic GMP (cGMP) as shown in Figure 6. The latter eventually leads to dephosphorylation of the light chains of myosin (149). The resultant hemodynamic effect is the basis of dilation of epicardial coronary arteries, systemic resistance vessels and veins, always associated with a reduction in the coronary vascular resistance that contributes to the efficacy (150–154). Thus, their main action is peripheral vasodilation, either venous (low doses), or both venous and arterial (higher doses). As a result, pooling of blood in the veins reduces venous return and also the ventricular volume (preload). This reduction in enlargement of the heart wall decreases oxygen demand and the pain of angina is relieved quickly. However, it has been found that nitrates act only on the large coronary vessels to exert their effect. The lack of ability of minor vessels to convert nitrate to NO is the main reason for nitrates being ineffective in minor vessels (Fig. 6).

The use of nitrates leads to reflex activation of the sympathetic nervous system that increases the heart rate spontaneously and the myocardial contractility. Reduction in the ventricular wall tension decreases the myocardial oxygen consumption. At the same time, nitrates improve myocardial oxygen supply by increasing the coronary blood flow to the endocardium. Thus nitrates alter the imbalance of myocardial oxygen consumption and supply, which is the basis of angina pectoris. The main pharmacological effect of organic nitrates is relaxation of vascular smooth muscle that results into vasodilation. Organic nitrate provides an exogenous source of nitric oxide that augments the actions of EDRF, normally impaired with coronary artery diseases. It has been suggested that nitrates may be useful as antiplatelet and antithrombic agents in the management of intracoronary thrombi. Although the exact mechanism of action of nitrates on antiplatelet aggregation is unknown, it is postulated that activation of cGMP inhibits the calcium influx resulting in fibrinogen binding to glycoprotein IIb/IIIa receptors. Nitrates may also release prostacyclin [35121-78-9], $C_{20}H_{32}O_5$, from the endothelial lining of the vasculature and relax vascular

smooth muscle. Prostacyclin is a potent endogenous vasodilator and inhibitor of platelet aggregation (155,156).

4.6. Vasodilating Agents. All vasodilators can be divided into three types depending on their pharmacological site of action. These include (*1*) cerebral; (*2*) coronary, and (*3*) peripheral vasodilators. However, in this article, we will focus our attention on various compounds currently used as coronary and peripheral vasodilators represented in Table 2. Some of their properties such as bioavailability, half-life, and some possible side effects are also discussed in the text.

Amyl Nitrate. It is a light sensitive aliphatic compound with an unpleasant odor, volatile and inflammable liquid, immiscible in water. A stabilizer such as diphenylamine or epoxolol is added to the commercial product. Amyl nitrate can be administered to patients with coronary artery disease by nasal inhalation for acute relief of angina pectoris. It has also been used to treat heart murmurs resulting from stenosis and aortic or mitral valve irregularities. Amyl nitrate acts within 30 s after administration and sustantial hemodynamic effects such as increased heart rate and decreased diastolic pressure occurs within 30 s and duration of action persists ~3–5 min. However, this drug has a number of adverse side effects such as tachycardia and headache.

Glyceryl Trinitrate (GTN). Also called nitoglycerin, it was introduced as a drug for the treatment of angina pectoris in 1879. It is a powerful explosive and the undiluted drug occurs as a volatile, white-to-pale yellow, thick flammable liquid with a sweet burning taste. It is slightly soluble in water and soluble in alcohol. Nitroglycerin is diluted with lactose, dextrose, alcohol, propylene glycol, or another inert excipient to permit safe handling. It is administered lingually, sublingually, intrabuccally, orally, topically, by IV infusion, or a transdermal route. However, ~40–80% of the dose is normally lost during IV administration due to the absorption by plastic material used to administer the dose. The transdermal nitroglycerin adhesive or band aid patches overcome problems of handling controlled dosing, ie, eliminate the peaks and valleys of plasma levels associated with conventional therapy, to achieve a prolonged duration of action. Glyceryl trinitrate is a short-acting trinitrate ester of glycerol, with duration of action of 30 min or so. The GTN is easily absorbed through skin and has a strong vasodilating effect. The plasma half-life of nitroglycerin is ~1–4 min and it is rapidly metabolized in the liver and other organs by glutathione organic nitrate reductase and in the blood of some species to pharmacologically inactive 1,3-glyceryl dinitrate, 1,2-glyceryl dinitrate, and glyceryl mononitrate. It is highly bound to plasma protein and has a large volume of distribution suggesting it is widely distributed in the body.

Glyceryl trinitrate is the only vasodilator drug known to stimulate the enhancement of coronary collateral circulation and capable of preventing myocardial infarction induced by coronary occlusion, and therefore is more widely used in preventing attacks of angina than in stopping them once they have instigated. Thus, nitroglycerin remains the drug of choice for treatment of angina pectoris. It has also been found useful for the treatment of congestive heart failure, myocardial infarction, peripheral vascular disease, such as Raynaud's disease, and mitral insufficiency, although the benefits of nitroglycerin in mitral insufficiency have been questioned. The principal side effects of nitroglycerin are

headache, dizziness, nausea, vomiting, diarrhea, flushing, weakness, syncope, and tachycardia can result.

Pentaerythritol Tetanitrate (PETN). PETN is a nitric acid ester of the tetrahydric alcohol namely pentaerythritol. Since PETN is a powerful explosive, it is normally mixed and diluted with other inert materials for safe handling purposes and to prevent accidental explosions. PETN is mainly used in the prophylactic management of angina to reduce the severity and frequency of attacks, since it has a similar mechanism of action, pharmacokinetic and toxic effects on vascular smooth muscle cells to induce vasodilation as other nitrates (156). It is available in regular formulation, however, PETNs duration of action can be prolonged by using a sustained release formulation.

Erythrityl Tetranitrate. It is a racemic mixture of 1, 2, 3, 4-butanetetrol tetranitrate. It is a less potent antinaginal agent than nitroglycerin but has a more porlonged duration of action. It can be administerared orally or sublingually. The onset time is 5–10 min following sublingual administration and 20–30 min if given orally. The duration of action for the above two routes lasts ~3 and 6 h, respectively. Erythrityl is readily absorbed from the gastrointestinal (GI) tract and undergoes an extensive first-pass metabolism in the liver by glutathione organic nitrate reductase. Adverse effects are similar to those described for nitroglycerin (156).

Isosorbide Dinitrate. It is a white crystalline rosettes soluble in water. Isosorbide dinitrate can be administrated by oral, sublingual, or intrabuccal routes and the approximate onset and duration of action depends on the administration route and various dosage forms. The approximate onset and duration of action of different dosage forms of isosorbide dinitrate varies, such as oral (1 and 5–6 h), extended release (30 min and 6–8 h), chewable (3 min to 0.5–2 h), and sublingual (within 3 min to 2 h).

Isosorbide dinitrate is metabolized to the corresponding mononitrates (2 and 5 mononitrate) within several minutes to hours depending on the route of administration. Isosorbide dinitrate is routinely used for the treatment and relief of acute angina pectoris as well as in the short and long-term prophylactic management of angina. It can also be used in combination with cardiac glycosides or diuretics for the possible treatment of congestive heart failure (157–159).

Isosorbide Mononitrate. It is the major active metabolite of isosorbide dinitrate and occurs as a white, crystalline, odorless powder. Similar to dinitrate, mononitrate is freely soluble in water and alcohol. Mononitrate is available commercially as conventional tablets or extended release formulation such as capsules or controlled release coated pellets containing a suitable matrix. Some of the extended release formulations and tablets always should be stored in tight, light resistance containers at room temperature. Isosorbide mononitrate is readily absorbed from the GI tract and is principally metabolized in the liver. But unlike isosorbide dinitrate, it does not undergo first pass hepatic metabolism and therefore the bioavailability of isosorbide mononitrate in conventional or extended release tablets is very high (100–80%, respectively). About 50% dose of isosorbide mononitrate undergoes denitration to form isosorbide, followed by partial dehydration to form sorbitol. Mononitrate also undergoes glucuronidation to form 5-mononitrate glucuronide. None of these metabolites have any apparent pharmacological activity.

Similar to isosorbide dinitrate, mononitrate is used for the acute relief of angina pectoris, for prophylactic management in situations likely to provoke angina attacks, and also for long term management of angina pectoris (160,161).

Isoxsuprine Hydrochloride. This vasodilator is structurally related to nylidrin and occurs as a white crystalline powder, sparingly soluble in water (162). It causes vasodilation by direct relaxation of vascular smooth muscle cells. It acts by decreasing the peripheral resistance, and at high doses is even known to reduce the blood pressure. It also stimulates β-adrenergic receptors. It is used as an adjunct therapy in the management of peripheral vascular diseases such as Burger's disease, Raynaud's disease, arteriosclerosis obliterans, and for the relief of cerebrovascular insufficiency (163–166).

Nicorandil. It is a nicotinamide analogue possessing a nitrate moiety. It is known to exhibit a dual mechanism of action as both nitrovasodilator and potassium channel activator (167,168). It is a balanced arterial and venous dilator and also offers cardioprotection. Nicorandil is used as an antianginal agent, known to improve the myocardial blood flow resulting in decreased systemic vascular resistance and blood pressure, pulmonary capillary wedge and left ventricular end-diastolic pressures (169,170). It is relatively well tolerated when used orally or intravenously in patients with stable angina. However, the use of nicorandil in patients undergoing cardiopulmonary bypass surgery needs further evaluation since severe vasodilation and hypotension requiring significant vasoconstrictor support was observed (171).

4.7. Pharmacokinetics and Tolerance of Organic Nitrates. All organic nitrates exhibit similar pharmacological effects. The foremost factor contributing to the pharmacokinetics of glycerol trinitrates (GTN) and other longer acting organic nitrates is the existence of high capacity hepatic nitrate reductase in the liver that eliminates the nitrate groups in a stepwise process. But in serum, nitrates are metabolized independent of glutathione (151,172,173). In general, the organic nitrates are well absorbed from the oral mucosa following administration lingually, sublingually, intrabuccally, or as chewable tablets. The organic nitrates are also well absorbed from the GI tract and then undergo the first-pass metabolism in the liver. Nitroglycerin is well absorbed through the skin if applied topically as an ointment or transdermal system. Orally administered nitrates and topical nitroglycerin are relatively long acting. However, rapid development of tolerance to the hemodynamic and antianginal effects of these dosage forms is known to occur with continuous therapy. Therefore, an approximately 8 h/day nitrate-free period is needed to prevent tolerance. Slow release transdermal patches of GTN are the most favored form of achieving prolonged nitrate levels. Highly lipophilic nitrates, following intravenous infusion, are widely distributed in to vascular and peripheral tissues, while less lipophilic nitrates are not as widely distributed. At plasma concentrations of 50–500 ng/mL, nitrates are ~30–60% bound to plasma proteins.

4.8. Side Effects. The principal side effects of nitrates include dilation of cranial vessels causing headaches, which can limit the dose used. More serious side effects are tachycardia and hypotension resulting in corresponding increase in myocardial oxygen demand and decreased coronary perfusion, both of which have an adverse effect on myocardial oxygen balance. Another well-documented problem is the development of tolerance to nitrates. Blood vessels become

hypo- or nonreactive to the drugs, particularly if large doses, frequent dosing regimes and long-acting formulations are used. To avoid this, nitrates are best used intermittently, allowing a few hours without treatment in each 24-h period.

4.9. Calcium Channel Blockers. Verapamil was the first calcium channel blocker (CCB). It has been used since 1962 in Europe, and then in Japan, for its antiarrhythmic and coronary vasodilatory effects. The CCBs have become prominent cardiovascular drugs during the last 40 years and are widely used in the treatment of various types of angina, hypertension, certain arrhythmias, heart failure, acute myocardial infarction, cardioprotection, cerebral vasospasm, and cardiomyopathy as well. Many experimental and clinical studies have defined their mechanism of action, the effects of new drugs in this therapeutic class, and their indications and interactions with other drugs.

Calcium plays a significant role in the excitation–contraction coupling processes of the heart and vascular smooth muscle cells as well as the conduction cells of the heart and failure to maintain intracellular calcium homeostatis results in cell death. The membranes of conduction cells contain a network of numerous inward channels that are selective for calcium and activation of these channels leads to the plateau phase of the action potential of cardiac muscle cells. Please refer to the earlier section for a detailed discussion on calcium channels, mechanism of action, and their role in cardiovascular diseases.

4.10. Applications. Calcium channel blocking agents are the first drugs of choice for the management of Prinzmetal angina. It has been suggested that extended release or intermediate-long acting calcium channel blocking agents may be useful in the management of hypertension in patients with diabetes mellitus due to their fewer adverse side effects on glucose homeostasis, lipid, and renal function. However, the data from limited clinical studies indicates that patients with impaired glucose metabolism receiving calcium channel blockers are at higher risks of nonfatal MI and other adverse cardiovascular events than those receiving ACE inhibitor or β-adrenergic agents (174).

A number of recent reviews are also available that describe the utility of Ca^{2+} channel blockers in the treatment of hypertension (175). Some of the new drugs have greater selectivity since they can be used to treat hypertension in the presence of concomitant diseases, such as angina pectoris, hyperlipidemia, diabetes mellitus, or congestive heart failure. Sometimes reflex tachycardia and vasodilator headache are the major side effects that limit the use of these agents as antihypertensives (175).

The calcium channel blockers can be divided into four different classes of compounds based upon their pharmacophore and chemical structure. These include (*1*) arylalkylamines; (*2*) benzothiazepines; (*3*) 1–4 dihydropyridines; and (*4*) Mibefradil, which has been assigned its own class. These drugs have wide applications in cardiovascular therapy due to their effects such as (a) arterial vasodilation resulting in reduced afterload; (b) slowing of impulse generation and conductance in nodal tissue; (c) reduction in cardiac work and sometimes myocardial contractility, ie, negative inotropic effect so as to improve myocardial oxygen balance. We will discuss in detail each of the above class of compounds and their pharmacological action.

Arylalkylamines and Benzothiazepines. These drugs vary in their relative cardiovascular effects and clinical doses, but they have the most pronounced

direct cardiac effects (eg, verapamil) (Table 3). Various drugs that are currently in use are discussed next.

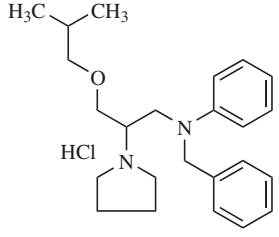
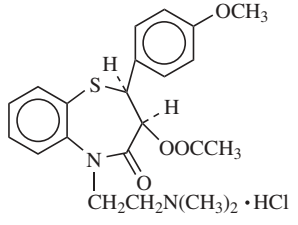
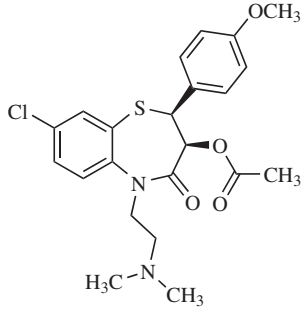
Bepridil Hydrochloride. It is a nondihydropyridine calcium channel blocking agent with antianginal and antiarrhythmic properties. It inhibits calcium ion influx across L-type (slow, low voltage) calcium channels (176). However, unlike other agents, it also inhibits calcium ion influx across receptor operated channels, and inhibits intracellular calmodulin-dependent processes by hindering the release of calcium and sodium influx across fast sodium channels. Thus, it exhibits both calcium and sodium channel blocking activity, and also possesses some electrophysiological properties of class I antiarrhythmic agents by prolonging QT and QTc intervals (177). Although the precise mechanism of action remains to be fully determined, it reduces in a dose-dependent manner heart rate and arterial pressure at rest by dilating peripheral arterioles and reducing total peripheral resistance. This leads to a modest decrease in (<5 mmHg) systolic and diastolic blood pressure and larger decreases in hypertensive patients. If given intravenously, it also reduces left ventricular contractility and increases filling pressure.

Although, bepridil hydrochloride is usually administered orally for the treatment of chronic stable angina, it is not the first choice of drugs due to its arrhythmogenic potential and associated agranulocytosis and is given only if a patient fails to respond to other antianginal agents (178,179). When used alone or in combination with other antianginal agents, it is as effective as β-adrenergic blocking drugs or other dihydropyridine calcium channel blockers. However, bepridil can aggravate existing arrhythmias or induce new arrhythmias to the extent of potentially severe and fatal ventricular tachyarrhythmias, related to increase in QT and QTc interval (180). Bepridil is rapidly and completely absorbed after oral administration and 99% bound to plasma proteins. It has a half-life of 26–64 h. Bepridil is almost completely metabolized in the liver, resulting in 17 various metabolites, including pharmacologically most effective 4-hydroxy-*N*-phenylbepridil.

Diltiazem Hydrochloride. Like bepridil, it is also a non-dihydropyridine calcium channel blocker but belongs to a benzothiazepine family of compounds (181,182). The (+)-cis form of the compound is the pharmacologically active isomer. It is a light sensitive crystalline powder, soluble in water and formulated as either a hydrochloride or malate salt. Diltiazem shows pharmacologic actions similar to other calcium channel blockers, ie, by inhibiting the transmembrane influx of extracellular calcium ions across the myocardial cell membrane and vascular smooth muscle cells (183,184). However, unlike dihydropyridine calcium channel blockers, diltiazem exhibits inhibitory effects on the cardiac conduction system mainly at the AV node and minor effects on sinus node. The frequency dependent effect of diltiazem on AV nodal conduction selectively decreases the heart ventricular rate during tachyarrhythmias involving AV node. However, in patients with SA node dysfunction, it decreases the heart rate and prolongs sinus cycle length resulting in a sinus arrest. Diltiazem shows no or little effect on QT interval.

Diltiazem is administered as the hydrochloride salt orally as tablets or extended release capsules for the treatment of Printzmetal angina and chronic stable angina and hypertension. The intravenous infusion is the most preferred

Table 3. **Antianginal Agents: Arylalkylamines and Benzothiazepins (Calcium Channel Blockers)**

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Structure
bepridil hydrochloride	[74764-40-2]	$C_{24}H_{35}ClN_2O$	Angopril, Bepadin, Cordium, Vascor	antianginal	
diltiazem hydrochloride	[33286-22-5]	$C_{22}H_{27}ClN_2O_4S$	Adizem, Anginyl, Angizem, Bruzem, Calcicard, Cardizem, Citizem, Deltazen, Diladel, Dilzem, Masdil, Tildiem	antianginal, antihypertension, antiarrhythmic	
clentiazem	[96125-53-0]	$C_{22}H_{25}ClN_2O_4S$	Logna	antihypertension	

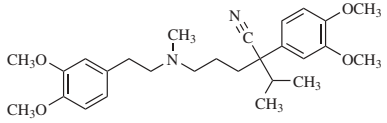
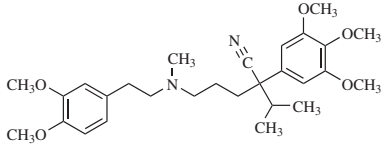
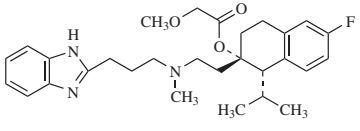
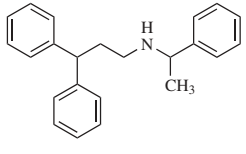
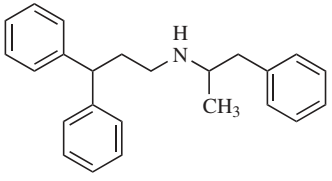
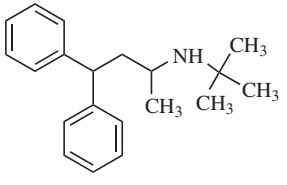
verapamil hydrochloride	[152-11-4]	$C_{27}H_{38}N_2O_4$	Apramyl, Calan, Cordilox, Dignover, Isoptin, Securon, Univer, Vasolan, Veraptin, Verelan, Verexamil, Veramix	antihypertension, antianginal, antiarrhythmic	
gallopamil	[16662-46-7]	$C_{28}H_{40}N_2O_5$	Algocor, Procorum	antianginal	
mibefradil	[116666-63-8]	$C_{29}H_{38}FN_3O_3$	Posicor	antihypertension	
fendiline	[13636-18-5]	$C_{23}H_{25}N \cdot HCl$	Cordan, Fendilar, Sensit	coronary vasodilator	

Table 3 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Structure
prenylamine	[390-64-7]	$C_{24}H_{27}N$	Angormin, Crepasin, Reocorin, Roinin, Sedolatan, Synadrin	coronary vasodilator	
terodiline	[7082-21-5]	$C_{20}H_{27}N$	Bicor, Mictrol, Micturin, micturol	antianginal	

formulation for the treatment of supraventricular tachyarrhythmias. A controlled study also indicates that simultaneous use of diltiazem and a β-adrenergic blocking agent in patients with chronic stable angina reduces the frequency of attacks and increases an exercise tolerance (185). The absorption of diltiazem from the GI tract after po dosing is nearly complete. It undergoes extensive first-pass metabolism in the liver and only 40% of the po dose is bioavailable. About 70–80% of the drug is bound to plasma protein. The onset of action is ~15 min and the peak effect occurs at 30 min. Diltiazem is metabolized by deacetylation, and *N*- and *O*-demethylation. The principal metabolite, desacetyldiltiazem has 25–50% of the pharmacological activity and 10–20% of the plasma levels of the parent compound. About 30–35% of the drug is excreted by the kidneys as metabolites and 2–4% as unchanged drug. Almost 60% is excreted in the feces as metabolites. The elimination half-life of diltiazem is 3–4.5 h. Elimination half-life and plasma levels are increased in patients with liver disease (154,155,186).

The side effects of diltiazem therapy are less than those of verapamil or nifedipine therapy and occur in ~4% of the patients (154,155,186).

