Drugs Used in Heart Failure

Bertram G. Katzung, MD, PhD*

CASE STUDY

A 65-year-old man developed shortness of breath with exertion several weeks after experiencing a viral illness. This was accompanied by swelling of the feet and ankles and increasing fatigue. On physical examination he is now found to be mildly short of breath lying down, but feels better sitting upright. Pulse is 105 bpm and regular, and blood pressure is 110/70 mm Hg. Crackles are noted at both lung bases, and his jugular venous pressure is elevated. The liver is enlarged, and there is 3+ edema of the ankles and feet. An echocardiogram shows a dilated, poorly contracting heart with a left ventricular ejection fraction of about 20% (normal: 60%). The presumptive diagnosis is dilated cardiomyopathy secondary to a viral infection with stage C, class III heart failure. What treatment is indicated?

Heart failure occurs when cardiac output is inadequate to provide the oxygen needed by the body. It is a highly lethal condition, with a 5-year mortality rate conventionally said to be about 50%. The most common cause of heart failure in the USA is coronary artery disease, with hypertension also an important factor. Two major types of failure may be distinguished. Approximately 50% of younger patients have systolic failure, with reduced mechanical pumping action (contractility) and reduced ejection fraction. The remaining group has diastolic failure, with stiffening and loss of adequate relaxation playing a major role in reducing filling and cardiac output. Ejection fraction may be normal (preserved) in diastolic failure even though stroke volume is significantly reduced. The proportion of patients with diastolic failure increases with age. Because other cardiovascular conditions (especially myocardial infarction) are now being treated more effectively, more patients are surviving long enough for heart failure to develop, making heart failure one of the cardiovascular conditions that is actually increasing in prevalence.

Heart failure is a progressive disease that is characterized by a gradual reduction in cardiac performance, punctuated in many cases by episodes of acute decompensation, often requiring hospitalization. Treatment is therefore directed at two somewhat different goals: (1) reducing symptoms and slowing progression as much as possible during relatively stable periods and (2) managing acute episodes of decompensated failure. These factors are discussed in Clinical Pharmacology of Drugs Used in Heart Failure.

Although it is believed that the primary defect in early systolic heart failure resides in the excitation-contraction coupling machinery of the myocardium, the clinical condition also involves many other processes and organs, including the baroreceptor reflex, the sympathetic nervous system, the kidneys, angiotensin II and other peptides, aldosterone, and apoptosis of cardiac cells. Recognition of these factors has resulted in evolution of a variety of drug treatment strategies (Table 13–1).

Large clinical trials have shown that therapy directed at noncardiac targets is more valuable in the long-term treatment of heart failure than traditional positive inotropic agents (cardiac glycosides [digitalis]). Extensive trials have shown that angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), certain β blockers, aldosterone receptor antagonists, and combined

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A small rise in free cytoplasmic calcium, brought about by the amount of calcium released from the sarcoplasmic reticulum (SR), increases contractility without increasing energy consumption, i.e., the rate of transition of myosin from a low-actin-binding state to the high-actin-binding state. This in turn is dependent on the balance of calcium influx (primarily through the voltage-gated membrane L-type calcium channels) and calcium efflux, the amount removed from the cell (primarily via the sodium-calcium exchanger, a transporter in the cell membrane). The amount of Ca\(^{2+}\) released from the SR depends on the response of the RyR channels to trigger Ca\(^{2+}\).

**TABLE 13–1 Therapies used in heart failure.**

<table>
<thead>
<tr>
<th>Chronic Systolic Heart Failure</th>
<th>Acute Heart Failure</th>
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<tbody>
<tr>
<td>Diuretics</td>
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<td>Aldosterone receptor antagonists</td>
<td>Vasodilators</td>
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<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Beta agonists</td>
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<tr>
<td>Angiotensin receptor blockers</td>
<td>Bipyridines</td>
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<td>Beta blockers</td>
<td>Natriuretic peptide</td>
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<tr>
<td>Cardiac glycosides</td>
<td>Left ventricular assist device</td>
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<tr>
<td>Vasodilators</td>
<td>Resynchronization therapy</td>
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Control of Normal Cardiac Contractility

The vigor of contraction of heart muscle is determined by several processes that lead to the movement of actin and myosin filaments in the cardiac sarcomere (Figure 13–1). Ultimately, contraction results from the interaction of activator calcium (during systole) with the actin-troponin-tropomyosin system, thereby releasing the actin-myosin interaction. This activator calcium is released from the sarcoplasmic reticulum (SR). The amount released depends on the amount stored in the SR and the amount of trigger calcium that enters the cell during the plateau of the action potential.