Clentiazem. It is a chlorinated derivative of diltiazem and is currently undergoing clinical evaluation for the treatment of angina pectoris and hypertension. The primary mechanism of clentiazem responsible for the antihypertensive effects seems to be reduction in the peripheral arterial resistance due to calcium channel blockade (187,188).

Verapamil Hydrochloride. Like diltiazem, verapamil is also a non-dihydropyridine calcium channel blocker. It is available as a racemic mixture and occurs as a crystalline powder, soluble in water. The L-isomer of verapamil, which is 2–3 times more active than the corresponding D-isomer for its pharmacodynamic response on A-V conduction, has been shown to inhibit the ATP-dependent calcium transport mechanism of the sarcolemma (189). It acts by a similar pharmacological mechanism of action to other calcium channel blocking agents by reducing afterload and myocardial contractility. However, verapamil also exerts negative dromotropic effects on the AV nodal conduction and is classified as a class IV antiarrhythmic agent (190). These effects of verapamil on nodal impulse generation and conduction are useful in treating certain types of arrhythmias and its effects on myocardial contractility can be a problem in patients with heart failure. Therefore, verapamil is used in the treatment and prevention of supraventricular tachyaarhythmias and in hypentensive patients, not affected by cardiodepressent effects (191).

It is also used orally in the treatment of Prinzmetal angina or chronic stable angina and is as effective as any other β-adrenergic blocking agent or calcium channel blocker. Intravenous verapamil is the first choice of drugs used in the management of supraventricular tachyarrhythmia, including rapid conversion to sinus rhythm of PSVT (those associated with Wolf-Parkinson-White or Lown-Ganong-Levine syndrome) and temporary relief of atrial fibrillation. It is also used as a monotherapy or in combination with other antihypertensive agents for the treatment of hypertension.

Gallopamil. Gallopamil is a more potent methoxy analogue of verapamil and the drug has demonstrated efficacy in effort and rest angina, hypertension, and supraventricular tachycardia (192–195). However, intracoronary

administration of gallopamil may be useful in treating myocardial ischemia during percutaneous transluminal coronary angioplasty (196).

Intrarenal gallopamil has shortened the course of acute renal failure. It has been suggested that the role of inhaled gallopamil in asthma remains to be defined, and well-controlled potential comparisons with verapamil are needed to define the place in therapy of gallopamil for all indications.

Mibefradil. This compound has been assigned its own class and it is a T- and L-type CCB, primarily approved in 1997 by U.S. Food and Drug adminstration (FDA) for management of hypertension and chronic stable angina (197–200). However, postmarketing surveillance discovered potential severe life-threatening drug–drug interactions between mibefradil and β-blockers, digoxin, verapamil, and diltiazem, especially in elderly patients, resulting in one death and three cases of cardiogenic shock with intensive support of heart rate and blood pressure. Therefore, manufacturer voluntarily withdrew mibefradil from the U.S. market in 1998 (201).

Fendiline. Fendiline is used in the long-term treatment of coronary heart disease. Fendiline is a coronary vasodilator and clinical studies have established at least equal therapeutic efficacy in the treatment of angina pectoris as isosorbide dinitrate or diltiazem (202–206). Recently, the action of fendiline on cardiac electrical activity has also been investigated in guinea pig papillary muscle, suggesting that a frequency and concentration dependent block of Na^+ and L-type Ca^{2+} channels occurs in presence of fendiline, leading to inhibition of fast and slow conduction and inactivation of Ca^{2+} channels (207).

Further studies show that fendiline also induces an increase in Ca^{2+} concentration in Chang liver cells by releasing stored Ca^{2+} in an inositol 1,4,5-triphosphate independent manner and by causing extracellular Ca^{2+} influx (208).

Prenylamine. Prenylamine is a homologue of fendiline and normally is used in the treatment of chronic coronary insufficiency and prophylaxis of anginal paroxysms. The latter is recognized by a disturbance in brain blood circulation and sometimes hypertension, but prenylamine is not sufficiently effective in very acute anginal paroxysms (209). Since it is a coronary vasodilator, it acts as a calcium antagonist, but without any substantial effect on the contractility of the myocardium. However, it improves the vascular blood circulation due to vasodilation and thereby oxygen supply of the myocardium. It also decreases the amount of norepinephrine and serotonin in the myocardium and brain and therefore possesses a slight blocking effect on β-adrenergic receptors. Since it enhances the antihypertensive effect of beta blockers, the dose needs to be controlled. But if given in high doses and in cases of tachycardia, it could lead to the deceleration of cardiac related physical activity (210).

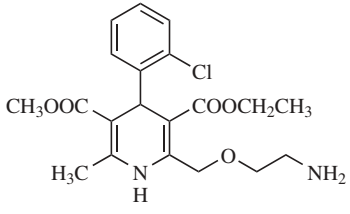
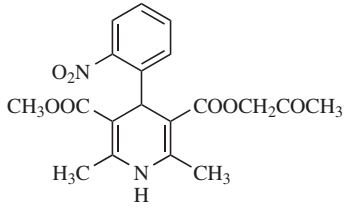
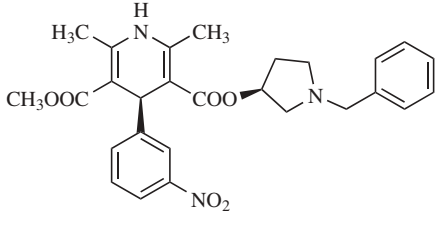
Terodiline. It is an alkyl analogue of fendiline and is used as a calcium channel antagonist. However, it also possesses anticholinergic and vasodilator activity (211). When administered twice daily, terodiline has been demonstrated effective in the treatment of urinary urge incontinence (211). Comparative studies with other agents used in urge incontinence are required to determine if the dual mechanism of action and superior absorption of terodiline offer clinical advantages. Safety concerns about ventricular arrhythmias have suspended general clinical investigations.

Dihydropyridine Derivatives. This is an important class of compounds that are widely used as vasodilators. In general, 1,4-Dihydropyridines demonstrate slight selectivity toward vascular versus myocardial cells, and therefore have greater vasodilatory effect than other calcium channel blockers. 1,4-Dyhydropyridines are also known to possess insignificant electrophysiological and negative inotropic effects compared to verapamil or diltiazem. The dihydropyridines have no significant direct effects on the heart, although they may cause reflex tachycardia. Structures and properties of some of the first and second generation dihydropyridines are given in Table 4. Most of the newer drugs have longer elimination half-lives but also higher rates of hepatic clearance and hence low bioavailability. The only exception is amlodidpine, which has a much higher bioavailability (60%) and a long elimination half-life. Several metabolic pathways of DHP-type calcium channel blockers have been identified in humans. However, the most important metabolic pathway appears to be the oxidation of 1,4-Dihydropyridine ring into pyridine, catalyzed by the cytochrome P450 (CYP) 3A4 isoform and the oxidative cleavage of carboxylic acid (212). Calcium antagonists are known to block calcium influx through the voltage-operated calcium channels into smooth muscle cells. Some of the compounds of 1,4-DHP category such as Nifedipine, Nisoldipine, or Isradipine have been demonstrated to be useful in the management of coronary artery diseases. Nevertheless these already available calcium antagonists have some major disadvantages: they are photosensitive and decompose rapidly, they are not soluble in water, and because of their depressive effects on myocardium they have negative inotropic effects. The CCBs account for almost $4 billion in sales and dihydropyridines like lercanidipine are the fastest growing class of CCB. There are 13 derivatives of DHP calcium channel blockers currently licensed for the treatment of hypertension and widely used. Some of the most prescribed drugs include amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine. Currently, thiazide diuretics or β-blockers are recommended as first line therapy for hypertension. Calcium channel blockers, ACE inhibitors or α-adrenergic blockers may be considered when the first line therapy is not tolerated, contraindicated or ineffective.

Amlodipine Besylate. This compound belongs to the 1,4-dihydropyridine family of compounds possessing structural resemblance to nifedipine, felodipine, nimodipine, and others. It is a light sensitive, selective, and potent calcium channel blocking agent with a long duration of action. Amlodipine has a long half-life of $>$33 h after intravenous dosing and its bioavailability with po doses is 52–88% (213). It is mainly used orally, either alone or in combination with other antihypertensive agents to treat hypertension and Prinzmetal and chronic stable angina, along with other antianginal agents (214,215).

Aranidipine. It is a 1,4-dihydropyridine calcium channel blocker with vasodilating and antihypertensive actions, and therefore used for the treatment of hypertension (216–218). It is used either alone or in combination with a diuretic or β-blocker, for the once-daily treatment of mild-to-moderate essential hypertension. The drug is under investigation for the treatment of angina pectoris, but available data are limited to preclinical animal studies. It decreases T- and L-type calcium currents in a concentration-dependent manner. The duration of aranidipine's antihypertensive effect is longer than that of nifedipine and

Table 4. **Antianginal Agents: 1,4-Dihydropyridine Calcium Channel Blockers**

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name[a]	Structure
amlodipine besylate	[111470-99-6]	$C_{26}H_{31}ClN_2O_8$	Antacal, Istin, Monopina, Norvasc	
amlodipine maleate	[88150-47-4]	$C_{24}H_{29}ClN_2O_9$	Lotrel	
aranidipine	[86780-90-7]	$C_{19}H_{20}N_2O_7$	NA	
barnidipine	[104713-75-9]	$C_{27}H_{29}N_3O_6$	NA	

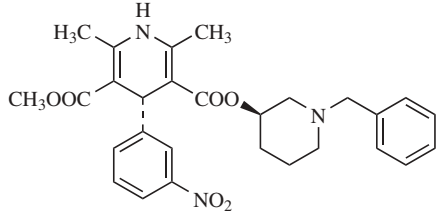
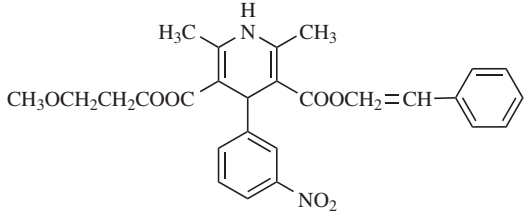
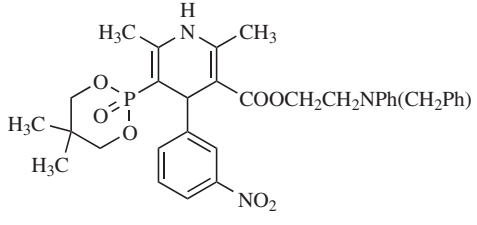
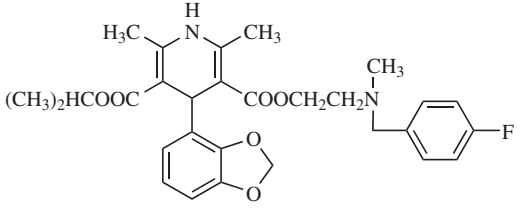
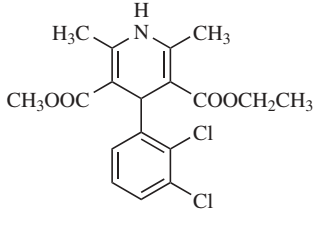
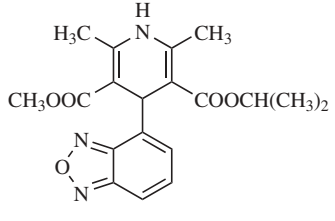
benidipine	[105979-17-7]	$C_{28}H_{31}N_3O_6$	Coniel	
cilnidipine	[132203-70-4]	$C_{27}H_{28}N_2O_7$	NA	
efonidipine	[111011-63-3]	$C_{34}H_{38}N_3O_7P$	NA	

Table 4 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name[a]	Structure
elgonidipine	[119413-55-7]	$C_{29}H_{33}FN_2O_6$	NA	
felodipine	[72509-76-3]	$C_{18}H_{19}Cl_2NO_4$	Agon, Hydac, Plendil, Lexxel	
isradipine	[75695-93-1]	$C_{19}H_{21}N_3O_5$	Esradin, Lomir, Prescal	

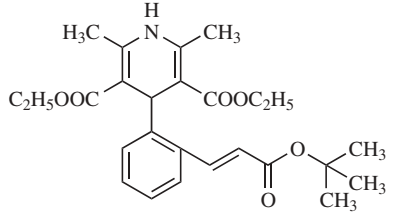
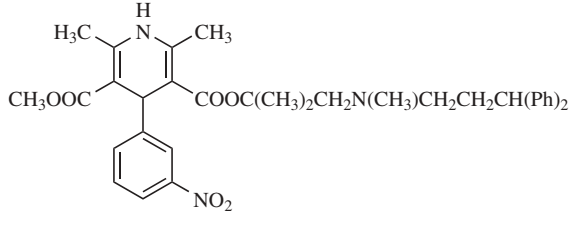
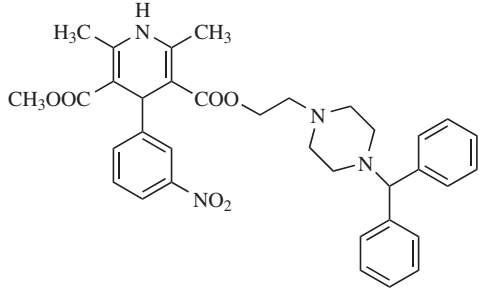
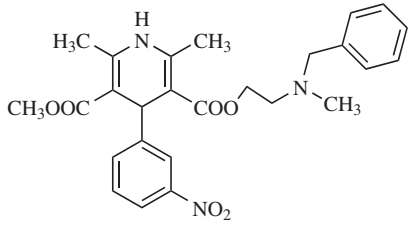
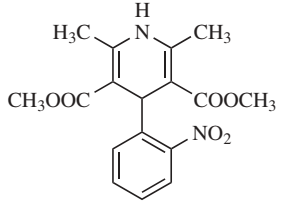
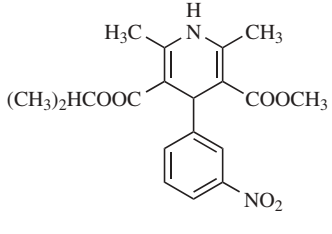
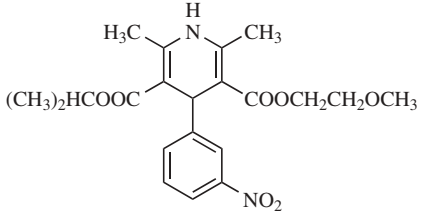
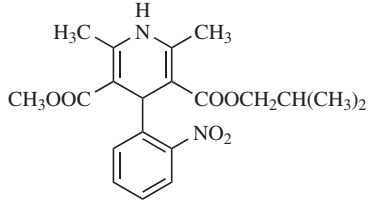
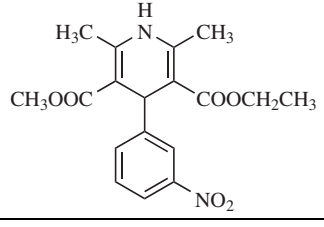
lacidipine	[103890-78-4]	$C_{26}H_{33}NO_6$	Caldine, Motens, Lacipil, Lacirex	
lercanidipine	[100427-26-7]	$C_{36}H_{41}N_3O_6$	Lerdip, Zanidip	
manidipine	[89226-50-6]	$C_{35}H_{38}N_4O_6$	Calslot	

Table 4 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name[a]	Structure
nicardipine	[54527-84-3]	$C_{26}H_{29}N_3O_6$	Barizin, Cardene, Lecibral, Loxen, Nicant, Nicodel, Nimicor, Ranvil, Rydene	
nifedipine	[21829-25-4]	$C_{17}H_{18}N_2O_6$	Adapress, Alfadat, Aprical, Citilat, Introcor, Nifedicor, Tibricol	
nilvadipine	[75530-68-6]	$C_{19}H_{19}N_3O_6$	Escor, Nivadil	

nimodipine	[66085-59-4]	$C_{21}H_{26}N_2O_7$	Admon, Nimotop, Periplum	
nisoldipine	[63675-72-9]	$C_{20}H_{24}N_2O_6$	Norvasc, Syscor, Zadipina	
nitrendipine	[39562-70-4]	$C_{18}H_{20}N_2O_6$	Baypress, Bylotensin, Nidrel	

[a]NA = not applicable.

nicardipine. It does not significantly affect heart rate, cardiac output, or stroke volume index at rest or after exercising in patients with mild-to-moderate hypertension. However, it significantly increases left ventricular fractional shortening (FS) and left ventricular ejection fraction (EF) at rest. It does not adversely affect hemodynamics or lipoprotein or carbohydrate metabolism and the pharmacokinetics of aranidipine are not altered in the elderly or in patients with renal failure (216–218).

Barnidipine. The long-acting calcium antagonist barnidipine was launched in Japan in September 1992 under the brand name Hypoca(R), and sales of this drug are increasing steadily. Barnidipine is used in Europe under the brand name Vasexten(R). A long-acting calcium antagonist requires administration only once a day for the treatment of angina and hypertension (219–221). It is available as a modified release formulation with a gradual and long duration of action. It is a selective calcium channel antagonist leading to the reduction of peripheral vascular resistance, secondary to its vasodilatory action (222). Recently, it was suggested that Barnidipine administration for a week decreased the blood pressure and made the sodium balance negative by increasing the urinary sodium excretion in patients with essential hypertension. The natriuretic effect of this drug could contribute at least in part to its antihypertensive effect (223). Also, the possible use of barnidipine for protective effects on cerebrovascular lesions in salt-loaded stroke-prone spontaneously hypertensive rats was evaluated by magnetic resonance imaging (mri) (224).

Benidipine. This is a new, potent dihydropyridine and long-lasting calcium antagonist (225). The administration of benidipine once daily effectively decreases blood pressure and attenuates blood pressure response to mental stress. Reflex tachycardia, deterioration of diurnal blood pressure change, and excessive lowering of nighttime blood pressure were not observed after benidipine administration. Therefore, it has been suggested that it may be useful for the treatment of elderly hypertensive patients with cardiovascular disease. It has also been suggested that it also might be useful as an antianginal medication, however, no clinical data is yet available (226).

Cilnidipine. It is a unique calcium antagonist that has both L- and N-type voltage-dependent calcium channel blocking action (227–231). Cilnidipine is under investigation for the treatment of hypertension in Europe.

Recently, cilnidipine, its analogues and other dihydropyridine derivatives were evaluated for their state-dependent inhibition of L-type of Ca^{2+} channels, demonstrating that structurally related DHPs act in distinct ways to inhibit the L-type channel in the resting, open, and inactivated states. Cilnidipine and some related DHPs probably exert their blocking action on the open channel by binding to a receptor distinct from the known DHP-binding site (232). Further effects of cilnidipine on left ventricular (LV) diastolic function in hypertensive patients, as assessed by pulsed doppler echocardiography and pulsed tissue Doppler imaging, has been examined, and suggests that changes in LV diastolic performance in patients with essential hypertension following cilnidipine treatment were biphasic with an initial increase in early diastolic transmitral flow velocity and a later increase in early diastolic LV wall motion velocity. The initial and later changes can be related to an acute change in afterload and a later improvement in LV relaxation (233).

Efonidipine. This is a new long acting dihydropyridine calcium channel blocker derivative used in the treatment of hypertension (234–237). When the use of efonidipine was studied in open-chest anesthetized dogs on Endothelin-1 (ET-1), it was concluded that efonidipine attenuates the ET-1-induced coronary vasoconstriction, and therefore the drug would be useful for some patients with variant angina, in which ET-1 is involved in the genesis of coronary vasoconstriction (238).

Recently, to gain insight into the renoprotective mechanism of efonidipine hydrochloride, the acute effects of efonidipine on proteinuria, glomerular haemodynamics and the tubuloglomerular feedback (TGF) mechanism in anaesthetized 24–25-week-old spontaneously hypertensive rats (SHR) with glomerular injury were evaluated. The results indicate that efonidipine attenuates the TGF response in SHR by dilating the afferent arteriole, thus maintaining the level of renal plasma flow (RPF) and glomerular filtration rate (GFR) despite reduced renal perfusion pressure (239).

Elgodipine. It is a novel type of DHP, very selective, and potent coronary vasodilator calcium channel blocker (240). Elgodipine is very stable to light (2% degradation after 1 year of exposure to room light and temperature) in comparison with other currently available compounds that decompose in 24 h and is water soluble. It is very selective against vascular smooth muscle, in particular coronary vessels. Since elgodipine is >100-folds selective versus vessels than cardiac fibers, it has few negative inotropic effects. Elgodipine seems to be potentially useful as coronary vasodilator during PTCA (percutaneous transluminal coronary angioplasty) because its stability and solubility allows intracoronary administration, in patients with stable angina and because the lack of negative inotropic effects, in patients with moderate heart failure (241–243).

Some of the preliminary electrophysiological data in volunteers have shown that elgodipine differs from other calcium channel blockers in its effects on atrioventricular conduction.

On the other hand, chemical stability of elgodipine allows its incorporation into suitable polymeric matrices for transdermal administration. Preliminary *in vitro* and *in vivo* data in volunteers have shown that elgodipine penetrates into the skin. Studies are in progress to determine the daily effective dose and therefore, the feasibility of transdermal patches (244).

Felodipine. It is a member of DHP calcium channel blocker family. It is insoluble in water and is freely soluble in dichloromethane and ethanol. It exists as a racemic mixture. Felodipine is used to treat high blood pressure, Raynaud's syndrome, and congestive heart failure (245–246). It reversibly competes with nitrendipine and/or other CCBs for dihydropyridine binding sites, and blocks voltage-dependent Ca^{2+} currents in vascular smooth muscle more than in cardiac muscle.

Following oral administration, felodipine is almost completely absorbed and undergoes extensive first-pass metabolism. However, following intravenous administration, the plasma concentration of felodipine declines triexponentially with mean disposition half-lives of 4.8 min, 1.5, and 9.1 h. Following oral administration of the immediate-release formulation, the plasma level of felodipine also declines polyexponentially with a mean terminal half-life of 11–16 h.

The bioavailability of felodipine is influenced by the presence of high fat or carbohydrate food and increases approximately twofold when taken with grapefruit juice. A similar finding has been seen with other dihydropyridine calcium antagonists, but to a lesser extent than that seen with felodipine (247–249).

Felodipine produces dose-related decreases in systolic and diastolic blood pressure that correlates with the plasma concentration of felodipine. Felodipine can lead to increased excretion of potassium, magnesium, and calcium (250). It has been recommended that in order to prevent side effects of the drug, individuals who are taking felodipine should avoid grapefruit and its juice (251). This is because grapefruit (juice) is an inhibitor of Cytochrome P450 isoforms 3A4 and 1A2, which are needed for the normal metabolism of felodipine.

Isradipine. It is a calcium antagonist available for oral administration. It binds to calcium channels with high affinity and specificity and inhibits calcium flux into cardiac and smooth muscle. It is used in the management of hypertension, either alone or concurrently with thiazide-type diuretics (252–255). In patients with normal ventricular function, isradipine's afterload reducing properties lead to some increase in cardiac output. Effects in patients with impaired ventricular function have not been fully studied.

In humans, peripheral vasodilation produced by isradipine is reflected by decreased systemic vascular resistance and increased cardiac output. In general, no detrimental effects on the cardiac conduction system were seen with the use of isradipine.

Isradipine is 90–95% absorbed and is subject to extensive first-pass metabolism, resulting in a bioavailability of ~15–24%. Isradipine is completely metabolized prior to excretion and no unchanged drug is detected in the urine. Six metabolites have been characterized in blood and urine, with the mono acids of the pyridine derivative and a cyclic lactone product accounting for >75% of the material identified. The reaction mechanism ultimately leading to metabolite transformation to the cyclic lactone is complex.

Lacidipine. It also belongs to a DHP class of calcium channel blockers (256). Recently, it was shown that lacidipine can slow the progression of atherosclerosis more effectively than atenolol, according to the results of the European lacidipine study on atherosclerosis (257). The improvement of focal cerebral ischemia by lacidipine may be partly due to long-lasting improvement of collateral blood supply to the ischemic area (258). When comparative effects of both lacidipine and nifedipine were measured, both drugs reduced blood pressure significantly during the 24-h period with one dosage daily; only lacidipine reduced left ventricular mass significantly after 12 weeks of treatment (259).

Lercanidipine. It is a member of the dihydropyridine calcium channel blocker class of drugs. Recently, a New Drug Application with the FDA to market lercanidipine for the treatment of hypertension has been submitted, although it has been available in European countries for >4 years with an established record of antihypertensive effect and safety in millions of patients (260,261). In fact, it has grown to be the third most prescribed CCB in Italy due to its favorable side effects. Lercanidipine prevents calcium from entering the muscle cells of the heart and blood vessels, which enable the blood vessels to relax, thereby lowering blood pressure. It has a short plasma half-life but its high lipophilicity allows accumulation in cell membranes resulting in a long duration of action. It

has been suggested that lercanidipine causes fewer vasodilatory adverse side effects than other CCBs, and therefore is being promoted for the treatment of isolated systolic hypertension (ISH) in elderly patients (262).

Manidipine. It is effective in the treatment of essential hypertension (263,264). When the effect of manidipine hydrochloride on isoproterenol-induced left ventricular hypertrophy and the expression of the atrial natriuretic peptide (ANP) transforming growth factor was evaluated, it was found that manidipine hydrochloride prevented cardiac hypertrophy and changes in the expression of genes for ANP and interstitial components of extracellular matrix induced by isoproterenol (265).

Nicardipine. It belongs to the 1,4-dihydropyridine calcium channel blocking family of compounds. Nicardipine is tissue selective and produces relaxation of coronary vasculature at dose levels that produce little or no inotropic effects. It has been shown to increase exercise tolerance and reduce nitroglycerin consumption and frequency of anginal attacks. It is usually administered orally or by slow continuous intravenous infusion when oral administration is not viable, for the treatment of chronic stable angina and short-term management of hypertension. It is used as a monotherapy or in combination with other antianginal or antihypertensive drugs.

Nicardipine is almost completely absorbed after po administration. Administration of food decreases absorption. It undergoes extensive first-pass metabolism in the liver. Systemic availability is dose-dependent because of saturation of hepatic metabolic pathways. A 30-mg dose is ~35% bioavailable. Nicardipine is highly protein bound (>95%). Peak plasma concentrations are achieved in 0.5–2.0 h. The principal path of elimination is via hepatic metabolism by hydrolysis and oxidation. The metabolites are relatively inactive and exert no pharmacological activity. The elimination half-life is 8.6 h. About 60% of the dose is excreted in the urine as metabolites (<1% as intact drug) and 35% as metabolites in the feces (154,155,186,266).

Nifedipine. The principle physiological action of nifedipine is similar to other 1,4-dihydropyridine derivatives and functions by inhibiting the transmembrane influx of extracellular calcium ions across the myocardial membrane cells and vascular smooth muscle cells, without affecting plasma calcium concentrations. Although the exact mechanism of action of nifedipine is unknown, it is believed to deform the slow channel and hinder the ion control gating mechanism of the calcium channel by interfering with the release of calcium ions from the sarcoplasmic reticulum. The inhibition of calcium influx dilates the main coronary and systemic arteries due to the impediment of the contractile actions of cardiac and smooth muscle. This reduced myocardial contractility, results in increased myocardial oxygen delivery while decreasing the total peripheral resistance associated by a modest lowering of systemic blood pressure, small increase in heart rate and reduction in the afterload ultimately leading to reduced myocardial oxygen consumption.

Unlike verapamil and diltiazem, nifedipine does not exert any effect on SA or AV nodal conduction at therapeutic dosage levels. Nifedipine is administered orally and extended release tablets in various dosage forms. It is rapidly absorbed (90%) from the GI tract following oral administration and its plasma protein binding is concentration dependent. It has a plasma half-life of 2–5 h

and is rapidly and completely metabolized in the liver to inactive metabolites. It is mainly used in the treatment of Prinzmetal angina and chronic stable angina. In the latter case, it is as effective as β-adrenergic agents or oral nitrates, but used only when the patient has low tolerance for adequate doses of these drugs. Nifedipine is also used in the management of hypertension, Raynaud's condition and as a second line tocolytic agent. Common adverse side effects include nausea, heartburn, muscle cramps, nervousness and mood changes, and nasal congestion. GI complaints occur occasionally.

Nilvadipine. It is marketed as a racemic mixture for the treatment of hypertension and angina (267–269). Nilvadipine also provides protective effects against cerebral ischemia in rats having chronic hypertension, and the effects are dependent on the duration of treatment (270). Results of one of the clinical studies in the United States, in which the combination of imidapril with a diuretic, β-adrenoceptor antagonist or calcium channel blocker, such as nilvadipine, indicate a reasonable and safe, treatment option when striving for additive pharmacodynamic effects not accompanied by relevant pharmacokinetic interactions (271).

Nimodipine. It is a structural analogue of nifedipine and the (*S*) (−) enantiomer is primarily responsible for the calcium channel blocking activity. The position of the nitro substituent on the aryl ring and planarity of the 1,4-dihydropyridine moiety contribute greatly to the pharmacological effects of nimodipine. Nimodipine is a light-sensitive yellowish crystalline powder. The mechanism of action of nimodipine is similar to other calcium channel blockers; however, the preferential binding affinity of nimodipine toward cerebral tissue is yet to be fully understood. Nimodipine functions by binding to the stereoselective high affinity receptor sites on the cell membrane in or near the calcium channel and inhibiting the influx of calcium ions. The vasodilatory effect of nimodipine also seems to arise partly from the inhibition of the activities of sodium–potassium activated ATPase, an enzyme required for the active transport of sodium across the myocardial cell membranes.

Nisoldipine. It is a lipophilic, light sensitive, vascular selective dihydropyridine analogue, similar to nifedipine but 5–10 times more potent as a vasodilator, and has a little effect on myocardial contractility. Nisoldipine is available as a long-acting extended release preparation and appears effective in treating mild to moderate hypertension and angina, once-a-day by oral administration (272–274). Nisoldipine selectively relaxes the muscles of small arteries causing them to dilate, but has little or no effect on muscles or the veins of the heart. This indicates that it may not be useful in congestive heart failure.

In vitro studies show that the effects of nisoldipine on contractile processes are selective, with greater potency on vascular smooth muscle than on cardiac muscle. The effect of nisoldipine on blood pressure is principally a consequence of a dose-related decrease of peripheral vascular resistance. While nisoldipine, like other dihydropyridines, exhibits a mild diuretic effect, most of the antihypertensive activity is attributed to its effect on peripheral vascular resistance.

Nisoldipine is highly metabolized into five major urinary metabolites. The major biotransformation pathway appears to be the hydroxylation of the isobutyl ester. A hydroxylated derivative of the side chain, present in plasma at concentrations approximately equal to the parent compound, appears to be the only

active metabolite and has ~10% of the activity of the parent compound. Cytochrome P450 enzymes play a key role in the metabolism of nisoldipine. The particular isoenzyme system responsible for its metabolism has not been identified, but other dihydropyridines are metabolized by cytochrome P450 3A4 isozyme. Nisoldipine should *not* be administered with grapefruit juice, as it interferes with nisoldipine metabolism. Since very little information is available about its use in patients with severe congestive heart failure, this calcium channel blocker should be used with caution in any patient with heart failure.

Recently, antianginal and antiischemic effects of nisoldipine and ramipril in patients with Syndrome X (typical angina pectoris, positive treadmill exercise test but negative intravenous ergonovine test and angiographically normal coronary arteries) were evaluated, indicating that they have similar anti-ischemic and antianginal effects in patients with syndrome X (275).

Nitrendipine. It is used to treat mild to moderate hypertension (276,277).

In summary, calcium antagonists inhibit the influx of extracellular calcium ions into the cells, and prevent intracellular calcium from reaching the critical concentration necessary to initiate contraction, resulting in decreased vascular smooth muscle tone and vasodilation and, leading to a reduction in blood pressure. The 1,4-dihydropyridine derivatives (aranidipine, cilnidipine, amlodipine, nisoldipine, nifedipine, felodipine, nitrendipine, nimodipine) differ from the benzothiazepine (eg, diltiazem) and phenylalkylamine (eg, verapamil) classes of calcium antagonists with regard to potency, tissue selectivity, and antiarrhythmic effects. In general, dihydropyridine agents are the most potent arteriolar vasodilators, producing the least negative inotropic and electrophysiological effects; in contrast, verapamil and diltiazem slow AV conduction and exhibit negative inotropic activity while also maintaining some degree of arteriolar vasodilatation.

The calcium antagonists produce beneficial effects in angina by reducing coronary artery spasm, slowing heart rate or decreasing contractile force. Calcium channel blockers are commonly used to treat high blood pressure, angina, and even some forms of arrhythmia. In the treatment of hypertension and chronic heart failure, a combination therapy enhances therapeutic efficacy. Pharmacodynamically, combinations of ACE inhibitor plus a diuretic, β-adrenoreceptor antagonist, or calcium channel blocker are the most promising.

The most common side effects of calcium antagonists are hypotension, facial flushing, dizziness, headache, weakness, sedation, skin rash, edema, and abdominal discomfort such as nausea, vomiting, constipation and, epigastric pressure.

5. Antilipemic Agents

Increased cholesterol levels, due to the consumption of a diet rich in saturated fat, stimulates the liver to produce cholesterol [57-88-5], $C_{27}H_{46}O$, a lipid needed by all cells for the synthesis of cell membranes and in some cells for the synthesis of other steroids. Cholesterol is the principal reversible determinant of risk of heart disease. Low density lipoproteins (LDLs, also referred as "bad" cholesterol) transport cholesterol from the liver to other tissues, whereas high density lipoproteins (HDLs, also referred as "good" cholesterol) transport cholesterol from

tissues back to the liver to be metabolized. Triglycerides are transported from the liver to the tissues mainly as very low density lipoproteins (VLDLs). The VLDLs are the precursors of the LDLs. The LDLs are characterized by high levels of cholesterol, mainly in the form of highly insoluble cholesteryl esters. However, there exists a strong relationship between high LDL levels and coronary heart disease, and a negative correlation between HDL and heart disease. Total blood cholesterol is the most common measurement of blood cholesterol and various total blood cholesterol levels and risk factors accepted by most physicians and the American Heart Association are discussed next. In general, for people who have total cholesterol >200 mg/dL, heart attack risk is relatively low, unless a person has other risk factors. If the total cholesterol level is 240 mg/dL, the person has twice the risk of heart attack as people who have a cholesterol level of 200 mg/dL. If total cholesterol level is 240 or more, it is definitely high and the risk of heart attack and, indirectly, of stroke is greater. About 20% of the U.S. population has high blood cholesterol levels. The LDL cholesterol level also greatly affects risk of heart attack and, indirectly, of stroke. Some times the ratio of total cholesterol to HDL cholesterol is used as another measure and the goal is to keep the ratio below 5:1; the optimum ratio is 3.5:1. It is assumed that people with high triglycerides (>200 mg/dL) have underlying diseases or genetic disorders. In such cases, the main treatment is to change the lifestyle by controlling weight and limiting the carbohydrate intake, since they raise triglycerides and lower HDL cholesterol levels.

During the last few years, there has been firm evidence that coronary artery disease (CAD) is a complex genetic disease involving a number of genes associated with lipoprotein abnormalities and genes influencing hypertension, diabetes, obesity, immune, and clotting systems play an important role in atherosclerotic cardiac disorders. Researchers have identified genes regulating LDL cholesterol, HDL cholesterol, and triglyceride levels based upon common apo E genetic variation (278–282). Many genes linked to CAD are involved in how the body removes LDL cholesterol from the bloodstream. If LDL is not properly removed, it accumulates in the arteries and can lead to CAD. The protein that removes LDL from the bloodstream is called the LDL receptor (LDLR). In 1985, Michael Brown and Joseph Goldstein were awarded a Nobel Prize for determining that a mutation in this gene was responsible for familial hypercholesterolemia, or FH. People with FH have abnormally high blood levels of LDL (283).

As with LDLR, mutations in the *apo E* gene affect blood levels of LDL. Although, <30 mutant forms of *apo E* have been identified, people carrying the E4 version of the gene tend to have higher cholesterol levels than the general population, but levels in people with the E2 version are significantly lower. The *apo E* gene has also been implicated in Alzheimer's disease (284). Even though cardiovascular disease due to atherosclerosis remains the leading cause of death in the United States, most of the risk reduction strategies have traditionally focused on detection and treatment of the disease. However, some of the risk factors of cardiac diseases are reversible and changes in the life style could significantly contribute toward decreasing the mortality risk of CHD. One can reduce the risk of hypercholesterolemia by reducing the total amount of fat in diet, being physically active since exercise can help to increase HDL,

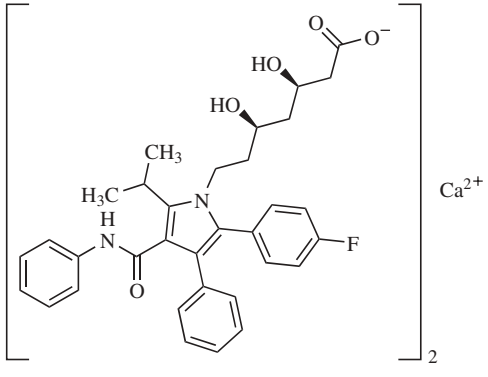
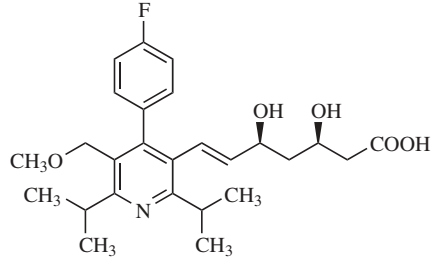
avoiding cigarette smoking and exposure to second-hand smoke, and also by reducing sodium intake (285). In people whose cholesterol level does not respond to dietary intervention, and for those having genetic predisposition to high cholesterol levels, drug therapy may be necessary.

There are now several very effective medications available for treating elevated cholesterol levels and preventing heart attacks and death. These include hydroxymethylglutartaryl-coenzyme A (HMG-CoA) reductase inhibitors such as statins, namely, atorvastatin, cerevastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and most recently approved rosuvastatin (lowers LDL cholesterol by 30–50% and increases HDL) and Cholestyramine resin (Table 5). Fibrates such as clofibrate, bezafibrate, micronized fenofibrate, and gemfibrozil (Table 5) also lower elevated levels of blood triglycerides and increase HDL. These agents are represented in the Table 2 and some of them are discussed in detail next.

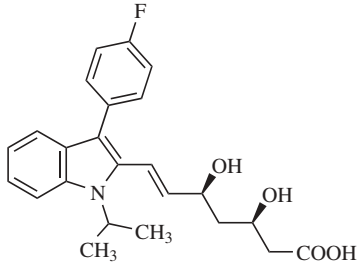
5.1. HMG-CoA Reductase Inhibitors. In humans, biosynthesis of cholesterol from Acetyl CoA in the liver accounts for 60–70% of the total cholesterol pool. The pathway to cholesterol synthesis is shown in Figure 7. Statins are antilipemic agents that are structurally similar to HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid, an early precursor of cholesterol. Statins produce selective and reversible competitive inhibition of HMG-CoA reductase by binding to two separate sites on the enzyme. Statins are either fungus derived (fermentation product of *Aspergillus terreus*) or are synthetically produced by chemical modification of lovastatin (286). Fully synthetic statins exist either as racemic mixtures or as pure enantiomers. All commercially available statins contain a nucleus that interacts with the coenzyme A recognition site of HMG-CoA reductase and a β,δ-dihydroxy acid side chain that competes with HMG-CoA for interaction with the enzyme (287). The nucleus consists of either a hexahydronapthalene moiety, or an indole–pyrrole–pyridine moiety, and any modification alters the lipophilicity of statins. The β,δ-dihydroxy acid chain is essential for catalytic activity, either as an active dihydroxy acid salt or inactive lactone. Compounds possessing the dihydroxy acid salt are orally active, while those with lactone moiety are prodrugs and have little antilipemic activity until hydrolysed *in vivo* to the corresponding dihydroxy form. Statins introduced in the late 1980s, are fast becoming the most widely prescribed drugs to lower cholesterol.

The exact mechanism by which statins reduce serum concentrations of LDL–cholesterol, VLDL–cholesterol, apoB, and triglycerides is complex, but well understood. Normally, the cell synthesizes cholesterol *de novo* for use in cell membrane and steroid—hormone synthesis, or acquires it from circulating LDLs via receptor mediated endocytosis. Statins are rapidly absorbed to different extents following oral administartion and undergo extensive first pass metabolsim in the liver. The absolute bioavailabilities of atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin, are 14, 60, 24, 5, 17, and 5% respectively. Mean peak plasma concentrations of active inhibitors occur at 0.6–4 h following oral administration and appear to be slightly higher in women than in men. All statins are 95–99% plasma protein bound except pravastatin, which is just 50% bound. Atorvastatin, lovastatin, and simvastatin are metabolized by cytochrome P450 (CYP), mainly by the isoenzyme 3A4 (CYP3A4).