A. Sensitivity of the Contractile Proteins to Calcium and Other Contractile Protein Modifications

The determinants of calcium sensitivity, i.e., the curve relating the shortening of cardiac myofibrils to the cytoplasmic calcium concentration, are incompletely understood, but several types of drugs can be shown to affect calcium sensitivity in vitro. Levosimendan is the most recent example of a drug that increases calcium sensitivity (it may also inhibit phosphodiesterase) and reduces symptoms in models of heart failure. A recent report suggests that an experimental drug, omecamtiv mecarbil (CK-1827452), alters the activity (it may also inhibit phosphodiesterase) and reduces symptoms in large clinical trials to date, other positive inotropic drugs have usually reduced survival in chronic failure or had no benefit, and their use is discouraged.

B. Amount of Calcium Released from the Sarcoplasmic Reticulum

A small rise in free cytoplasmic calcium, brought about by calcium influx during the action potential, triggers the opening of calcium-gated, ryanodine-sensitive (RyR2) calcium channels in the membrane of the cardiac SR and the rapid release of a large amount of the ion into the cytoplasm in the vicinity of the actin-troponin-tropomyosin complex. The amount released is proportional to the amount stored in the SR and the amount of trigger calcium that enters the cell through the cell membrane. (Ryanodine is a potent negative inotropic plant alkaloid that interferes with the release of calcium through cardiac SR channels.)

C. Amount of Calcium Stored in the Sarcoplasmic Reticulum

The SR membrane contains a very efficient calcium uptake transporter known as the sarcoplasmic endoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA). This pump maintains free cytoplasmic calcium at very low levels during diastole by pumping calcium into the SR. SERCA is normally inhibited by phospholamban; phosphorylation of phospholamban by protein kinase A (activated, e.g., by cAMP) removes this inhibition. The amount of calcium sequestered in the SR is thus determined, in part, by the amount accessible to this transporter and the activity of the sympathetic nervous system. This in turn is dependent on the balance of calcium influx (primarily through the voltage-gated membrane L-type calcium channels) and calcium efflux, the amount removed from the cell (primarily via the sodium-calcium exchanger, a transporter in the cell membrane). The amount of Ca\(^{2+}\) released from the SR depends on the response of the RyR channels to trigger Ca\(^{2+}\).

D. Amount of Trigger Calcium

The amount of trigger calcium that enters the cell depends on the concentration of extracellular calcium, the availability of membrane calcium channels, and the duration of their opening. As described in Chapters 6 and 9, sympathomimetics cause an increase in calcium influx through an action on these channels. Conversely, the calcium channel blockers (see Chapter 12) reduce this influx and depress contractility.

E. Activity of the Sodium-Calcium Exchanger

This antiporter (NCX) uses the sodium gradient to move calcium against its concentration gradient from the cytoplasm to the extracellular space. Extracellular concentrations of these ions are much less labile than intracellular concentrations under physiologic conditions. The sodium-calcium exchanger’s ability to carry out this transport is thus strongly dependent on the intracellular concentrations of both ions, especially sodium.

F. Intracellular Sodium Concentration and Activity of Na\(^+/K^-\)ATPase

Na\(^+/K^-\)ATPase, by removing intracellular sodium, is the major determinant of sodium concentration in the cell. The sodium influx through voltage-gated channels, which occurs as a normal part of almost all cardiac action potentials, is another determinant; although the amount of sodium that enters with each action potential is much less than 1% of the total intracellular sodium. Na\(^+/K^-\)ATPase appears to be the primary target of digoxin and other cardiac glycosides.

hydralazine-nitrate therapy are the only agents in current use that actually prolong life in patients with chronic heart failure. These strategies are useful in both systolic and diastolic failure. Positive inotropic drugs, on the other hand, are helpful mainly in acute systolic failure. Cardiac glycosides also reduce symptoms in chronic systolic heart failure. In large clinical trials to date, other positive inotropic drugs have usually reduced survival in chronic failure or had no benefit, and their use is discouraged.