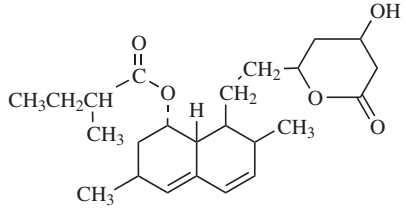
Table 5. **Antilipemic Agents**

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
		HMG-CoA Reductase Inhibitors (Statins)		
atrovastatin calcium	[134523-03-8]	$C_{66}H_{68}CaF_2N_4O_{10}$	Lipitor, Sortis, Xarator	
cerivastatin sodium	[143201-11-0]	$C_{26}H_{33}FNNaO_5$	Baycol, Lipobay	

fluvastatin sodium	[93957-55-2]	$C_{24}H_{25}FNNaO_4$	Lescol, Lescol XL



lovastatin	[75330-75-5]	$C_{24}H_{36}O_5$	Mevacor



pravastatin sodium	[81131-70-6]	$C_{23}H_{35}NaO_7$	Pravachol

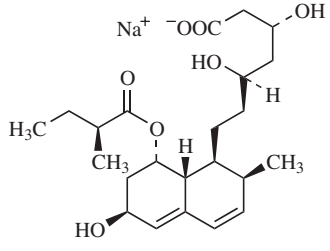
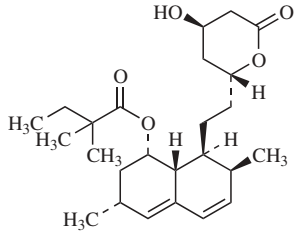
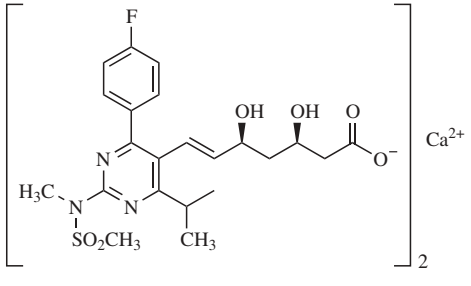
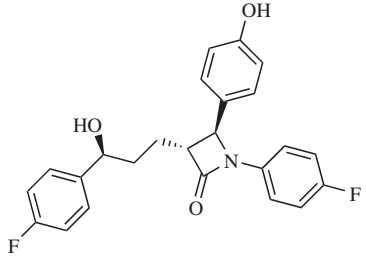
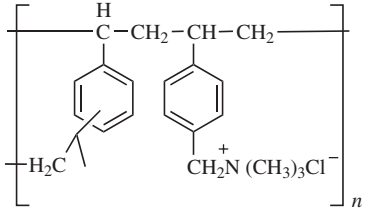
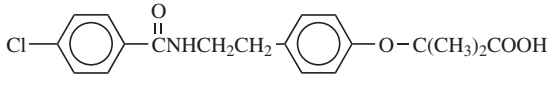
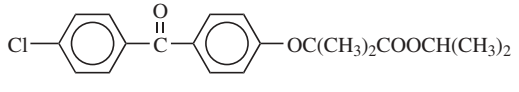
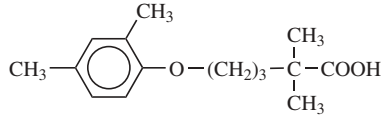


Table 5 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
simvastatin	[79902-63-9]	$C_{25}H_{38}O_5$	Zocor	
rosuvastatin calcium	[147098-202]	$2C_{22}H_{27}FN_3O_6S.\ Ca$	Crestor	
			ACAT Inhibitors	
SCH 58235	[163222-33-11]	$C_{24}H_{21}F_2NO_3$	Ezetimibe (zetia)	

			Resins	
cholestyramine resin	[11041-12-6]	polymer	Locholest, Questran, Cholestyramine, Prevalite	
colestipol hydrochloride	[37296-80-3]	polymer	Colestid	
			Fibric Acid Derivatives	
clofibrate	[637-07-0]	$C_{12}H_{15}ClO_3$	Atromid-S, Clofibrate	
bezafibrate	[41859-67-0]	$C_{19}H_{20}ClNO_4$	Bezalip, Bezatol, Cedur,	
fenofibrate	[49562-28-9]	$C_{20}H_{21}ClNO_4$	Fenotard, Lipantil, Lipidil, Tricor	
gemfibrozil	[25812-30-0]	$C_{15}H_{22}O_3$	Genlip, Lopid, Lipur	
			Other	
niacin			Niacor, Niaspan	

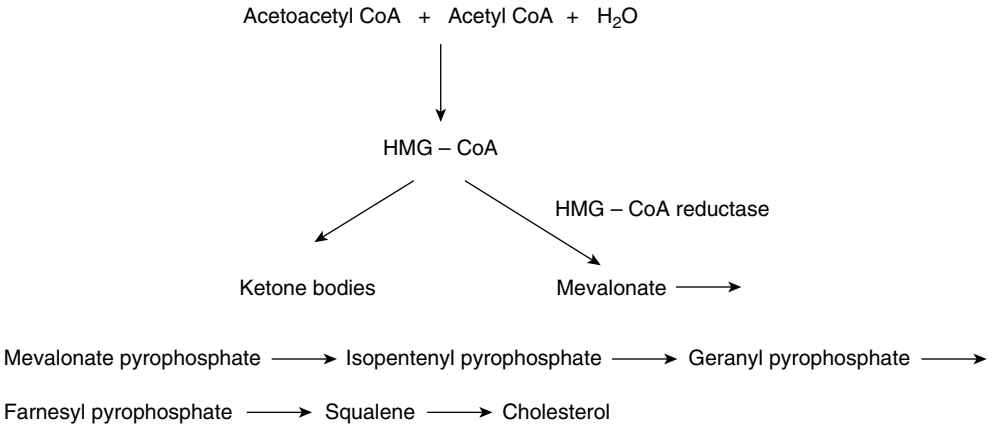


Fig. 7. The pathway to cholesterol synthesis is shown.

Cerevastatin is metabolized by both CYP3A4 and CYP2C8, while fluvastatin is metabolized by isoenzyme 2C9 (CYP2C9). With the exception of atorvastatin (plasma half-life of 14 h) all statins have relatively short half-lives between 0.5 and 4 h.

HMG-CoA reductase inhibitors (Statins) are used as adjuncts to dietary therapy in the management of hypercholestereolemia to reduce the risks of acute coronary events such as CHD, atherosclerosis, MI, or angina. All statins are admistered orally, once a daily, from 10–80 mg/day as per the individual requirements and response. At usual doses, statins are well tolerated and have very few adverse effects. The most common adverse effects are GI disturbances, fatigue, localized pain, and headache. The following five statins are the most prescribed drugs currently on the market.

Atorvastatin Calcium (Lipitor). It is a synthetic antilipemic agent that exists as an active dihydroxy acid. It is the most potent statin for lowering LDL cholesterol (bad cholestrol) and is the most commonly prescribed statin drug. It is used as an adjunct therpy to decrease elevated serum total and LDL, apoB, and triglyceride concentrations and to increase HDL levels. It is also shown to reduces the risk of recurrent ischemic events in patients with CHD having elevated LDL levels. The clinical trials demonstrating the ability of Lipitor to prevent heart attacks and early mortality have not been conducted.

Cerivastatin Sodium (Baycol). It was the most inexpensive statin, however, it was removed from the market in 2001 due to several deaths resulting from severe muscle disease caused by the drug. Other statins are also known to cause similar muscle disease, however, the adverse effects are comparatively mild.

Fluvastatin sodium (Lescol). It is a synthetic and enantiomerically pure antilipemic agent and used as a first line therapy in the treatment of type IIa and IIb hyperlipoproteinemia.

Lovastatin (Mevacor). It is the first statin approved for the use by FDA and the patent expired in 2002 resulting in significantly reduced prices. It is a δ-lactone and produced by fermentation of *Aspergillus terreus* and used similar to other statins to lower bad cholesterol.

Simvastatin (Zocor). It is the second most potent statin drug used to lower LDL cholesterol. Zocor has been found to be the most effective drug as compared to other statins in raising HDL (good) cholesterol levels. It is the first statin used in a study indicating that statins can significantly reduce heart attacks and stroke in high risk patients regardless of cholesterol levels. Similar to Mevacor, zocor is a δ-lactone and produced by the fermentation of *Aspergillus terreus*.

Pravastatin sodium (Pravachol). It is a HMG-CoA inhibitor and differs from other statins where a methyl group on the hexahydronapathalene rings is substituted by a hydroxyl group. The latter change increases the hydrophilicity of Pravastatin making it 100-fold more soluble in water than other statins. A clinical study indicates that Pravachol is also an efficient statin with a capability to prevent heart attacks and early mortality than any other statin. It does not cause drug–drug interactions.

Rosuvastatin (Crestor). Recently a new statin named Rosuvastatin (Crestor), superior to the most widely prescribed statins including atorvastatin, has been approved by the FDA to lower LDL levels. It also increases the HDL significantly more than atorvastatin. Rosuvastatin is an enhanced HMG-CoA reductase inhibitor with a number of advantageous pharmacological properties, relative hydrophilicity, and selective uptake activity by hepatic cells. In one study, crestor (10-mg dose) reduced LDL cholesterol by 49% as compared to 37% with simvastatin (20-mg dose) and 28% with pravastatin (20-mg dose). Similar to other statins, crestor is safe and well tolerated alone or in combination with fenofibrate, extended release niacin and cholstyramine. Crestor undergoes minimal metabolism by P450 (CYP) and is mainly metabolized by 2C9 and 3A4 to a small extent. A new study is underway to examine the efficacy of crestor on atherosclerosis and cardiovascular morbidity and mortality (288).

5.2. New ACAT Inhibitors. Although the statin class of compounds dominate the lucrative market of lipid lowering drugs and are very successful owing to their high efficacy in reducing LDL and total cholesterol, many patients still continue to have higher than normal recommended levels of LDL and total cholesterol. However, in recent years increasing the levels of HDL and reducing levels of triglycerides is becoming the principal focus of antilipemic research and has spurred the development of novel lipid lowering drugs. As discussed earlier, serum cholesterol is regulated by the liver (which produces cholesterol during digestion) and the intestine that absorbs cholesterol from food and bile. Since statins inhibit cholesterol biosynthesis in the liver, new agents that inhibit cholesterol absorption in the intestine would have a synergistic effect if used in combination with statins. Therefore, Acyl coA: cholesterol acyltransferase (ACAT), an enzyme responsible for cholesterol absorption in the intestines, is the target of choice for a new class of compounds that inhibit cholesterol absorption in the intestines.

Ezetimbie is the first member of a new class of cholesterol lowering agents referred to as the cholesterol absorption inhibitors and was recently approved by FDA for the reduction of cholesterol levels in patients with hypercholesterolemia (289). Ezetimibe consists of an azetidione nucleus and an SAR study indicates that essential elements required for inhibition of cholesterol absorption are an N1-aryl group, a (4*S*)-alkoxyaryl substituent and a C3 arylalkyl sunbstituent

Table 6. **Other Novel Potential Antihyperlipemic Agents**[a]

Class	Compound	Phase status	Company
ACAT inhibitor	avasimibe (CI-1011)	phase III	Pfizer
MTP inhibitor	implitapide	phase III	Bayer
MTP inhibitor	CP-346086	phase II	Pfizer
MTP inhibitor	R-103757	phase I	Janssen
CETP inhibitor	JTT-705	phase II	Tobacco
CETP inhibitor	CP-529414	phase II	Pfizer

[a]Ref. 295.

(290–294). Ezetimibe is administered alone or in combination with statin as an adjunct therapy to diet for lowering elevated levels of LDL, Apo B, and total cholesterol, in patients with primary hypercholesterolemia. Following 10 mg orally/once daily dose of ezetimibe has been shown to reduce LDL levels, total cholesterol levels apoB, and triglyceride levels accompanied by increases in HDL. Ezetimibe is 18% more effective when used in combination with simvastatin at reducing LDL than simvastatin alone. Table 6 gives other novel antilipemic agents that are under various phases of development and act as ACAT inhibitors, MTP (Microsomal triglyceride transfer protein) inhibitors and CETP (cholesteryl ester transfer protein) inhibitors.

5.3. Bile Acid Sequestrants (BAS). The bile acid binding resins, colestipol [26658-42-4] and cholestyramine, have been in use for ~20 years and are used as an adjunct therapy to decrease elevated serum and LDL–cholesterol levels in the management of type IIa and IIb hyperlipoproteinemia. These drugs are known to reduce the risks of CHD and myocardial infarction (296). Cholestyramine is an anion exchange (stryrene–divinyl benzene) copolymer having Mol. Wt. $>10^6$. It is commercially available as a powder for oral suspension (297).

Colestipol, also an anion-exchange copolymer, is composed of diethylenetriamine [111-40-0], $C_4H_{13}N_3$, and 1-chloro-2, 3-epoxypropane [106-89-8], C_3H_5ClO. Its metabolism and formulation is quite similar to cholestyramine. Following oral administration, these resins lower cholesterol indirectly by binding with bile acids in the intestinal tract. Bile acids are made in the liver from cholesterol and are needed for food digestion. By tying up bile acids, these drugs prompt the liver to make more bile acids. Since the liver uses cholesterol to make the acids, less cholesterol is available to reach the bloodstream. The drug–bile acid complex is eventually excreted along with unchanged resin in the feces, effectively reducing the total cholesterol pool in the body. This results in increased hepatic oxidation and eventual excretion of cholesterol. These agents decrease LDL by up to 20% and do not affect hepatic metabolism; they are, therefore, a good choice in patients with hepatic disease and in young patients. These resins are effective in decreasing both LDL–cholesterol and total serum cholesterol. The drug-induced reduction in cholesterol can be significant; as much as 50% reduction can be observed over long-term therapy (298). Thus control of serum cholesterol can contribute to the antiatherosclerotic attributes of this class of drug.

Because colestipol and cholestyramine are not absorbed, but simply pass through the body by the GI tract, few severe side effects occur. Patients often complain of distaste and constipation, however, more severe side effects such as GI bleeding are relatively uncommon (297). The bile acid sequestrants antilipemic drugs are known to have reduced or no GI absorption and are normally regarded as safe in pregnant patients. One drawback to these agents is a long list of drugs with which they will bind in circulation. It is important to take these agents 1 h prior or at least 4 h after a bile acid dose to reduce the potential for drug interactions.

Colesevelam hydrochloride is a second generation bile acid sequestrant antilipemic agent and is pharmacologically related to other agents in this class such as cholestyramine and colestipol. Colesevelam hydrochloride, alone or in combination with a HMG-CoA reductase inhibitor is used as an adjunct to dietary therapy and exercise to reduce serum LDL–cholesterol in the primary management of hypercholesterolemia. Colesevelam reduces serum total cholesterol, LDL–cholesterol and apolipoprotein B (apo B) and increases high density lipoprotein (HDL) cholesterol concentrations. However, similar to other BAS, colesevelam may cause slight increases in serum triglyceride concentrations and is not absorbed from the GI tract.

It is administered orally, once or twice daily with meals, and at recommended dosages does not appear to interfere with the absorption of fat-soluble vitamins. It is marketed as Welchol from GelTex.

5.4. Fibric Acid Derivatives. Fibrates can be regarded as broad-specturm lipid modulating agents and their main action is to decrease serum triglycerides, LDL–cholesterol, serum VLDL, and to raise HDL–cholesterol. Fibrates are simple small organic molecules. Fibrates reduce the hepatic synthesis and release of VLDL. They also lower triglycerides by up to 50% and raise HDL levels by up to 35%. Fibrates are particularly useful in patients with familial hyperlipidemia and diabetes.

A large number of fibrate analogues have been synthesized and tested for their antihyperlipoproteinemia. The most widely used fibrates include clofibrate, bezafibrate, ciprofibrate, micronized fenofibrate, and gemfibrozil shown in Table 2 (299,300).

All fibrates contain an isobutyric acid side chain, are readily and completely absorbed from the GI tract and 95–98% plasma protein bound. The mechanism of action of fibrates in controlling plasma lipids appears to be primarily through mediation of lipoprotein lipase activity. In addition, gemfibrozil stimulates apolipoprotein AI synthesis (301), presumably leading to increased HDL particles. In fact, the mechanistic effects of the fibrates in lowering serum cholesterol are complex, from indirect regulation of lipoprotein synthesis, to regulation of key enzymes and receptors involved in lipid metabolism. These drugs are well absorbed after oral administration.

The most common adverse side effects of the fibric acid derivatives are similar to those of the bile acid sequestrants. Patients complain of GI effects, including nausea and vomiting.

Clofibrate (Atromid-S). Clofibrate is the ethyl ester of *p*-chlorophenoxy isobutyric acid and is structurally similar to gemfibrozil. Clofibrate is mainly used in the management of severe hypertriglyceridemia (types IV and V). It

has been used with good results to prevent or control polydipsia, polyuria, and dehydration in patients with diabetes insipidus. It is rapidly hydrolyzed by serum enzymes *in vivo* to clofibric acid and is subsequently conjugated in the liver with glucuronic acid. Peak plasma clofibric acid concentrations 4–6 h after oral administartion of 500-mg dose average 49–53 μg/mL. Clofirbic acid has an elimination half-life of 12–35 h in normal patients and 29–88 h in patients with renal failure.

Bezafibrate (Bezalip). It is used in hyperlipidaemias of types IIa, IIb, IV, and V in patients who have not responded adequately to diet and other appropriate measures.

Fenofibrate (Tricor). It is structurally and pharmacologically related to clofibrate and and gemfobrozil. Fenofibrate is a pro-drug and it has no antilipemic activiy until it is hydrolyzed by plasma and serum esterases *in vivo* to fenofibric acid. The antilipemic activity of fenofibrate appears to be related to its effects on the clearnce of triglyceride-rich particles. Data from *in vivo* and *in vitro* studies indicate that fenofibric acid activates lipoprotein lipase and reduces production of apolipoprotein C-III (apo C-III), an inhibitor of lipoprotein lipase activity and increases the clearnce of triglyceride rich particles. This in turn alters the size of LDL–cholesterol from small to dense and larger partciles that can be rapidly catabolized. Fenofibric acid appears to activate peroxisome proliferator activated receptor that induces the synthesis of HDL–cholesterol, apo-A-I and apo-A-II. Further clinical studies with two different formulations of fenofibrate (micronized and nonmicronized) indicate that micornized dosage formulation has gretaer bioavailability and it is the only commercial fenofibrate preparation currently available in the United States.

Gemfibrozil (Lopid). Although it is structurally related to clofibric acid, it is a nonhalogenated phenoxypentanoic acid, antilipemic agent. It is mainly used to reduce the risk of developing CHD in patients with type IIb hyperlipoproteinemia and to reduce the risk of recurrent coronary events such as MI and stroke. Gemfibrozil is also used as an adjunct therapy to decrease the elevated serum triglycerides and cholesterol concentrations either alone or in combination with other antilipemic agents, bile acid sequestrants, statins and niacin. Many of the pharmacological effects of gemfibrozil are similar to those of clofibrate. Gemfibrozil also shares the potential adverse side effects of the fibrate class of compounds due to structural similarity. It is rapidly and completely absorbed from the GI tract (97%) and peak plasma concentrations of the drug occur within 1–2 h. The elimination half-life of gemfibrozil is ~1.5 h after a single dose in individuals with normal renal function. Gemfibrozil appears to be metabolized in the liver to four major metabolites produced via three metabolic pathways.

Niacin (Niacor). It is a water-soluble, B-complex vitamin that is used as an antilipemic agent. Large doses of niacin are known to lower triglycerides. In addition, niacin can lower LDL–cholesterol and increase HDL–cholesterol, both beneficial effects. Niacin in its extended release form (Niaspan) is better tolerated and also the combination of lovastatin and niacin (Advicor, recently approved by the FDA) is very effective at lowering LDL and TGs while raising HDL. Niacin is rapidly and extensively absorbed following oral administration and peak plasma concentrations of niacin are attained within 30–60 min (Niacor) or 4–5 h (Niaspan).

6. Antihypertensive Agents

Hypertension may result from a single or a combination of several pathogenic states. Physiologically, blood pressure is determined not only by the amount of blood pumped through the heart, but also by the resistance of the blood flow through the arteries, veins, and capillaries, ie, the blood vessels. Abnormalities or malfunctions in the nervous system (the sympathetic-parasympathetic nervous system effects heart rate and blood vessel tone), hormonal system, kidneys, and peripheral vasculature may all contribute to increased blood pressure.

The most common form of high blood pressure is essential hypertension. It is one of the two major factors responsible for cardiovascular diseases, such as CHD, stroke, and CHF. Of the patients diagnosed to have essential hypertension, ~70% have mild hypertension where the diastolic blood pressure is from 90 to 104 mm Hg (12–13.9 Pa), 20% have moderate hypertension, ie, 105–114 mm Hg (14–15.2 Pa), and 10% have severe hypertension, >115 mm Hg (15.3 Pa). According to the National Health and Nutritional Examination Survey III, ~50 million Americans ages 6 and older have high blood pressure and 31.6% do not know that they have it. Of all people with high blood pressure, 27.2% are on adequate medications, 26.2% are on inadequate medications, and 14.8% are not on any therapy. From 1999 to 2000, the death rate in United States due to high blood pressure increased 21.3% , while the actual number of deaths increased by 49.1%. On average, the estimated annual cost of antihypertensive prescriptions in United States is ~$ 15.5 billion.

The treatment of hypertension is usually tailored to the individual. Initially, nonpharmacological treatments, such as a change in diet and an increase in exercise, may be recommended to lower blood pressure. However, should these measures fail to have an effect, drug therapy is the next option for controlling hypertension. With regard to chemotherapy, the therapeutic regiment is tailored to the individual, and relevant factors affecting each patient are taken into consideration in choosing an antihypertensive drug. The first drug is usually an angiotensin converting enzyme (ACE) inhibitor, a β-adrenoceptor blocker, a calcium channel blocker, or a diuretic. One drug can normalize the blood pressure of ~50–60% of the hypertensive patients, and the combination of two complementary drugs normalizes that of >80% patients. The main goal of hypertension chemotherapy is to give the fewest number of drugs, using the smallest effective amounts having the lowest frequency of dosing and minimum side effects (302,303). An optimal drug regiment should reduce all risk factors of coronary heart diseases, reverse the hemodynamic abnormalities present by preserving cardiac output and tissue perfusion, and lower total peripheral resistance. The physician's challenge is to choose the best antihypertensive drug for concomitant existing diseases while maintaining a good quality of life (304–315).

The drugs used as antihypertensive agents may be classified according to their mechanism of action as follows: (*1*) agents affecting the renin-angiotensin system (angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors, aldosterone receptor antagonists, and vasopeptidase inhibitors; (*2*) agents affecting the adrenergic nervous system (ganglionic blockers, neuronal blockers, neuronal norepinephrine depleting agents, α-adrenoceptor blockers, β-adrenoceptor blockers, and α/β-adrenoceptor blockers); (*3*) calcium

channel blockers; (*4*) diuretics (low ceiling diuretics, high ceiling diuretics, aldosterone antagonists, and potassium sparing diuretics); (*5*) centrally acting agents; (*6*) vasodilators; and potassium channel openers. To view structures of select agents used in the treatment of hypertension, the reader is referred to Table 7.

6.1. Agents Affecting the Renin–Angiotensin System. The renin–angiotensin system (RAS) plays an important role in the regulation of arterial blood pressure in the body (316,317). The enzyme renin, which is synthesized and released from the kidney, catalyzes the formation of angiotensin I, a decapeptide, from the substrate angiotensinogen, a α_2-globulin, synthesized in the liver and released into the blood stream (Fig. 8). ACE, a nonspecific carboxypeptidase, cleaves a dipeptide from the carboxyl terminal of angiotensin I to form angiotensin II, an octapeptide. The blood vessels of the pulmonary circulation are the main site for this conversion. Angiotensin II is further cleaved to the heptapeptide, angiotensin III by the action of tissue aminopeptidase. Angiotensin II is the most potent product of this cascade. Angiotensin I is relatively inactive, whereas angiotensin III is less potent than angiotensin II as a vasoconstrictor, but is as active as angiotensin II in stimulating the release of aldosterone.