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FIGURE 13–1 Schematic diagram of a cardiac muscle sarcomere, with sites of action of several drugs that alter contractility. Na⁺/K⁺-ATPase, the sodium pump, is the site of action of cardiac glycosides. NCX is the sodium–calcium exchanger. Caᵥ-L is the voltage-gated, L-type calcium channel. SERCA (sarcoplasmic endoplasmic reticulum Ca²⁺-ATPase) is a calcium transporter ATPase that pumps calcium into the sarcoplasmic reticulum. CalS is calcium bound to calsequestrin, a high-capacity Ca²⁺-binding protein. RyR (ryanodine RyR2 receptor) is a calcium-activated calcium channel in the membrane of the SR that is triggered to release stored calcium. Z is the Z-line, which delimits the sarcomere. Calcium sensitizers act at the actin-tropomyosin-troponin complex where activator calcium brings about the contractile interaction of actin and myosin. Black arrows represent processes that initiate contraction or support basal tone. Green arrows represent processes that promote relaxation.
Pathophysiology of Heart Failure

Heart failure is a syndrome with many causes that may involve one or both ventricles. Cardiac output is usually below the normal range ("low-output" failure). Systolic dysfunction, with reduced cardiac output and significantly reduced ejection fraction (EF < 45%; normal > 60%), is typical of acute failure, especially that resulting from myocardial infarction. Diastolic dysfunction often occurs as a result of hypertrophy and stiffening of the myocardium, and although cardiac output is reduced, ejection fraction may be normal. Heart failure due to diastolic dysfunction does not usually respond optimally to positive inotropic drugs.

"High-output" failure is a rare form of heart failure. In this condition, the demands of the body are so great that even increased cardiac output is insufficient. High-output failure can result from hyperthyroidism, beriberi, anemia, and arteriovenous shunts. This form of failure responds poorly to the drugs discussed in this chapter and should be treated by correcting the underlying cause.

The primary signs and symptoms of all types of heart failure include tachycardia, decreased exercise tolerance, shortness of breath, and cardiomegaly. Peripheral and pulmonary edema (the congestion of congestive heart failure) are often but not always present. Decreased exercise tolerance with rapid muscular fatigue is the major direct consequence of diminished cardiac output. The other manifestations result from the attempts by the body to compensate for the intrinsic cardiac defect.

Neurohumoral (extrinsic) compensation involves two major mechanisms (previously presented in Figure 6–7)—the sympathetic nervous system and the renin-angiotensin-aldosterone hormonal response—plus several others. Some of the detrimental as well as beneficial features of these compensatory responses are illustrated in Figure 13–2. The baroreceptor reflex appears to be reset, with a lower sensitivity to arterial pressure, in patients with heart failure. As a result, baroreceptor sensory input to the vasomotor center is reduced even at normal pressures; sympathetic outflow is increased, and parasympathetic outflow is decreased. Increased sympathetic outflow causes tachycardia, increased cardiac contractility, and increased vascular tone. Vascular tone is further increased by angiotensin II and endothelin, a potent vasoconstrictor released by vascular endothelial cells. Vasoconstriction increases afterload, which further reduces ejection fraction and cardiac output. The result is a vicious cycle that is characteristic of heart failure (Figure 13–3). Neurohumoral antagonists and vasodilators reduce heart failure mortality by interrupting the cycle.