The primary effects of angiotensin II are (*1*) producing vasoconstriction directly or indirectly through activation of the adrenergic nervous system; (*2*) eliciting cardiac stimulation; (*3*) stimulating aldosterone and vasopressin secretion; and (*4*) evoking dipsogenesis. All of these actions, directly or indirectly, elevate blood pressure (316).

6.2. Angiotensin Converting Enzyme Inhibitors. ACE inhibitors are very efficacious in reducing high blood pressure. The antihypertensive activity is better correlated with the vascular tissue ACE inhibition than plasma ACE inhibition. Plasma ACE activity returns to predrug level while significant lowering of the blood pressure is still observed. Teprotide, a nonapeptide ACE inhibitor, was demonstrated to have potent antihypertensive effects after IV administration. The drawback of teprotide is lack of oral activity. Captopril, a sulfhydryl containing small molecule, was the first practical nonpeptide ACE inhibitor in humans (318). Since the advent of captopril, several non-sulfhydryl ACE inhibitors have come on line: benzapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

ACE inhibitors are used in the first-line therapy of hypertension (319–325). Initially it was thought that ACE inhibitors were efficacious only in patients having high plasma renin activity (PRA) such as in renal or malignant hypertension. Captopril, however, was found to be efficacious in patients having essential hypertension, particularly those with high or moderately high PRA. Only ~20% of patients having essential hypertension have high to moderately high PRA, but ACE inhibitor used as monotherapy is effective in 50–60% of all patients.

ACE inhibitors lower the elevated blood pressure in humans with a concomitant decrease in total peripheral resistance. Cardiac output is increased or unchanged; heart rate is unchanged; urinary sodium excretion is unchanged; and potassium excretion is decreased. ACE inhibitors promote reduction of left ventricular hypertrophy. Other mechanisms of action, such as potentiation of the bradykinin effect, and increased production of prostaglandins have been reported to explain, in part, the antihypertensive effects of ACE inhibitors during chronic therapy (326,327). The inhibition of angiotensin II production is

Table 7. **Antihypertensive Agents**

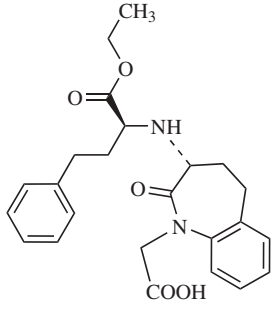
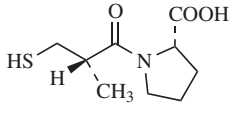
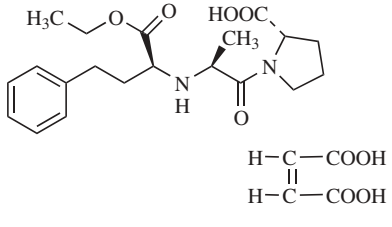
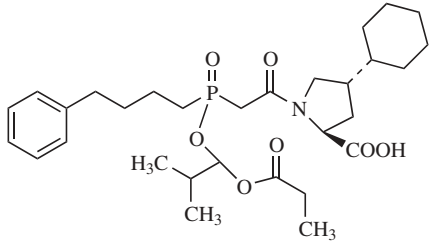
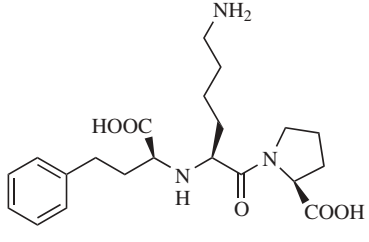
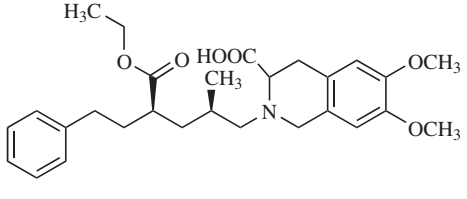
Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
			ACE Inhibitors	
benazepril hydrochloride	[86541-74-4]	$C_{24}H_{29}ClN_2O_5$	Lotensin, Lotrel, Lotensin HCT	
captopril	[110075-07-5]	$C_9H_{15}NO_3S$	Capoten, Capozide	
enalapril maleate	[76095-16-4]	$C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$	Vasotec, Vaseretic, Lexxel	

Table 7 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
fosinopril sodium	[88889-14-9]	$C_{30}H_{45}N \cdot NaO_7P$	Monopril	
lisinopril	[83915-83-7]	$C_{21}H_{31}N_3O_5 \cdot 2H_20$	Prinvil, Zestril, Prinzide, Zestoretic	
moexipril HCl	[82586-52-5]	$C_{27}H_{34}N_2O_7 \cdot HCl$	Univasc, Uniretic	

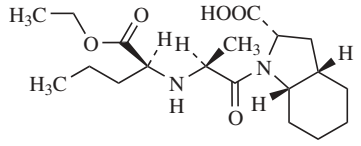
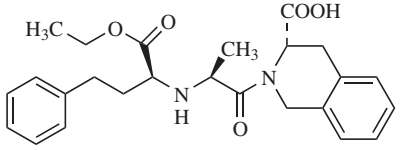
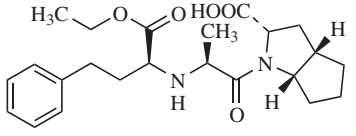
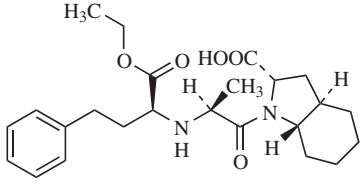
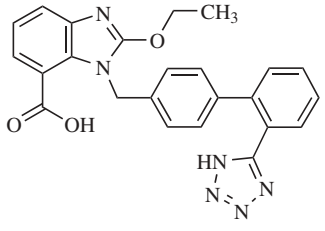
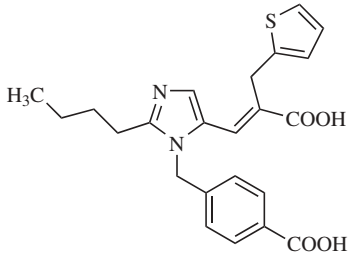
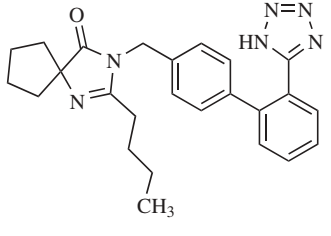
perindopril erbumine	[107133-36-8]	$C_{19}H_{32}N_2O_5 \cdot C_4H_{11}N$	Aceon	
quinapril	[82586-55-8]	$C_{25}H_{30}N_2O_5 \cdot HCl$	Accupril	
ramipril	[87333-19-5]	$C_{23}H_{32}N_2O_5$	Altace	
trandolapril	[87679-37-6]	$C_{24}H_{34}N_2O_5$	Mavik, Tarka	

Table 7 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
		Angiotensin II Receptor Blockers		
candesartan	[139481-59-7]	$C_{24}H_{20}N_6O_3$	Atacand, Amias, Kenzen	
eprosartan	[1333040-01-4]	$C_{23}H_{24}N_2O_4S$	Teveten	
irbesartan	[138402-11-6]	$C_{25}H_{28}N_6O$	Avapro, Avalide	

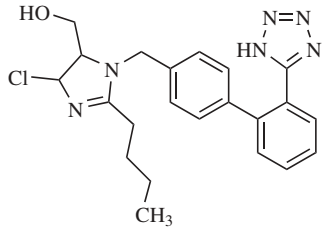
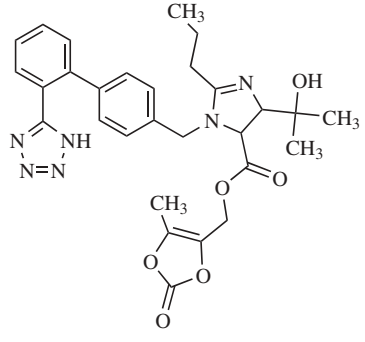
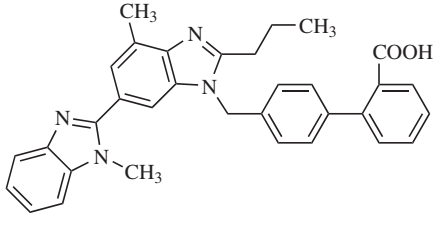
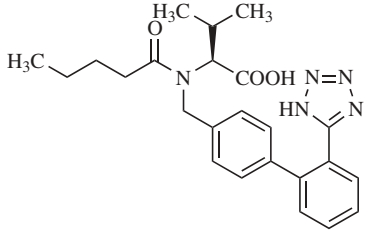
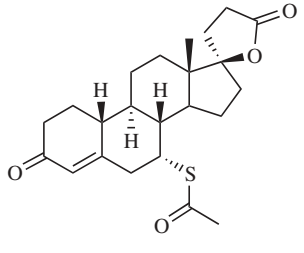
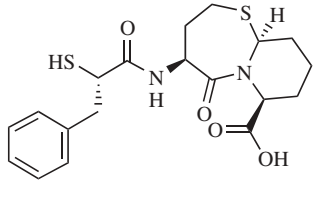
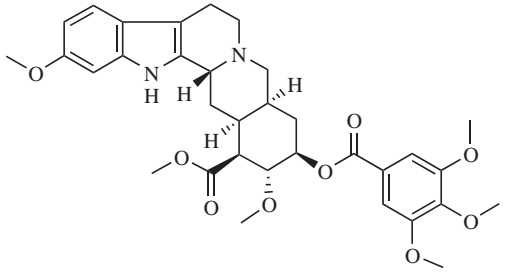
losartan	[124750-99-8]	$C_{22}H_{22}ClKN_6O$	Cozaar, Hyzaar	
olmesartan	[144689-63-4]	$C_{29}H_{30}N_6O_6$	Olmesatran, Medoxomil	
telmisartan	[144701-48-4]	$C_{33}H_{30}N_4O_2$	Micardis, Pritor	

Table 7 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
valsartan	[137862-53-4]	$C_{24}H_{29}N_5O_3$	Diovan, Diovan HCT	
		Aldosterone Receptor Antagonists		
spironolactone	[52-01-7]	$C_{24}H_{32}O_4S$	Verospiron, Xenalon	
		Vasopeptidase Inhibitors		
omapatrilat	[167305-00-2]	$C_{19}H_{24}N_2O_4S_2$	BMS-186716	

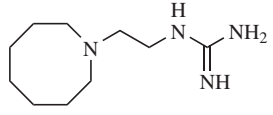
Neuronal Norepinephrine Depleting Agents

reserpine	[50-55-5]	$C_{33}H_{40}N_2O_9$	Rivasin, Sandril, Serfin, Serpasol



Adrenergic Neuronal Blockers

guanethidine monosulfate	[60-02-6]	$(C_{10}H_{22}N_4)_2 \cdot H_2SO_4$	Ismelin Sulfate



α-Adrenoceptor Blockers

doxazosin mesylate	[77883-43-3]	$C_{23}H_{25}N_5O_5 \cdot CH_3SO_3H$	Cardura

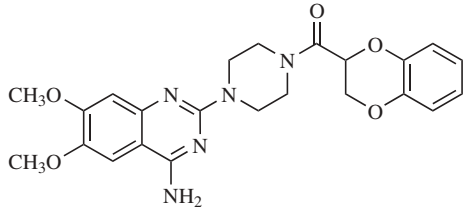
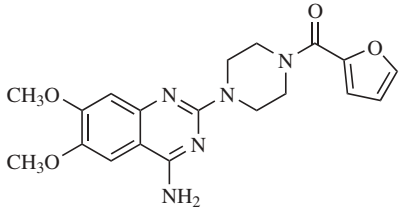
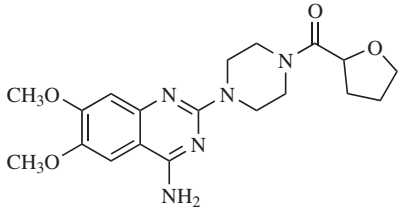
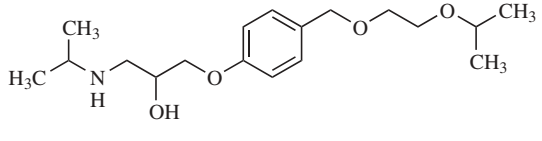
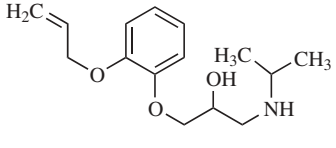
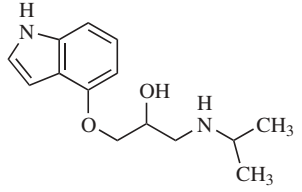
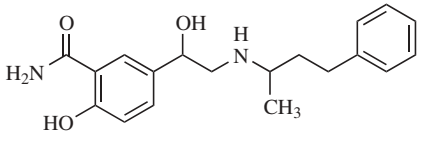


Table 7 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
prazosin HCl	[19237-84-4]	$C_{19}H_{21}N_5O_4 \cdot HCl$	Minipress, Minizide	
terazosin HCl	[63590-64-7]	$C_{19}H_{25}N_5O_4 \cdot HCl$	Hytrin, Terazosin	
			β-*Adrenoceptor Blockers*[*]	
bisoprolol fumarate	[104344-23-2]	$C_{18}H_{31}NO_4 \cdot 1/2\ C_4H_4O_4$	Zebeta, Ziac	
oxprenolol	[6452-71-7]	$C_{15}H_{23}NO_3$	Coretal, Laracor, Paritane, Trasacor	

pindolol	[13523-86-9]	$C_{14}H_{20}N_2O_2$	Visken	

α- and β-Adrenoceptor Blockers

labetalol HCl	[32780-64-6]	$C_{19}H_{24}N_2O_3 \cdot HCl$	Normodyne, Trandate	

* Other β-blockers that are included as antihypertensive agent in the text are shown in Table 1, as they are also categorized as antiarrhythmic agents.

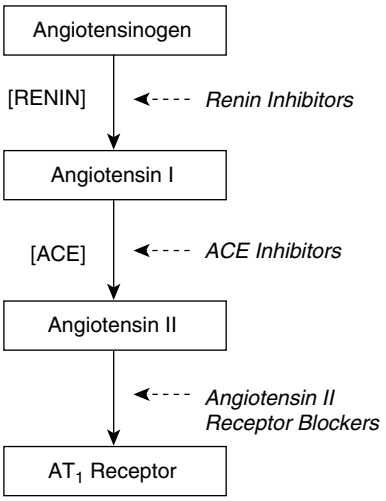


Fig. 8. The renin–angiotensin system. Renin catalyzes the generation of angiotensin I from angiotensinogen. Angiotensin-converting enzyme, ACE, cleaves angiotensin I to form the active octapeptide–angiotensin II. Angiotensin II activates a G-protein-coupled-receptor—AT_1. AT_1, when activated, produces several effects including vasoconstriction and the stimulation of aldosterone release.

considered the primary, if not the only, mechanism of action of ACE inhibitors, even though the circulating angiotensin II levels may not accurately reflect the situation. Headache, dizziness, fatigue, skin rash, and cough are the most common side effects of ACE inhibitors. Cough in patients treated with an ACE inhibitor is considered to be caused by the build-up of bradykinin and prostaglandins.

6.3. Angiotensin II Receptor Blockers. Angiotensin II binds to Angiotensin II type 1 (AT_1) receptors to constrict blood vessels. Thus, angiotensin II receptor blockers act not by inhibiting the production of Angiotensin II, but instead, exert their effect by blocking the binding of angiotensin II to AT_1 (Fig. 8), which, in turn, reduces blood pressure (328). However, unlike ACE inhibitors, agents in this class do not inhibit bradykinin metabolism (328), and consequently do not possess the cough inducing side effect that is associated with ACE inhibitors. The FDA has approved losartan, eprosartan, olmesartan, valsartan, irbesartan, candesartan, and telmisartan as therapeutics for hypertension. With the exception of eprosartan, the angiotensin II receptor blockers are structurally similar, containing a characteristic biphenyltetrazole substructure. Eprosartan possesses a carboxylate moiety in place of the tetrazole. Such an interchange of functional groups, with similar capacities to ionize under physiological pH, is a good example of how the principles of isosterism are used during the drug development process. Clinically, the efficacy of these agents has been shown in a number of controlled trials (329–343).

6.4. Renin Inhibitors. There have been significant efforts to develop compounds that would block the cleavage of angiotensinogen by renin, as such molecules would effectively inhibit the entire RAS (Fig. 8). However, to date only one compound—aliskren—has shown promise in early clinical trials (328). Factors contributing to the lack of success of these compounds include: poor bioa-

vailability, lack of antihypertensive efficacy, and lack of specificity. Furthermore, the success of the ACE inhibitors and angiotensin II blockers has overshadowed the need for renin inhibitors.

6.5. Aldosterone Receptor Antagonists. Studies have indicated that high levels of aldosterone may contribute to, or cause, hypertension (344,345). Supporting this evidence is the fact that treatment with spironolactone, the only aldosterone receptor antagonist (ARA) that is clinically available, produces decreases in blood pressure in patients with refractory hypertension (346). A drawback of this compound is that it, resembling a steroid, has progestational and antiandrogenic side effects (328). As a result, research to generate ARAs with improved specificity is underway, and has resulted in the generation of eplerenon (347), which has been approved by the FDA.

6.6. Vasopeptidase Inhibitors. This is a new, still investigational class of agents. The vasopeptidase inhibitors (VPIs) act by inhibiting both ACE and neutral endopeptidase (NEP), which is responsible for the hydrolysis of atrial natriuretic peptide (328). Simultaneous inhibition of ACE and NEP decreases blood pressure with greater efficacy than ACE inhibition alone. Several VPIs are under clinical development: fasidotril, gemopatrilat, omapatrilat, MDL-100240, sampatrilat, and Z-13752A (328). Clinical trials using omapatrilat have indicated that this compound can cause angioedema (328).

6.7. Agents Affecting the Adrenergic Nervous System. Historically, the vasopressor systems, particularly the adrenergic nervous system, drew the most attention in hypertension research, and many drugs affecting this system have been introduced. Agents antagonize this system either by decreasing the number of nerve impulses traveling down the nerves, by blocking ganglia, by blocking the release of the adrenergic neurotransmitter (norepinephrine), by depleting the norepinephrine stores in the neurons, or by blocking the adrenoceptors in the blood vessels. Vascular tone is maintained mainly by the adrenergic nervous system, and decreasing the tone by any of the mechanisms, listed above, results in a lowering of blood pressure.

6.8. Ganglionic Blockers. Ganglionic blocking agents such as hexamethonium, trimethaphan, and chlorisondamine, block the autonomic ganglia, and thus decrease sympathetic outflow. Tolerance develops quickly to these agents. Because of such disturbing side effects as severe orthostatic hypotension, sexual dysfunction, dry mouth, and urinary retention, these drugs have become obsolete.

6.9. Adrenergic Neuronal Blockers. The adrenergic neuronal blocking agents, guanethidin, bretylium, debrisoquin, and guanadrel, produce hypotension by blocking the release of norepinephrine from the nerve terminals of adrenergic neurons. These drugs are taken up by the neurons and decrease sympathetic tone, heart rate, cardiac output, and total peripheral resistance. Some deplete norepinephrine stores, and thus produce an initial sympathomimetic response increasing these various responses. Orthostatic hypotension, severe sexual dysfunction, and impairment, fluid retention, and diarrhea are the primary side effects of this class of agents, which is obsolete and used only when all other therapeutic agents fail to work.

6.10. Neuronal Norepinephrine Depleting Agents. Reserpine is the most active alkaloid derived from *Rauwolfia serpentina*. The principal

antihypertensive mechanism of action primarily results from depletion of norepinephrine from peripheral sympathetic nerves and the brain adrenergic neurons. The result is a drastic decrease in the amount of norepinephrine released from these neurons, leading to a decrease in vascular tone and lowering of blood pressure. Reserpine also depletes other neurotransmitters, including epinephrine, serotonin, and dopamine. Reserpine is efficacious in all forms of hypertension, particularly with the concomitant use of a thiazide diuretic. The most serious side effect is mental depression. Other side effects include nasal congestion, sedation, drowsiness, lethargy, decreased libido, impotence, and nightmares.

6.11. α-Adrenoceptor Blockers. Nonselective α-adrenoceptor blockers (Table 8), such as phentolamine, which block both α_1- and α_2-adrenoceptors, produce vasodilation by antagonizing the effects of endogenous norepinephrine. They also produce severe tachycardia and have been replaced by selective α_1-adrenoceptor blockers, such as prazosin, terazosin, and doxazosin, which do not usually cause severe tachycardia.

Prazosin is a selective α_1-adrenoceptor antagonist that exerts its antihypertensive effect by blocking the vasoconstrictor action of adrenergic neurotransmitter, norepinephrine, at α_1-adrenoceptors in the vasculature (348–350). Prazosin lowers blood pressure without producing a marked reflex tachycardia. It causes arteriolar and venular vasodilation, but a significant side effect is fluid retention. Prazosin increases HDL–cholesterol, decreases LDL–cholesterol, and does not cause glucose intolerance.

Doxazosin, a prazosin derivative, is a highly selective α_1-adrenoceptor blocker (351,352). It has no significant antagonistic effects on presynaptic or postsynaptic α_2-adrenoceptors. Blocking the activation of α_1-adrenoceptors prevents the breakdown of phosphatidylinositol, resulting in vasoconstriction. The lowering of blood pressure by doxazosin is not accompanied by an increase in heart rate or cardiac output. Its duration of action is as long as 24 h. Doxazosin in chronic hypertension treatment reduces total cholesterol, LDL–cholesterol, and triglyceride levels, and increases HDL–cholesterol.