After a relatively short exposure to increased sympathetic drive, complex down-regulatory changes in the cardiac β1-adrenoceptor–G protein-effector system take place that result in diminished stimulatory effects. Beta2 receptors are not down-regulated and may develop increased coupling to the inositol 1,4,5-trisphosphate–diacylglycerol (IP₃-DAG) cascade. It has also been suggested that cardiac β₂ receptors (which do not appear to be down-regulated in failure) may mediate negative inotropic effects. Excessive β activation can lead to leakage of calcium from the sarcoplasmic reticulum via RyR channels and contributes to stiffening of the ventricles and arrhythmias. Prolonged β activation also increases caspases, the enzymes responsible for apoptosis. Increased angiotensin II production leads to increased aldosterone secretion (with sodium and water retention), to increased afterload, and to remodeling of both heart and vessels. Other hormones are released, including natriuretic peptide, endothelin, and vasopressin (see Chapter 17). Within the heart, failure-induced changes

![Figure 13–2](image-url) Some compensatory responses (orange boxes) that occur during congestive heart failure. In addition to the effects shown, sympathetic discharge facilitates renin release, and angiotensin II increases norepinephrine release by sympathetic nerve endings (dashed arrows).

![Figure 13–3](image-url) Vicious spiral of progression of heart failure. Decreased cardiac output (CO) activates production of neurohormones (NE, norepinephrine; AII, angiotensin II; ET, endothelin), which cause vasoconstriction and increased afterload. This further reduces ejection fraction (EF) and CO, and the cycle repeats. The downward spiral is continued until a new steady state is reached in which CO is lower and afterload is higher than is optimal for normal activity. Circled points 1, 2, and 3 represent points on the ventricular function curves depicted in Figure 13–4.
have been documented in calcium handling in the SR by SERCA and phospholamban; in transcription factors that lead to hypertrophy and fibrosis; in mitochondrial function, which is critical for energy production in the overworked heart; and in ion channels, especially potassium channels, which facilitate arrhythmogenesis, a primary cause of death in heart failure. Phosphorylation of RyR channels in the sarcoplasmic reticulum enhances and dephosphorylation reduces Ca\(^{2+}\) release; studies in animal models indicate that the enzyme primarily responsible for RyR dephosphorylation, protein phosphatase 1 (PP1), is up-regulated in heart failure. These cellular changes provide many potential targets for future drugs.

The most important intrinsic compensatory mechanism is **myocardial hypertrophy.** The increase in muscle mass helps maintain cardiac performance. However, after an initial beneficial effect, hypertrophy can lead to ischemic changes, impairment of diastolic filling, and alterations in ventricular geometry. **Remodeling** is the term applied to dilation (other than that due to passive stretch) and other slow structural changes that occur in the stressed myocardium. It may include proliferation of connective tissue cells as well as abnormal myocardial cells with some biochemical characteristics of fetal myocytes. Ultimately, myocytes in the failing heart die at an accelerated rate through apoptosis, leaving the remaining myocytes subject to even greater stress.

### Pathophysiology of Cardiac Performance

Cardiac performance is a function of four primary factors:

1. **Preload:** When some measure of left ventricular performance such as stroke volume or stroke work is plotted as a function of left ventricular filling pressure or end-diastolic fiber length, the resulting curve is termed the left ventricular function curve (Figure 13–4). The ascending limb (< 15 mm Hg filling pressure) represents the classic Frank-Starling relation described in physiology texts. Beyond approximately 15 mm Hg, there is a plateau of performance. Preloads greater than 20–25 mm Hg result in pulmonary congestion. As noted above, preload is usually increased in heart failure because of increased blood volume and venous tone. Because the function curve of the failing heart is lower, the plateau is reached at much lower values of stroke work or output. Increased fiber length or filling pressure increases oxygen demand in the myocardium, as described in Chapter 12. Reduction of high filling pressure is the goal of salt restriction and diuretic therapy in heart failure. Venodilator drugs (eg, nitroglycerin) also reduce preload by redistributing blood away from the chest into peripheral veins.

2. **Afterload:** Afterload is the resistance against which the heart must pump blood and is represented by aortic impedance and systemic vascular resistance. As noted in Figure 13–2, as cardiac output falls in chronic failure, a reflex increase in systemic vascular resistance occurs, mediated in part by increased sympathetic outflow and circulating catecholamines and in part by activation of the renin-angiotensin system. Endothelin, a potent vasoconstrictor peptide, is also involved. This sets the stage for the use of drugs that reduce arteriolar tone in heart failure.