Terazosin is a selective α_1-adrenoceptor blocker having hypotensive efficacy equal to that of prazosin. Terazosin has a longer duration of action and better GI absorption profile than prazosin.

6.12. β-Adrenoceptor Blockers. There is no satisfactory mechanism to explain the antihypertensive activity of β-adrenoceptor blockers (Table 8) in humans, particularly after chronic treatment (353–355). Reductions in heart rate correlate well with decreases in blood pressure and this may be an important mechanism. Other proposed mechanisms include reduction in PRA, reduction in cardiac output, and a central action. During long-term treatment, the cardiac output is restored despite the decrease in arterial blood pressure and total peripheral resistance. Atenolol, which does not penetrate into the brain, is an efficacious antihypertensive agent. During short-term treatment, the blood flow to most organs (except the brain) is reduced, and the total peripheral resistance may increase.

Treatment with β-adrenoceptor blockers is effective in patients having high PRA; however, most of these agents are not efficacious in patients having low PRA or in elderly patients. β-Adrenoceptor blockers usually lower arterial

Table 8 **Antihypertensive Agents: Diuretics**

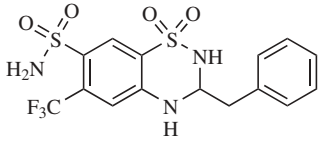
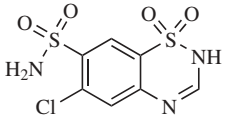
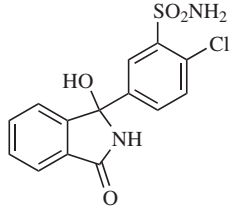
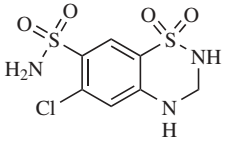
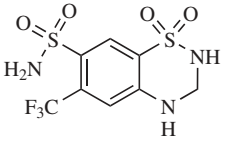
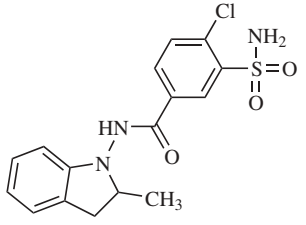
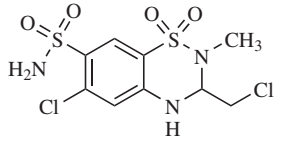
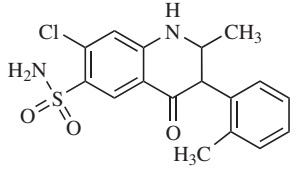
Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Structure
			Thiazide Diuretics		
bendroflumethiazide	[73-48-3]	$C_{15}H_{14}F_3N_3O_4S_2$	Naturetin, Rauzide, Corzide	antihypertensive	
chlorothiazide Na	[7085-44-1]	$C_7H_5ClN_3NaO_4S_2$	Diuril, Aldoclor	antihypertensive	
chlorthalidone	[77-36-11]	$C_{14}H_{11}ClN_2O_4S$	Thalitone, Combipress, Tenoretic	antihypertensive	
hydrochlorothiazide	[58-93-5]	$C_7H_8ClN_3O_4S_2$	Microzide, Esidrix, HydroDiural, Oretic, Aquazide-H etc.	antihypertensive	

Table 8 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Structure
hydroflumethiazide	[135-09-1]	$C_8H_8F_3N_3O_4S_2$	Diucardin, Saluron, Salutensin	antihypertensive	
Indapamide	[26807-65-8]	$C_{16}H_{16}ClN_3O_3S$	Lozol	antihypertensive	
methylclothiazide			Enduron, Aquatensen, Dilutensen	antihypertensive	
metolazone	[17560-51-9]	$C_{16}H_{16}ClN_3O_3S$	Mykrox, Zaroxolyn	antihypertensive	

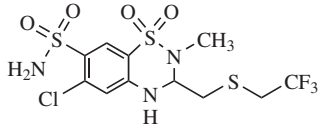
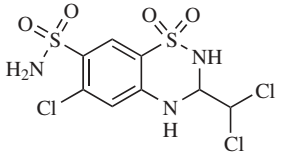
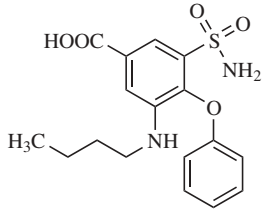
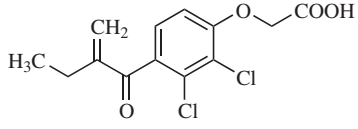
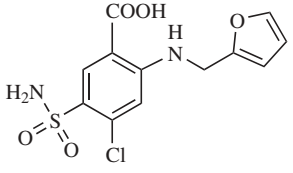
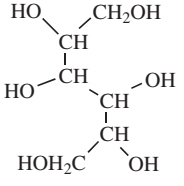
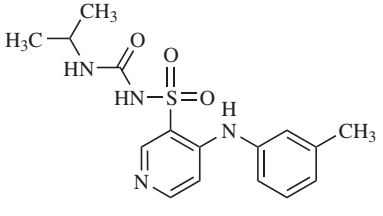
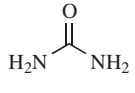
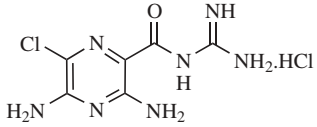
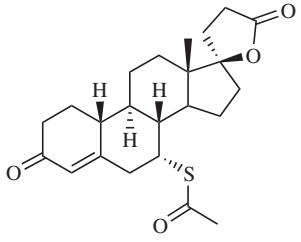
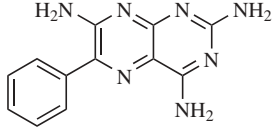
polythiazide	[346018-9]	$C_{11}H_{13}ClF_3N_3O_4S_3$	Renese, Minizide	antihypertensive	
trichlormethiazide	[133-67-5]	$C_8H_8Cl_3N_3O_4S_2$	Aquazide, Naqua	antihypertensive	
bumetanide	[28395-03-1]	$C_{17}H_{20}N_2O_5S$	Bumex	antihypertensive	
ethacrynic acid	[6500-81-8]	$C_{13}H_{11}Cl_2NaO_4$	Edecrin	antihypertensive	

Table 8 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Structure
furosemide	[54-31-9]	$C_{12}H_{11}ClN_2O_5S$	Lasix	antihypertensive	
mannitol	[69-65-8]	$C_6H_{14}O_6$	Osmitrol	antihypertensive	
torsemide	[56211-40-6]	$C_{16}H_{20}N_4O_3S$	Demadex	antihypertensive	
urea	[57-13-6]	CH_4N_20	Ureaphil	antihypertensive	

Potassium Sparing Diuretics

amiloride HCl	[17440-83-4]	$C_6H_9Cl_2N_7O \cdot 2H_2O$	Midamor, Moduretic	antihypertensive	
spironolactone	[52-01-7]	$C_{24}H_{32}O_4S$	Aldactone, Aldactazide	antihypertensive	
triamterene	[396-01-0]	$C_{12}H_{11}N_7$	Dyrenium, Dyazide, Maxzide	antihypertensive	

Direct Vasodilators

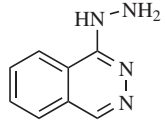
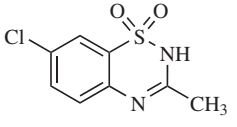
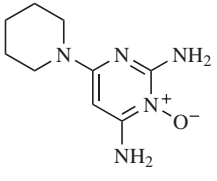
hydralazine	[304-20-1]	$C_8H_8N_4 \cdot HCl$	Apresoline, Alphapress	

Table 8 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Structure
diazoxide	[364-98-7]	$C_8H_7ClN_2O_2S$	Proglycem		
minoxidil	[38304-91-5]	$C_9H_{15}N_5O$	Rogain		
nitroprusside			Nitropress		

blood pressure ~10 mm Hg (1.3 kPa). Side effects include lethargy, dyspnea, nausea, dizziness, headache, impotency, cold hands and feet, vivid dreams and nightmares, bronchospasm, bradycardia, and sleep disturbances.

β-Adrenoceptor blockers for the treatment of hypertension include (*1*) the cardioselective β_1-adrenoceptor blockers without intrinsic sympathomimetic activity (ISA), ie, atenolol, bisoprolol, and metoprolol; (*2*) the cardioselective with ISA, ie, acebutolol; (*3*) the noncardioselective without ISA, ie, propranolol and timolol; and (*4*) the noncardioselective with ISA, ie, oxprenolol and pindolol.

6.13. α- and β-Adrenoceptor Blocking Agents. Labetalol possesses both α- and β-adrenoceptor blocking effects, with the (+)-(*SR*) isomer exhibiting more α-blocking activity (356). In particular, this agent possesses β_2-adrenoceptor antagonistic effects, and produces a significant reduction in blood pressure and a slight decrease in heart rate (357). It is efficacious in mild, moderate, and severe hypertension. The cardiac output is maintained due to an increase in stroke volume. Exercise-induced blood pressure increases are blunted and the heart rate is reduced. In chronic treatment, PRA is reduced. Side effects produced by this agent include gastrointestinal discomfort and dizziness.

6.14. Diuretics. Diuretics are drugs that increase the excretion of salts such as sodium chloride (NaCl) since the primary goal and principal mechanism of the hypotensive effects of diuretics is salt and fluid depletion leading to reduction of ECF volume (358,359). Diuretics are someitimes called water pills and are used to treat CHF, high blood pressure or edema (water retention). They are also used for certain types of kidney and or liver diseases. Acute effects of diuretics lead to a decrease in cardiac output and an increase in total peripheral resistance. However, during chronic administration, cardiac output and blood volume return toward normal and total peripheral resistance decreases to below pretreatment values. As a result, the blood pressure falls. The usual reduction in blood volume is ~5%. A certain degree of sustained blood volume contraction has to occur before the blood pressure decreases. The usual decrease in blood pressure achieved using a diuretic is ~20/10 mm Hg (2.7/1.3 kPa) (systolic/diastolic pressures).

Intake of a large amount of sodium chloride negates the antihypertensive effects of diuretics. Other mechanisms, such as direct vasodilating action, decreased responsiveness to vasopressor agents, stimulation of prostacyclin [35121-78-9], $C_{20}H_{32}O_5$, production, and reduction in the intracellular calcium ion concentration are some of the factors that play a trivial role in the overall antihypertensive effects of diuretics.

Diuretics, such as those of the thiazide type, have been the cornerstone of first-line antihypertensive treatments for decades. However, popularity and use have eroded as a result of increases in sudden death in patients on diuretic therapy, and unfavorable effects on blood lipid profiles, ie, increasing cholesterol and triglyceride levels. These effects have been implicated as possible causes for the lack of decrease in the mortality rate resulting from acute MI in patients treated with a diuretic (359,360). However, diuretics do protect against stroke and CHF.

Diuretics are needed to return to normal the expanded extracellular volume that other antihypertensive agents produce, such as fluid retention and blood volume expansion, via compensatory mechanisms of the body. The loss of efficacy

of antihypertensive agents can be restored if a diuretic is used concomitantly. In the treatment of hypertension, high ceiling or loop diuretics, such as furosemide, ethacrynic acid, and bumetanide, are no more efficacious than the thiazide-type of diuretics. In fact, these agents cause more side effects, such as dehydration, metabolic alkalosis, etc, and therefore, should not be used except in situations where rapid elimination of fluid volume is clearly indicated.

Diuretics can cause hypokalemia, hyperglycemia, and hyperuricemia. After long-term treatment they may increase serum triglyceride and cholesterol (361). There are three types of diuretic medicines and each type works differently, but they all reduce the amount of salt and water in the body, which helps to lower blood pressure.

Thiazide and Thiazide-like Diuretics. Thiazide (benzothiadiazine) diuretics are derivatives of 1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (Table 8). Substitution of the thiazide nucleus (R_2 and R_3 positions) increases the potency of the compounds. Most of the thiazids have a saturated 3,4-bond and either Chloro or CF_3 substituent at the 6-position of the thiazide nucleus. Thiazides occur as white crystalline powders and are insoluble in water. Thiazides enhance excretion of sodium, chloride and water by interfering with the transport of sodium ions across the renal tubular epithelium and cortical diluting segment of nephron. It is the only type of diuretic that has a vasodilatory effect. Thiazides also increase the excretion of other electrolytes such as potassium, bicarbonate, and to some extent calcium. These compounds also exercise a weaker diuretic effect as compared to loop diuretics. Most commonly used drugs include chlorothiazide (Diuril), hydrochlorothiazide (Microazide, Esidrix, Oretic), benzthiazide, cyclothiazide, indapamide (Lozol), chlorthalidone (Thalitone), bendroflumethiazide (Naturetin), and metolazone (Mykrox). They are mainly used as a first line therapy for mild to moderate hypertension, edema, congestive heart failure, hypercalciuria and in combination with loop diuretics to treat severe resistant edema.

Thiazides are administered orally (except chlorothiazide which is administered intravenously). They are absorbed from the GI tract in varying degrees. The onset of duration of action following oral administration occurs within 2 h and peak effect occurs 3–6 h after administration. However, chlorothiazide (intravenous route) acts much faster (15 min) and peak effect lasts ~30 min, and therefore it is administered for emergency situations. The duration of diuretic action is determined by individual rates of excretion and varies from 2 to 72 h. Most thiazides are excreted in urine unchanged. One of the most common adverse effects of thiazide therapy is potassium depletion leading to cardiac arrhythmias.

Potassium Sparing Diuretics. They are weak diuretics that exert their effect mainly on collection tubes and act by blocking the Na^+ channel in the luminal membrane of the *principal cells* of the cortical collecting ducts. This reduces the Na^+ entry through the luminal membrane, and hence the net reabsorption of NaCl. Most commonly used drugs include amiloride (Midamor), triamterene (Dyrenium), spiranolactone (Aldactone), the latter is a competitive aldosterone antagonist at the cystolic receptor level (Fig. 8). Potassium sparing diuretics are used for the prevention of hypokalemia induced by loop or thiazide diuretics, secondary hyperaldosteronism due to hepatic cirrhosis and ascites, and Conn's syndrome.

Loop Diuretics. They are also called "high ceiling" diuretics due to their high diuretic potential since they can eliminate up to 20% of the filtered load of NaCl and H_2O to be excreted in the urine. This class of compounds acts by inhibiting cotransport of Na and K chloride ions in the thick ascending limb of Henle's loop (ALH). These diuretics cause the kidneys to increase flow of urine. They are mainly used for the treatment of hypertension, CHF in the presence of renal insufficiency, ARF, CRF, ascites, and nephritic syndromes. Most of the commonly prescribed loop diuretics (Fig. 8) include: furosemide (Lasix), bumetanide (Bumex), torsemide (Demadex), and ethaycrynic acid (Edecrin).

Carbonic Anhydrase (CA) Inhibitors. This class of compounds acts by inhibiting CA in luminal membrane of proximal tubule, thereby reducing the proximal HCO_3^- reabsorption. They are used to reduce intracellular pressure in glaucoma, to lower mountain sickness and to reduce urine pH in cystinuria. Examples of these drugs include acetazolamide, methazolamide and dichlorphenamide.

Osmotic Diuretics. These are freely filterable nonreabsorbable osmotic agents and primarily act on the proximal tubule to lower the reabsorption of salts and water. They are used to treat or prevent acute renal failure and most commonly used drugs include mannitol (Osmitrol), glycerol and urea (Ureaphil).

6.15. Other Direct Vasodilators. Vasodilators dilate or relax the smooth muscles of the vasculature directly or indirectly by releasing endogenous vasodepressors or by antagonizing the endogenous vasopressors or vasopressor systems (362,363). Vasodilators may interfere with the entry, intracellular release, and utilization of calcium, the activation of the protein kinase C system, cGMP formation, and EDRF turnover.

Hydralazine (Apresoline). Hydralazine reduces perpheral resistance and blood pressure due to its direct vasodilatory effect on vascular smooth muscle cells and the effect is greater on arteries than on veins. It has beeen suggested that cyclic AMP causes relaxation of arterial smooth muscle cells through a calcium binding stimulating mechanism. As a result, diastolic blood pressure decreases more than systolic pressure and it is always accompained by increased heart rate, cardiac output and stroke volume. Hydralazine is readily absorbed from the GI tract and metabolized on first pass through the liver by acetylation. The plasma half-life of hydralazine is $\sim$2–4 h and is sometimes extended up to 8 h in some patients. It is mainly used in the management of moderate to severe hypertension and for the short-term treatment of severe CHF in conjunction with glycosides. Tachycardia, headache, dizziness, water, and sodium retention are principal side effects of hydralazine therapy.

Diazoxide (Proglycem). Diazoxide, chemically related to the thiazide diuretics, is a vasodilator and hyperglycemic agent having no diuretic effects. In fact, diazoxide has marked salt and water retention. It has been suggested that diazoxide has potassium channel opener effects. Because of rapid protein binding, diazoxide has to be given by rapid intravenous injection. Its use is limited to the treatment of hypertensive emergencies or crises. Diazoxide causes marked tachycardia, increases PRA, and causes hyperglycemia.

Minoxidil (Rogain). Minoxidil is a piperidineopyrimidine derivative and is one of the most potent vasodilators available for the treatment of hypertension. It also possesses hair growth stimulant properties. Minoxidil is a potassium

channel opener acting directly on the smooth muscle of the arterioles to decrease peripheral resistance and blood pressure. In long-term treatment, minoxidil causes severe fluid retention, tachycardia, and hair growth (hirsutism) in balding areas of androgenetic alopecia. It stimulates the adrenergic nervous system and the renin-angiotensin system. Because of side effects, minoxidil is reserved for use in hypertensive patients having renal failure or in patients having hypertension that is refractory to other antihypertensive drugs.

Nitroprusside (Nitropress). Sodium nitroprusside is a potent, fast-acting vasodilator that has to be administered intravenously. Nitroprusside exerts direct action on vascular smooth muscle, leading to peripheral vasodilation of arteries and veins. It acts on excitation–contraction coupling of vascular smooth muscle by interfering with both influx and intracellular activation of calcium. However, it has no effect on smooth muscle of the duodenum or uterus and is more active on veins than on arteries. Nitroprusside may also improve CHF by decreasing systemic resistance, preload and afterload reduction, and improved CO. It is used mainly in hypertensive crises and acute management of heart failure and to reduce bleeding during surgeries. Its effects terminate as soon as infusion of the drug is slowed or stopped, and returns to pretreatment levels within 1–10 min. The most common side effect is that it reacts with hemoglobin to produce cyanmethemoglobin and cyanide ion. Therefore, caution must be exercised as nitroprusside injection can result in toxic levels of cyanide. However, when used briefly or at low infusion rates, the cyanide produced reacts with thiosulfate to produce thiocyanate, which is excreted in the urine. It is rapidly metabolized by interaction with sulfhydral groups in the erythrocytes and tissues.

7. Antithrombolytic Agents

It has been well documented that the primary cause of acute myocardial infarction (AMI) is coronary arterial thrombosis (364). Thrombosis formation occurs at sites of ulcerated or fissured atheromatous plaques in the coronary circulation (365,366). Reperfusion of the coronaries to the ischemic–infarcted area within 6 h after the onset of AMI can salvage the myocardium and limit infarct size (367–369). Furthermore, the better the preservation of the ventricular function, the better the survival rate. Progressive irreversible myocardiac damage occurs 30 min after ischemia starts. Therefore, the faster the coronary arterial thrombus is lyzed, the less irreversible damage done on the myocardium. It is imperative that once an AMI is diagnosed, IV thrombolytic agent should be administered as quickly as possible.

The success of thrombus lysis depends mainly on how large the thrombus is and whether any blood flow still remains. The outcome is better if a large surface of the entire thrombus is exposed to the thrombolytic agent. As the clot ages, the polymerization of fibrin cross-linking and other blood materials increases and it becomes more resistant to lysis. Therefore, the earlier the thrombolysis therapy starts, the higher the frequency of clot dissolution. Various available thrombolytic agents used to dissolve blood clots are listed in Table 9 (370–385).

7.1. Glycoprotein IIb/IIIa Receptor Antagonists. These compounds are also called blood thinners since they thin blood by blocking platelet activity.

Table 9. **Antithrmobolytic Agents**

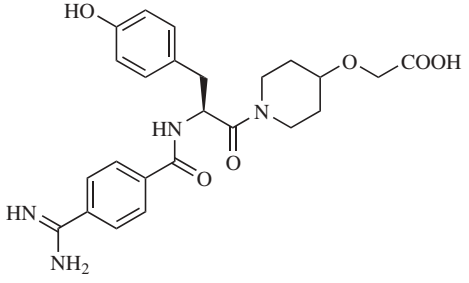
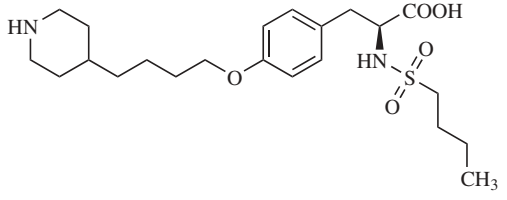
Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
		Glycoprotein IIb/IIIa Receptor Antagonists		
abciximb	[143653-53-6]		ReoPro	
eptifibatide	[188627-80-7]	$C_{35}H_{49}N_{11}O_9S_2$	Integrillin	
lamifiban	[144412-49-7]	$C_{24}H_{28}N_4O_6$		
tirofiban	[144494-65-5]	$C_{22}H_{36}N_2O_5S$	Aggrastat	

Table 9 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Structure
			Anticoagulants	
heparin sodium	[9041-08-11]			
dalteparin			Fragmin	
danaparoid			Orgaran	
enoxaparin			Lovenox	
tinzaparin			Innohep	
			Thrombolytic Agents	
human t-PA				
alteplase (TPA)	[105857-23-6]		Activase	
streptokinase	[9002-01-1]		Streptase, Kabikinase	
tenecteplase	[191588-94-0]		TNKase	
urokinase	[9039-53-6]		Abbokinase, Breokinase, Winkinase	
APSAC-anistreplase	[81669-57-0]			
prourokinase	[82657-92-9]			
duteplase	[120608-46-0]			

Platelet adhesion, activation, and aggregation are key processes leading to the formation of platelet-rich coronary artery thrombi and the development of acute coronary syndromes and ischemic complications during PCI. The platelet glycoprotein IIb/IIIa receptor inhibitor drugs are very beneficial for many patients with angina and do not appear to pose any elevated risk for stroke, including strokes caused by bleeding. Some of the most widely prescribed drugs include Abciximab (ReoPro, Centocor), eptifibatide (Integrelin), lamifiban, and tirofiban (Aggrastat). They are used to reduce the risk for heart attack or death in many patients with unstable angina and non-Q-wave myocardial infarctions when used in combination with heparin or aspirin. Patients with unstable angina showing elevated levels of troponin T factor are good candidates for these drugs. Some of the commonly used drugs are discussed.