3. **Contractility:** Heart muscle obtained by biopsy from patients with chronic low-output failure demonstrates a reduction in intrinsic contractility. As contractility decreases in the heart, there is a reduction in the velocity of muscle shortening, the rate of intraventricular pressure development (dP/dt), and the stroke output achieved (Figure 13–4). However, the heart is usually still capable of some increase in all of these measures of contractility in response to inotropic drugs.

4. **Heart rate:** The heart rate is a major determinant of cardiac output. As the intrinsic function of the heart decreases in failure and stroke volume diminishes, an increase in heart rate—through sympathetic activation of \(\beta\) adrenergceptors—is the first compensatory mechanism that comes into play to maintain cardiac output.

### BASIC PHARMACOLOGY OF DRUGS USED IN HEART FAILURE

Although digitalis is not the first drug and never the only drug used in heart failure, we begin our discussion with this group because other drugs used in this condition are discussed in more detail in other chapters.
DIGITALIS

Digitalis is the genus name for the family of plants that provide most of the medically useful cardiac glycosides, eg, digoxin. Such plants have been known for thousands of years but were used erratically and with variable success until 1785, when William Withering, an English physician and botanist, published a monograph describing the clinical effects of an extract of the purple foxglove plant (Digitalis purpurea, a major source of these agents).

Chemistry

All of the cardiac glycosides, or cardenolides—of which digoxin is the prototype—combine a steroid nucleus linked to a lactone ring at the 17’ position and a series of sugars at carbon 3 of the nucleus. Because they lack an easily ionizable group, their solubility is not pH-dependent. Digoxin is obtained from Digitalis lanata, the white foxglove, but many common plants (eg, oleander, lily of the valley, milkweed, and others) contain cardiac glycosides with similar properties.

Pharmacokinetics

Digoxin, the only cardiac glycoside used in the USA, is 65–80% absorbed after oral administration. Absorption of other glycosides varies from zero to nearly 100%. Once present in the blood, all cardiac glycosides are widely distributed to tissues, including the central nervous system (CNS).

Digoxin is not extensively metabolized in humans; almost two thirds is excreted unchanged by the kidneys. Its renal clearance is proportional to creatinine clearance, and the half-life is 36–40 hours in patients with normal renal function. Equations and nomograms are available for adjusting digoxin dosage in patients with renal impairment.

Pharmacodynamics

Digoxin has multiple direct and indirect cardiovascular effects, with both therapeutic and toxic consequences. In addition, it has undesirable effects on the CNS and gut.

At the molecular level, all therapeutically useful cardiac glycosides inhibit Na+/K+-ATPase, the membrane-bound transporter often called the sodium pump (Figure 13–1). Although several isoforms of this ATPase occur and have varying sensitivity to cardiac glycosides, they are highly conserved in evolution. Inhibition of this transporter over most of the dose range has been extensively documented in all tissues studied. It is probable that this inhibitory action is largely responsible for the therapeutic effect (positive inotropy) as well as a major portion of the toxicity of digitalis. Other molecular-level effects of digitalis have been studied in the heart and are discussed below. The fact that a receptor for cardiac glycosides exists on the sodium pump has prompted some investigators to propose that an endogenous digitalis-like steroid, possibly ouabain or marinobufagenin, must exist. Furthermore, additional functions of Na+/K+-ATPase have been postulated, involving apoptosis, cell growth, and differentiation, immunity, and carbohydrate metabolism. Indirect evidence for such endogenous digitalis-like activity has been inferred from clinical studies showing some protective effect of digoxin antibodies in preeclampsia.

A. Cardiac Effects

1. Mechanical effects—Cardiac glycosides increase contraction of the cardiac sarcomere by increasing the free calcium concentration in the vicinity of the contractile proteins during systole. The increase in calcium concentration is the result of a two-step process: first, an increase of intracellular sodium concentration because of Na+/K+-ATPase inhibition; and second, a relative reduction of calcium expulsion from the cell by the sodium-calcium exchanger (NCX in Figure 13–1) caused by the increase in intracellular sodium. The increased cytoplasmic calcium is sequestered by SERCA in the SR for later release. Other mechanisms have been proposed but are not well supported.