Abciximab (ReoPro). It is the Fab fragment of the chimeric human-murine monoclonal immunoglobulin antibody 7E3. It binds selectively to platelet glycoprotein (GP IIb/IIIa) receptors and inhibits platelet aggregation. Abciximab is also known to bind to the vitronectin receptor located on platelets and vascular endothelial and smooth muscle cells. It is used with heparin and aspirin as an adjunct to precutaneous coronary intervention (PCI) for the prevention of acute cardiac ischemic complications in patients undergoing PCI with unstable angina. The GP IIb/IIIa receptor inhibitors are also used for managing unstable angina or non-Q-wave MI. It is administered by direct IV injection or by IV infusion, and the most common adverse effect of abciximab is bleeding.

Eptifibatide (Integrilin). It is a synthetic cyclic heptapeptide and is a selective platelet—aggregation (GP IIb/IIIa receptor) inhibitor. It is structurally similar to barbourin, a peptide constituent of the venom of southeastern pigmy rattlesnake, *Sistrurus m. barbouri*. Eptifibatide is composed of six amino acids and a mercaptopropionyl residue with a disulfide bridge between the cysteine amide and the mercaptopropionyl moiety. The active domain of eptifibatide consists of a modified lysine-glycine-aspartate (KGD) amino acid sequence similar to the physiological arginine-glycine-aspartate (RGD) sequence that binds to GP IIb/IIIa receptor on activated platelet and causes platelet aggregation. The substitution of lysine for arginine in eptifibatide increases the receptor binding selectivity. The pharmacokinetics of eptifibatide is linear, and peak plasma concentrations occur within 5 min after intravenous loading. It has a rapid onset and short duration of action, maximal inhibition of platelet aggregation occurring within 15 min after initiation of therapy. Eptifibatide is ~25% bound to plasma proteins and is eliminated by renal and nonrenal mechanisms. It is metabolized by deamidation to a 41% active metabolite in addition to formation of other polar metabolites. It is mostly used to reduce the risk of acute cardiac ischemic events (MI or death) in patients with unstable angina or non-Q-wave MI syndromes.

Tirofiban (Aggrastat). Tirofiban hydrochloride is a synthetic nonpeptide tyrosine analogue and is a selective, competitive platelet aggregation inhibitor. Similar to abciximab and eptifibatide, tirofiban is a platelet glycoprotein IIb/IIIa receptor inhibitor. It is synthesized by addition of an *n*-butylsulfonyl group to the C-terminus and 4-(piperidin-4-yl) butyloxy group to the N-terminus of tyrosine, resulting in enhancement of the drug's potency. Tirofiban inhibits platelet aggregation by preventing the binding of fibrinogen to activated

GP IIb/IIIa receptors, in a concentration-dependent manner. It also has a rapid onset and short duration of action. However, it is 65% bound to plasma proteins but plasma concentrations decline in biphasic manner, the half-life being 1.2–2 h. Similar to GP IIb/IIIa antagonists, it is used to manage unstable angina or non-Q-wave MI and also during PCI, and coronary artery bypass grafting (CABG).

7.2. Anticoagulants. The most widely accepted indications for anticoagulant therapy include venous thrombosis and pulmonary embolism. Prevention of these conditions in high risk patients or those undergoing certain types of major surgery to prevent postoperative thrombosis is mostly recommended. The indirect acting synthetic anticoagulants include three-substituted derivatives of 4-hydroxy coumarin (dicumarol, warfarin), indan 1, 3-dione derivatives such as antisinidione. These drugs regulate the synthesis of blood coagulation factors II (prothrombin), VII (proconvertin), IX (plasma thromboplastin component) and X (Sturat-Prower-factor) in the liver by interfering with the action of vitamin K. The latter is required for the γ-carboxylation of several glutamic acid residues in the precursor proteins of these coagulation factors. This interference leads to the synthesis of several dysfunctional coagulation factors. Dicumarol, and antisinidione drugs are administered orally, in a single daily dose, while warfarin can be administered both orally as well as by intravenous injections when oral therapy is not feasible. They are mostly used for the prophylaxis and treatment of deep vein thrombosis or any complications associated with atrial fibrillation or coronary occlusion.

Heparin Sodium. It is an anionic, sulfated glycosaminoglycan that occurs in mast cells. Heparin is prepared from either bovine lung tissue or porcine intestinal mucosa and is commercially available as a sodium salt. It is a heterogeneous molecule with an average molecular weight of 12,000 kDa. Heparin acts as a catalyst to enhance the neutralization rate of antithrombin III by thrombin instantaneously and activates coagulation factor X. Heparin is administered by intravenous infusion, injection or deep subcutaneous injection since it is not absorbed by the GI tract. The onset of anticoagulant activity is immediate following direct intravenous injection and is known to bind extensively to LDL, globulins, and fibrinogen. The plasma half-life of heparin is 1–2 h and the metabolic pathway is unclear. The major adverse effect includes hemorrhagic complications. It is used for prophylaxis and treatment of venous thrombosis and as an adjunct therapy in a number of situations.

Dalteparin (Fragmin). It is a depolymerized heparin prepared by nitrous acid degradation of unfractionated heparin of porcine intestinal mucosa. It is commercially available as a sodium salt with a molecular weight of 2000–9000 kDa and therefore also called as low molecular weight heparin. Dalteparin is used for the prevention of postoperative deep vein thrombosis and associated pulmonary embolism in patients undergoing hip replacement or abdominal surgery. It is also used in combination with aspirin to reduce the risk of acute cardiac ischemic events such as unstable angina or non-Q-wave MI.

Danaparoid (Orgaran). It is also isolated from porcine intestinal mucosa and has an average molecular weight of 5500–6000 kDa and structurally it consists of known amounts of three specific glycosaminoglycans ($\sim$84% heparin sulfate, 12% dermatan sulfate, and 4% chondroitin sulfate). The mechanism

of action is similar to other heparins and is administered as subcutaneous injection. It also finds applications for the prevention of postoperative deep-vein thrombosis.

Enoxaparin (Lovenox). It is a depolymerized heparin produced by alkaline degradation of unfractionated benzylated heparin of porcine intestinal mucosa. The average molecular weight is 4,500 kDa and has a similar mode of action as other heparins. It is mostly used during and following, for the prevention of postoperative thrombosis in patients undergoing hip and knee replacement surgery.

Tinzaprin (Innohep). It is a depolymerized heparin prepared by bacterial enzymatic degradation of unfractionated heparin or porcine intestinal mucosa. The average molecular weight ranges from 5,500–7,500 kDa. The mechanism of action is similar to other heparins and it is generally used for the prevention of thrombosis.

All of these anticlotting agents, either anticoagulants or antiplatelet drugs, are generally used to treat unstable angina, to protect against heart attacks, and prevent blood clots during heart surgery. They can be used alone or in combinations, depending on the severity of the condition. Clopidogrel (Plavix), a platelet inhibitor, has been shown to be more effective than aspirin by 20% for reducing the incidence of a heart attack. Other promising anticlotting drugs comprise argatroban (Novastan) and forms of hirudin (bivalirudin lepidrudin or desirudi), a substance derived from the saliva of leeches. One study suggested that the hirudin agents may be superior to heparin in preventing angina and heart attack, although bleeding is a greater risk with hirudin.

8. Thrombolytic Agents

Streptokinase, prourokinase, and acetylated plasminogen streptokinase activator complex (APSAC) agents are indirect plasminogen activators, t-PA and urokinase are direct plasminogen activators, whereas alteplase and tenecteplase are recombinant human t-PA. All these activators convert the formation of the active proteolytic enzyme plasmin [9001-90-5] from the proenzyme, plasminogen, [9001-91-6] by cleaving the Arg_{560}–Val_{561} bond. After intravenous administration, all five thrombolytic agents achieve approximately the same incidence of reperfusion rate (60–70%) if used optimally. t-PA and prourokinase require simultaneous heparin [9005-49-6] administration when used; the other thrombolytics do not. Reocclusion rate is higher with t-PA if heparin use is not maximized. The half-life is short (5–8 min) using t-PA and prourokinase, medium (16–23 min) using urokinase and streptokinase, and long (105 min) using APSAC. When used at efficacious doses, each agent has similar degrees of bleeding complications. The least expensive thrombolytic agent is streptokinase, which is about one-tenth of the others. No single agent is superior when all factors are taken into consideration. Whereas t-PA is clot selective, it has a very short half-life and simultaneous use of heparin is required. Bleeding is therefore as much of a problem with t-PA as the less clot selective agent, such as streptokinase. Streptokinase causes severe systemic fibrinogen degradation leading to extensive hypofibrinogenemia. Under this condition, reocclusion is less and the

dissolution of the thrombus is more complete. This may explain why streptokinase has been shown, in most studies, to be as efficacious as t-PA. The most recent comparison study reporting the equal efficacy of t-PA, APSAC, and streptokinase tends to confirm this point. Results of the largest clinical trials show that these agents reduce patient mortality from 16 to 30%.

The dosage of each thrombolytic agent should be high enough to produce a lysis state long enough for complete clot dissolution to occur. Aspirin, a platelet aggregation inhibitor, has been demonstrated to decrease mortality of AMI by itself and it is further enhanced by the use of the thrombolytic agents if used concomitantly (386–388). The use of combinations of aspirin, heparin, vasodilator, and the thrombolytic agent decreases the incidence of rethrombosis.

8.1. Tissue-Type Plasminogen Activator (t-PA). Endogeneous human t-PA is a glycosylated, trypsin-like serine protease secreted mainly by vascular endothelial cells as a single chain polypeptide. It is a physiological activator of plasminogen in the body. The complete structure of human t-PA consists of a polypeptide of 562 amino acids, that include a leader sequence of 35 amino acids and a mature protein of 527 amino acids having Mol. Wt. ~64,000. It is also made in the liver, spleen, lungs, muscle, and other tissues. The commercial preparation is derived from using DNA recombinant technology and it is a recombinant rt-PA. The t-PA can occur in either a one- or two-chain form. Both forms are active but the two-chain form is longer acting (389–392).

t-PA has a much higher affinity for fibrin and fibrin-bound plasminogen as compared to the circulating plasminogen. For this reason, under normal conditions generalized (systemic) fibrinogenolysis in the circulation is thought not to occur. However, in the treatment of AMI, the large amount of t-PA used and infused for a prolonged period causes generalized fibrinogenolysis because of the activation of circulating plasminogen. In the treatment of AMI, a bolus intravenous injection of 10 mg is followed by an intravenous infusion of 50 mg/h for 1h and 20 mg/h for 2 h. The half-life of t-PA in the circulation is ~4–5 min. It is cleared by the liver. The activation of plasminogen by t-PA is accelerated by heparin. The primary side effect is bleeding or hemorrhage.

Alteplase (Activase). It is a biosynthetic (recombinant DNA) form of the enzyme human t-PA, thrombolytic agent. Alteplase is prepared from the cultures of genetically modified mammalian (chinese hamster ovary, CHO) cells using recombinant DNA technology. Commercially available alteplase is a glycoylated, predominantly (60–80%) one-chain form of t-PA consisting of 527 amino acids and 3 carbohydrate side chains and the molecular weight ranges from 65,000 to 70,000 kDa reflecting the variation in carbohydrate moieties. The amino acid sequence of alteplase is identical to that of human melanoma cell t-PA. Alteplase is a white lypholyzed powder and practically insoluble in water, but presence of arginine increases the auqeous solubility substantially. Alteplase is administerd by intravenous injection [usual adult dose 100 mg (58 million IU)] and used as a thrombolytic agent in selective cases of MI and coronary artery thrombosis. The most frequent and severe adverse effect of rt-PA is hemorrhage.

Tenecteplase (TNKase). Similar to alteplase, tenecteplase is a rt-PA and is a thrombolytic agent. Although tenecteplase is structurally and pharmacologically related to alteplase, it exhibits higher fibrin selectivity, gerater resistance

to PA inhibitors and has a longer plasma half-life than alteplase. It binds to fibrin and converts plasminogen to plasmin. It is administered by intravenous injection over 5 s and should be given as soon as possible or within 30 min after onset of acute MI.

Streptokinase (Streptase). Streptokinase is a nonenzymatic protein produced by a group of C β-hemolytic streptococci. It is a single-chain protein containing 415 amino acids, Mol. Wt. of 45,000–50,000 kDa (393–395). It is available as a lypholized powder and freely soluble in water. It is stable in solution at pH 6–8. In contrast to other anticoagulants, streptokinase promotes thrombolysis. But only after streptokinase combines with plasminogen on a 1:1 basis to form a streptokinase–plasminogen complex, to expose the active site of the plasminogen portion, does it become an active species. This complex then becomes a potent enzyme activator and converts residual plasminogen to plasmin. The complex has a half-life of ~23 min in the circulation. The usual dose used is 1.5 million units to ensure enough streptokinase. It is left after being cleared from the circulation by streptokinase antibodies and inhibitors in the blood stream. Thrombolytic activity lasts for 3–4 h. Streptokinase administration also causes fibrinolysis and fibrinogenolysis, through activation of plasma plasminogen, in the circulation and depletes plasma fibrinogen. Streptokinase is used as a thrombolytic agent in acute MI, coronary artery thrombosis and MI, deep vein thrombosis and pulmonary embolism.

The mortality is usually reduced from 12% in the control group to 9–10% in the streptokinase group. Side effects are bleeding, hemorrhage, fever, and allergy.

Urokinase (Abbokinase). Urokinase is direct plasminogen activator enzyme produced by the kidneys and endothelial cells and excreted in urine. It was first isolated from human urine, but now it is produced by cultured human fetal kidney cells. It is a double chain of 411 amino acids, Mol. Wt. 54,000–55,000 kDa, having a half-life of 16 min. It is metabolized in the liver. Urokinase is given at 4500 units/kg in a loading dose, and then at 4500 units/kg per hour by a continuous intravenous infusion. Urokinase converts plasminogen to plasmin with greater affinity for the fibrin-bound plasminogen. However, during therapy of AMI, the circulating plasminogen is also activated and catalyzes the breakdown of fibrin and also fibrinogen, causing a generalized (systemic) lytic state. Hemorrhage is the most serious side effect. Recently, the U.S. FDA approved the use of urokinase for the tretament of pulmonary embolism.

Acylated (Anisolyated) Plasminogen–Streptokinase Activator Complex (APSAC). After intravenous administration streptokinase becomes active only after forming a complex with plasminogen. This activated form is rapidly inactivated in the plasma and also causes generalized (systemic) fibrinogenolysis. Therefore, most of the active complex cannot reach the arterial thrombus in the coronary circulation. To overcome this, the active site (catalytic center) of the preformed streptokinase–plasminogen complex is protected or blocked by an acyl group and APSAC is formed (396–398). However, the fibrin-binding sites are not changed, therefore APSAC binds rapidly to the fibrin clot. So the local dissolution of the clot is preferentially obtained. Deacylation occurs slowly in plasma.

In the acylated form, the APSAC offers a prolonged half-life (105 min), greater lysis potency, and less systemic lytic state. APSAC is used at 30 U (30 mg) by intravenous injection.

Prourokinase. The single-chain urokinase-type plasminogen activator (scu-PA) urokinase does not have high fibrin specificity and therefore causes systemic fibrinogenolysis. In the early 1980s, a single-chain precursor of urokinase (prourokinase) was isolated and purified from human urine and cultured cell lines. Now, it is produced using recombinant DNA biotechnology. It was found that prourokinase was much more fibrin-specific than urokinase and is not effective in activating plasma plasminogen. Its mechanism of action was distinctly different from that of t-PA.

Prourokinase is a single-chain protein containing 411 amino acids. In clinical use, scu-PA does not bind to fibrin only and its use causes a decreased plasma fibrinogen of 80%. Its half-life in the circulation is 5 min and is cleared by the liver. It is used at 40–70 mg over 1 h and heparin is needed simultaneously. Fibrin specificity and thrombolytic efficacy are similar to that of t-PA.

In general, it has been found that t-PAs reduce 50–90% AMI mortality, 30% of AMI mortality, and 15% AMI mortality if administered in the first hour, within 6 h, and within 6–12 h of symptoms, respectively. The direct benefits of using t-PAs include chest pain relief, diminished ECG changes, lowering of MB creatinine kinase levels and decreased incidences of reinfarction, CHF and shock.

9. New Human t-PA Thrombolytic Agents Under Development

Several new recombinant expressions are currently being explored toward improvement of thrombolytic agents (399). Some of the important methods include construction of mutants of PA, chimeric PA, conjugates of PA with monoclonal antibodies, and PA from either bacterial or animal origin. Some of these thrombolytic agents have shown promise in animal models of venous and arterial thrombosis and are being further investigated in clinical trials. Monteplase is a modified tissue-type plasminogen activator (t-PA) synthesized by substitution of Cys84 by Ser in the epidermal growth factor domain and expressed in baby Syrian hamster kidney cells. This mutation prolongs the half-life by >20 min as compared to 4 min for native t-PA. This mutant has increased thrombolytic activity, slower clearance and enhanced resistance to the inhibitor PAI-1.

Reteplase is a non-glycosylated deletion mutant of wild-type human t-PA containing only kringle 2 and the protease domain, but lacking its kringle 1 and finger and growth factor domains. This structural modification leads to decreased fibrin binding, lower affinity toward endothelial and liver cells resulting into an extended half-life.

Lanoteplase is another deletion mutant of t-PA with >10 times the half-life than alteplase. YM866-is another mutant of human t-PA constructed by deleting 92–173 amino acids of kringle 1and replacing Arg 275 by glutamic acid that confers a longer half-life to the mutant. Also, recombinant glycosylated prourokinase is a rapid acting and safe t-PA, but with greater stability than recombinant unglycosylated pro-urokinase.

Staphylokinase (SAK) produced by *Staphylococcus aureus* induces efficient and rapid recanalization after bolus injection, however it is immunogenic. In patients with acute MI, reteplase, administered as bolus injection. However, the quest continues for plasminogen activators with enhanced potency, specific thrombolytic activity, fibrin selectivity and longer half-life.

The introduction of new clot buster drugs or thrombolytics has revolutionized the treatment of heart attack or AMI, and current research is focused on identifying better thrombolytic and adjunctive agents or mechanical interventions such as the use of angioplasty or stents. A possible future approach that could universally be adopted consists of combination therapy and adjunctive/rescue percutaneous intervention at hospitals.

10. Physiology and Biochemistry of Congestive Heart Failure

The heart, a four-chambered muscular pump, propels blood throughout the cardiovascular system. The left ventricle is the principal pumping chamber and is therefore the largest of the four chambers in terms of muscle mass. The efficiency of the heart as a pump can be assessed by measuring cardiac output, left ventricular pressure, and the amount of work required to accomplish any required amount of pumping.

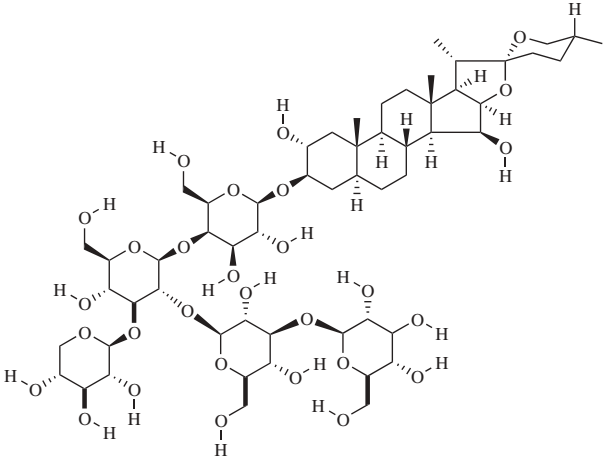
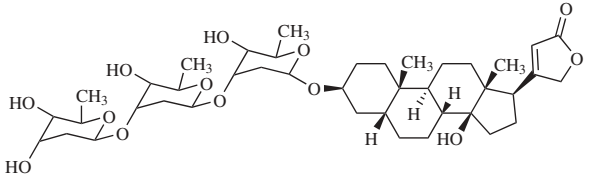
When the heart begins to fail as a pump, a number of pathophysiologic processes occur. Perhaps the easiest to perceive is simply that some of the blood within the left ventricle is not completely expelled during muscle contraction or systole. This subsequently requires more work during future systoles as additional blood returns from the pulmonary vein. A sort of congestion begins to develop as the heart cannot develop enough pumping ability to provide adequate oxygenated blood to the arterial circulation or removal of metabolic waste through the venous circulation.

There can be a number of underlying causes of CHF. The most prevalent is the lack of oxygenated blood reaching the heart muscle itself because of coronary artery disease with myocardial infarction (401). Hypertension and valvular disease also contribute to CHF as well, but to a lesser extent in terms of principal causes for the disease.

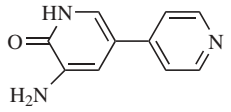
Both high energy containing ATP and calcium are integral components of cardiac muscle contraction. Hydrolysis of ATP is coupled to cross-linking of the actin–myosin contractile proteins, resulting in mechanical shortening of the functional unit of cardiac muscle, the sarcomere. Calcium is involved in binding of the contractile protein troponin, but the quantity of calcium entering the myocardial cell is finely regulated, concomitantly regulating the extent of cardiac muscle contraction. Imbalance in any aspects of the chemical process of contraction can result in reduced pumping ability and contribute to CHF.

10.1. Therapy of Congestive Heart Failure. Many of the drugs used to combat congestive heart failure are inotropic agents, some of which are shown in Table 10. Inotrope is a derivation of the Greek *ino* (fiber) and *tropikos* (changing or turning). A positive inotropic agent is therefore one that increases cardiac muscle contractility associated with CHF.

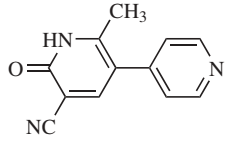
Table 10. **Other Therapeutics**

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Structure
			Inotropic Agents: Glycosides		
digitalin	[752-61-4]	$C_{36}H_{56}O_{14}$	Diginorgin	cardiotonic	
digitalis			Digitonin, Digitalin	cardiotonic	
digitogenin	[511-34-2]	$C_{27}H_{44}O_5$		cardiotonic	
digitonin	[11024-24-1]	$C_{56}H_{92}O_{29}$	Digitin	cardiotonic	
digitoxin	[71-63-6]	$C_{41}H_{64}O_{13}$	Digitalin, Carditoxin	cardiotonic	

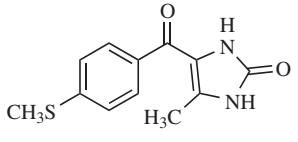
amrinone	[60719-84-8]	$C_{10}H_9N_3O$	Cartonic, Inocor	cardiotonic



milrinone	[78415-72-2]	$C_{12}H_9N_3O$	Corotrope, Primacor	cardiotonic



enoximone	[77671-31-9]	$C_{12}H_{12}N_2O_2S$	Perfane, Perfan	cardiotonic



dipyridamole	[58-32-2]	$C_{24}H_{40}N_8O_4$	Cardoxin, Coridil, Prandiol	cardiotonic

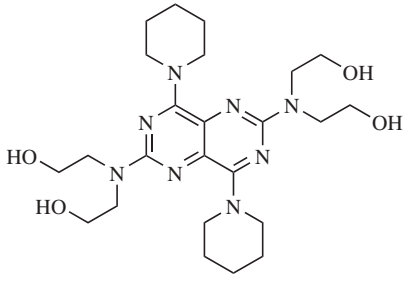
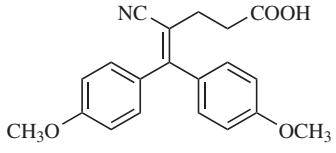
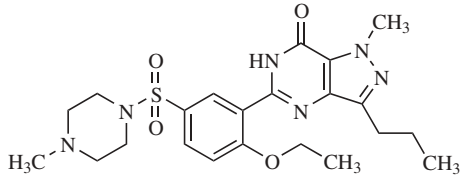
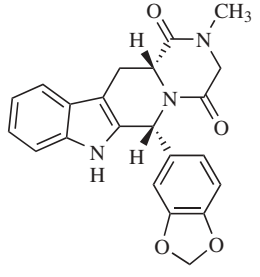
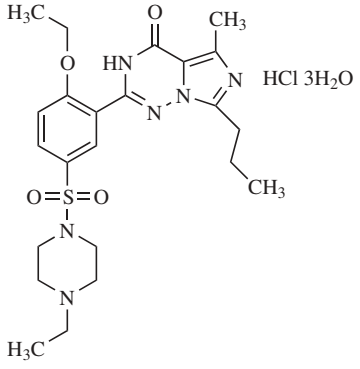


Table 10 (*Continued*)

Chemical/ generic name	CAS Registry Number	Molecular formula	Trade name	Uses	Structure
satigrel	[111753-73-2]	$C_{20}H_{19}NO_4$		antithrombotic	
sildenafil	[139755-83-2]	$C_{22}H_{30}N_6O_4S$	Viagra	erectile dysfunction	
tadalafil	[171596-29-5]	$C_{22}H_{19}N_3O_4$	Cialis	erectile dysfunction	

vardenafil	[224785-90-4]	$C_{23}H_{32}N_6O_4S \cdot HC \cdot 3H_2O$	Levitra		erectile dysfunction



Cardiac Glycosides. Glycosides are a distinct class of compounds that are either found in Nature or can be synthetically prepared. The natural glycosides are isolated from various plant species, namely, digitalis purpurea Linne, digitalis lanata Ehrhart, strophanthus gratus, or acokanthea schimperi. Therefore, these compounds are also named as digitalis, digoxin, digitoxin. Currently, digoxin is the only cardiac glycoside commercially available in the United States. Glycosides have a characteristic steroid (aglycone) structure complexed with one or more types of sugar moiety at the C3 position of the steroid through the β-hydroxyl group. Increasing, the number of hydroxyl groups on the aglycone or additional sugar moiety increases polarity and decreases lipid solubility. The sugar moiety further affects in part the activity of glycosides by influencing solubility, absorption, distribution, and toxicity. Glycosides are sparingly soluble in water and freely soluble in alcohol. All commercially available glycosides obtained from the *Digitalis* species contain the same basic aglycone but differ in the substitution at the C12 position of the aglycone and in the sugar substituent.

Glycosides are mainly used in the prophylactic management and treatment of congestive heart failure, atrial fibrillation, and recurrent atrial tachycardia. They are also used in conjunction with ACE inhibitors, diuretics, and β-adrenergic blocking agents. They are known to relieve the symptoms of systemic venous congestion (right-sided heart failure or peripheral edema) and pulmonary congestion (left-sided heart failure). However, glycosides also find applications to treat and prevent sinus and supraventricular tachycardia and symptoms of angina pectoris and myocardial infarction, but only in combination with β-adrenergic blocking agents and in patients with congestive heart failure.

The exact mechanism of pharmacological action of glycosides has not been fully elucidated. However, glycosides exhibit a positive inotropic effect accompanied by reduction in peripheral resistance and enhancement of myocardial contractility resulting in increased myocardial oxygen consumption. They also inhibit the activities of sodium–potassium activated ATPase, an enzyme required for the active transport of sodium across the myocardial cell membranes (402).

Glycosides are normally administered via various routes either orally or by intravenous injection and digoxin has a half-life of 36 h while that of digitoxin is to 5–7 days in normal patients. Cardiac glycosides undergo varying degrees of hepatic metabolism, enterohepatic elimination, renal filtration, and reabsorption depending on their polarity and lipid solubility. Cardiac glycosides increase plasma estrogen in women and decrease plasma testosterone in men. Toxic effects of glycosides are mainly GI, CNS, and biochemical in origin.

Nondigitalis Inotropic Agents. A number of inotropic agents that are not structurally related to the cardiac glycosides have been investigated for treatment of CHF. All are somehow mechanistically related to the complex series of events involved in normal cardiac muscle contraction, and in terms of pumping ability are capable of increasing left ventricular contractility. Many of these drugs do not perform in diseased cardiac tissue in a manner similar to that observed in normal, nondiseased muscle. Many of these agents act via the β-adrenergic receptors of the sympathetic nervous system (SNS).

Catecholamines. Simplistically, the SNS is composed of nerves capable of synthesizing and releasing various catecholamines that can bind appropriate

molecular receptors postsynaptically. Depending on their synthetic structure, they have the ability to bind, and therefore stimulate various postsynaptic events through α-adrenergic, β-adrenergic, and dopaminergic receptors.

Each receptor has a specific role, often vasodilation, which serves to facilitate the ability of a failing heart to pump against reduced systemic pressure. Side effects of catecholamines include arrhythmias and tachyphylaxis. In addition, potent vasodilators such as isoproterenol [7683-59-2], $C_{11}H_{17}NO_3$, have a dual effect, namely increased contractility through direct cardiac muscle stimulation (403). If combined with significant reductions in blood pressure, isoproterenol can produce detrimental effects through a combination of reduced venous return yet increased oxygen requirements of the rapidly contracting cardiac muscle. The orally active catecholamine pirbuterol [38677-81-5], $C_{12}H_{20}N_2O_3$, has many of these classic side effects (403). These drugs have been selectively developed to affect specific receptor subtypes through radioligand binding studies using microsomal membrane preparations from animal tissue. This rapid method of screening for selective agonists and antagonists has produced considerable quantities of chemical structures that have potential as drugs. Each results in positive, yet relatively short-term efficacy in patients having CHF (404).

Dobutamine, a positive inotrope from the sympathomimetic amine family, was introduced in the early 1980s and possesses an asymmetric carbon atom resulting in two enantiomers. The commercial product is a 50:50 racemic mixture of the optical isomers, producing a combined β-adrenergic agonist and α-adrenergic antagonist effect (405) from the (+) enantiomer. The (−) enantiomer is a potent α-adrenoceptor agonist (406). The positive inotropic activity is a result of the two enantiomers, especially as relates to functional, simultaneous effects on cardiac, and vascular smooth muscle. Because of this unique combination of activity, dobutamine is superior to isoproterenol, dopamine, epinephrine, and norepinephrine, primarily because of dobutamine's lesser effect on blood pressure reduction. At doses of 2.5–15 μg/(kg/min) dobutamine increases stroke volume, while reducing peripheral resistance. Even after drug infusion is stopped, the patient can continue to benefit (407). Because it is administered by infusion, the drug is not approved by the FDA for outpatient administration.

Agiotension-Converting Enzyme Inhibitors or α-Blockers. ACE inhibitors prevent the conversion of angiotension I to angiotension II, a potent vasoconstrictor, consequentially reducing plasma concentrations of angiotension II, and hence vasodilation. This results in attenuation of blood pressure. The ACE inhibitors also affect the release of renin from kidneys and increase the plasma renin activity (PRA). It has been suggested that the hypotensive effect of ACE inhibitors may decrease vascular tone due to inhibition of angiotension induced vasoconstriction and increased sympathetic activity. The reduced production of angiotension II lowers the plasma aldosterone concentration (due to less secretion of aldosterone from adrenal cortex) and hence the lower aldosterone excretion. The aldosterone is known to decrease the sodium extraction concentration and water retention resulting in desired hypotensive effect. Controlled clinical studies have shown the ACE inhibitors are at least equal in effectiveness to cardiac glycosides in treatment of CHF (408), and may actually elicit a positive effect on the pathophysiologic mechanism of CHF by inhibiting angiotensin II formation.

ACE inhibitors can be administered with diuretics (qv), cardiac glycosides, β-adrenoceptor blockers, and calcium channel blockers. Clinical trials indicate they are generally free from serious side effects. The effectiveness of enalapril, another ACE inhibitor, in preventing patient mortality in severe (Class IV) heart failure was investigated. In combination with conventional drugs such as vasodilators and diuretics, a 40% reduction in mortality was observed after 6 months of treatment using 2.5–40 mg/day of enalapril (409). However, patients complain of cough, and occasionally rash and taste disturbances can occur. Some of the most commonly prescribed ACE inhibitors were discussed earliet in antihypertensive agents section.

Phosphodiesterase Inhibitors. cGMP plays a critical role in the modulation of vascular function. Because of the complexity of the biochemical processes involved in cardiac muscle contraction, investigators have looked at manipulation of cGMP pathways for other means of drug intervention for CHF, angina pectoris, MI, and hypertension. Better understanding of regulation and mechanism of cGMP pathways are providing new opportunities through alteration of cGMP levels. Steady-state levels of cGMP are maintained by the rate of formation and degradation of the nucleotide phosphodiesterase (PDE). At least seven classes of phosphodiesterases possessing structural similarities and the amino acid sequences have been identified to date. However, each class is distinguished by its specificty for cAMP (cyclic adenosine phosphate) and cGMP regulation and their response to various agents. One of the areas of investigation involves increased cyclic adenosine monophosphate [60-92-4] (cAMP) through inhibition of phosphodiesterase [9025-82-5] (PDE). This class of compounds includes amrinone, considered beneficial for CHF because of positive inotropic and vasodilator activity. The mechanism of inotropic action involves the inhibition of PDE, which in turn inhibits the intracellular hydrolysis of cAMP (410). In cascade fashion, cAMP-catalyzed phosphorylation of sarcolemmal calcium channels follows, activating the calcium pump (411). A series of synthetic moieties including the bipyridines, amrinone and milrinone, piroximone, and enoximone [77671-31-9], $C_{12}H_{12}N_2O_2S$, all of which have been shown to improve cardiac contractility in short-term studies, were developed (412,413). These drugs initially had a wider therapeutic index than cardiac glycosides, and did not exhibit receptor down-regulation associated with β-adrenoceptor blockers. Questions have since surfaced concerning the detrimental effects of increased contractility upon accelerated deterioration of already diseased cardiac tissue, ie, these drugs can lead to shortened patient survival (414,415). An additional detrimental side effect is arrhythmogenesis (416).

Atrial Natriuretic Peptide. It is a substance released from the right atrium of the heart and other tissues into the bloodstream that stimulates the kidneys to excrete sodium ("natri-" = sodium) into the urine ("-uretic" = urine). For reasons that are not understood ANP is released in response to subarachnoid hemorrhage. Release of ANP is the cause of the hyponatremia (lower than normal content of sodium in the blood) that frequently complicates subarachnoid hemorrhage. Atrial natriuretic factor (ANP), a polypeptide hormone of 28 amino acids (ANF 28) with potent natriuretic, vasorelaxant, and diuretic properties was originally purified from animal and human atrial extracts (417). The responses evoked from the atrial extracts established the heart as an endocrine organ.

A number of different types of ANP have been described, but the original molecule is a polypeptide of 28 amino acids (qv). The natriuretic peptide family includes A-type (ANP 28), B-type designated as brain natriuretic peptide (BNP 32) and C-type natriuretic peptide (CNP) that are responsible for the body homeostasis and blood pressure control. Both ANP and BNP act on guanylase cyclase-A and CNP on guanylase cyclase-B receptors. The ANPs exert direct and indirect effects on kidneys to alter renal hemodynamics and to enhance salt and fluid excretion and also in part by synthesis and release of renin and aldosterone through renin-angiotensin-aldosterone (RAA) inhibition (418).

It has been shown that ANP s may prevent or attenuate ischemic renal failure (419).Significant benefits were also observed using 4-day infusion of ANP 32 after heart or liver transplantations (420–422). Renal function was improved and all patients developed a strong diuresis and natriuresis with 2–4 h indicating that a continuous low infusion of ANP 32 may present a new concept for treatment of postoperative acute renal failure resistant to conventional therapy (423).

Cardiovascular Disease: Statistics and the Pharmaceutical Industry. Cardiovascular disease (CVD) is a leading cause of death in developed countries, and affects millions of men and women worldwide (328). In the United States alone, 61 million people suffer from some form of CVD, with an estimated 2600 deaths a day attributed to CVD (424). Based on such numbers, it is not surprising that drugs used to treat CVD lead worldwide pharmaceutical sales. In 2003, sales of drugs used to treat CVD are projected to reach $56.6 billion dollars (425). In fact, at a time when new drug approvals are on the decline for most classes of therapeutics, the development times of CVD targeted therapeutics have decreased (ie, new approval times are shortening) (426). Several new classes of therapeutics, including angiotensin II receptor blockers, have contributed significantly to continued growth in this sector of the pharmaceutical industry. In 1997, four new antihypertensive agents were approved by the FDA. These included eprosartan and irbesartan, which are both angiotensin II receptor blockers; mibefradil (a calcium channel blocker), and fenoldopam, which is a selective dopamine1 receptor agonist used intravenously to treat short-term severe hypertension (427). In 2002, the FDA approved two CVD therapeutics used to treat hypertension: olmesartan (an angiotensin II receptor blocker) and eplerenon (a selective aldosterone receptor antagonist). The European AEMP approved telmisartan (an angiotensin II receptor blocker) for the treatment of hypertension, and Bosetan (an endothelin receptor antagonist) for pulmonary arterial hypertension (428). In addition, many new and diverse potential therapeutics are currently in development for the treatment of CVD, and range from phosphodiesterase inhibitors to A1 adenosine receptor agonists (429). The development of diverse new therapeutics to treat new biological pathways associated with CVD, coupled with an ever increasing incidence of CVD worldwide, will ensure that this sector of the pharmaceutical industry will continue to flourish in the foreseeable future.

11. Future Directions

The cardiovascular drug market is one of the larger pharmaceutical markets in the world, with global sales totaling >$50 billion/year and a number of drugs

individually exceed $1 billion in annual sales. Even though copious drug classes are used to treat heart failure patients and other cardiovascular diseases, new cases of CHD are growing at >10%/year and the risk of death is also rising incessantly. Therefore, there is an unmet medical need for novel therapeutic agents to treat CHD. Since various kinases are implicated in the catalysis of reversible phosphorylation of direct and indirect signaling pathways in cardiac cells, future discoveries may be made by exploiting such linkages. In particular, protein kinase C (PKC), the mitogen activated protein kinases (MAPKs), and phosphoinositide 3-kinase (PI3K) are associated with various functional responses in cardiac cells such as cell survival, cardiac protection, calcium regulation and contraction, and hypertrophy. Therefore, PKC, MAPK, and PI3K each represent a valid therapeutic target for cardiac function and further in depth elucidation of these kinase pathways is essential (430).

There is increasing evidence of a relationship between apoptosis and pathophysiology of both ischemic and nonischemic cardiomyopathies, and a large number of papers have been published since 1997 suggesting a link between some of the major genetic and biochemical regulators of apoptosis in the heart. There has been a quest for a therapeutical agent that would delay the onset of apoptosis in the ischemic heart. In the future, several therapeutic interventions can be developed to prolong survival of smooth muscle and endothelial cells, and to enhance the vascular contractility, tone, and eventually delay the process of atherosclerosis (431,432).

Elucidation of the phenomenon of myocardial preconditioning may hold the key to the development of a drug for the treatment of ischemic heart disease (433).

Several new therapeutic approaches are under investigation for hypertension. An inhaled prostacyclin analogue, iloprost, may allow ease of administration and minimize some adverse side effects. Oral prostacyclins and inhaled forms of NO therapy are also under study.

NO is a unique moiety implicated in the regulation of various physiological processes including smooth muscle contractility and platelet reactivity. Consequently, it has been suggested that NO may have a significant cardioprotection role in hypercholesterolemia, atherosclerosis, hypertension, and inhibition of platelet aggregation. As a result, the development of selective NOS inhibitors will address the potential beneficial therapeutic outcome of NO modulation to the pathophysiology of these disorders (434,435).

Over the past few years, a number of potent asymmetric aza analogues of the dihydropyrimidine types (DHPM), possessing a similar pharmacological profile to classical dihydropyridine calcium channel blockers, are being studied extensively to evaluate their molecular interactions at the receptor level. Some of the lead compounds (SQ 32926 or SQ 32547) are superior in potency and duration of antihypertensive activity to classical DHP analogues. These compounds compare favorably with second generation drugs such as nicardipine and amlodipine. This class of compounds (DHPM) might be the next generation of CCBs for the treatment of cardiovascular diseases (436).

Clinical administration of drugs with negative inotropic activity is not desirable because of their cardiosuppressive effects, especially in patients with a tendency toward heart failure. Therefore, there has been a search for cardioprotective agents acting through entirely different mechanisms. It has been

suggested that reevaluation of dihydropyridine calcium channel blockers might lead to the discovery of therapeutic agents that also have effects on other membrane channels. Efonidipine, possessing inhibitory effects on both L- and T-type Ca^{2+} channels shows potent bradycardic effects through a characteristic prolongation of the phase 4 depolarization, leading to minimum reflex tachycardia or to bradycardia. Both AHC-52 and AHC-93 seem to be interesting prototypes of cardioprotective drugs that act to modify anion homeostatis (437).

Additionally, there are a number of novel potential drug candidates undergoing various clinical studies. One of the most promising candidates is ranolazine. This drug represents the first in a new class of drugs called pFOX inhibitors (partial Fatty Acid Oxidation), which have the potential for treating chronic stable angina. The pFox inhibitors possess a unique method of action, and therefore patients may be able to find relief from the painful attacks of angina without some of the unwanted effects of current antianginal drugs. In particular, energy for cardiac functions such as contraction and relaxation is obtained from ATP breakdown; however, ATP is derived from the oxidation of fatty acids and carbohydrates. In the absence of hypoxia (nonischemic condition), the majority of the energy required for ATP synthesis comes from fatty acids. However, during ischemia fatty acid levels increase further and become a source of cardiac energy other than during nonischemic conditions. Animal studies indicate that pFOX inhibitors directly inhibit fatty acid oxidation of ischemic myocytes.

A new class of hypolipidaemic drugs known as SCAP (escaping high cholesterol) ligands has been proposed (438). Since statins inhibit the rate-limiting enzyme in the cholesterol synthesis pathway, these new compounds act indirectly, by increasing the level of expression of the cell surface LDL receptor (LDLR), which removes cholesterol from circulation. However, LDLR expression is governed by transcriptional activators known as sterol response element-binding proteins (SREBPs), which must travel from the cell's endoplasmic reticulum into the nucleus while undergoing a two-stage cleavage process. Thus, they are chaperoned by another protein called SCAP and new compounds act directly on SCAP to activate it, driving the cleavage and formation of new LDLR and ultimately lowering the LDL levels.

Finally, pharmacogenomics holds the promise that drugs might one day be tailor-made for individual treatment and adapted to each person's own genetic make up.

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