The net result of the action of therapeutic concentrations of a cardiac glycoside is a distinctive increase in cardiac contractility (Figure 13–5, bottom trace, panels A and B). In isolated myocardial preparations, the rate of development of tension and of relaxation are both increased, with little or no change in time to peak tension. This effect occurs in both normal and failing myocardium, but in the intact patient the responses are modified by cardiovascular reflexes and the pathophysiology of heart failure.

2. Electrical effects—The effects of digitalis on the electrical properties of the heart are a mixture of direct and autonomic actions. Direct actions on the membranes of cardiac cells follow a well-defined progression: an early, brief prolongation of the action potential, followed by shortening (especially the plateau phase). The decrease in action potential duration is probably the result of increased potassium conductance that is caused by increased intracellular calcium (see Chapter 14). All these effects can be observed at therapeutic concentrations in the absence of overt toxicity (Table 13–2).

At higher concentrations, resting membrane potential is reduced (made less negative) as a result of inhibition of the sodium pump and reduced intracellular potassium. As toxicity progresses, oscillatory depolarizing afterpotentials appear following normally evoked action potentials (Figure 13–5, panel C). The afterpotentials (also known as delayed after-depolarizations, DADs) are associated with overloading of the intracellular calcium stores and oscillations in the free intracellular calcium ion concentration. When afterpotentials reach threshold, they elicit action potentials.
(premature depolarizations, ectopic “beats”) that are coupled to the preceding normal action potentials. If afterpotentials in the Purkinje conducting system regularly reach threshold in this way, bigeminy will be recorded on the electrocardiogram (Figure 13–6). With further intoxication, each afterpotential-evoked action potential will itself elicit a suprathreshold afterpotential, and a self-sustaining tachycardia will be established. If allowed to progress, such a tachycardia may deteriorate into fibrillation; in the case of ventricular fibrillation, the arrhythmia will be rapidly fatal unless corrected.

Autonomic actions of cardiac glycosides on the heart involve both the parasympathetic and the sympathetic systems. At low therapeutic doses, cardioselective parasympathomimetic effects predominate. In fact, these atropine-blockable effects account for a significant portion of the early electrical effects of digitalis (Table 13–2). This action involves sensitization of the baroreceptors, central vagal stimulation, and facilitation of muscarinic transmission at the cardiac muscle cell. Because cholinergic innervation is much richer in the atria, these actions affect atrial and atrioventricular nodal function more than Purkinje or ventricular function. Some of the cholinomimetic effects are useful in the treatment of certain arrhythmias. At toxic levels, sympathetic outflow is increased by digitalis. This effect is not essential for typical digitalis toxicity but sensitizes the myocardium and exaggerates all the toxic effects of the drug.

The most common cardiac manifestations of digitalis toxicity include atrioventricular junctional rhythm, premature ventricular depolarizations, bigeminal rhythm, ventricular tachycardia, and second-degree atrioventricular blockade. However, it is claimed that digitalis can cause virtually any arrhythmia.

B. Effects on Other Organs
Cardiac glycosides affect all excitable tissues, including smooth muscle and the CNS. The gastrointestinal tract is the most common site of digitalis toxicity outside the heart. The effects include anorexia, nausea, vomiting, and diarrhea. This toxicity is caused in

![Figure 13–5](image-url)
but is available only in parenteral form. It has an elimination half-life of 3–6 hours, with 10–40% being excreted in the urine. An older congener, inamrinone, has been withdrawn in the USA.

**Pharmacodynamics**

The bipyridines increase myocardial contractility by increasing inward calcium flux in the heart during the action potential; they may also alter the intracellular movements of calcium by influencing the sarcoplasmic reticulum. In addition, they have an important vasodilating effect. Inhibition of phosphodiesterase results in an increase in cAMP and the increase in contractility and vasodilation.

The toxicity of inamrinone includes nausea and vomiting; arhythmias, thrombocytopenia, and liver enzyme changes have also been reported in a significant number of patients. As noted, this drug has been withdrawn. Milrinone appears less likely to cause bone marrow and liver toxicity, but it does cause arrhythmias. Milrinone is now used only intravenously and only for acute heart failure or severe exacerbation of chronic heart failure.

**BETA-ADRENOCEPTOR AGONISTS**

The general pharmacology of these agents is discussed in Chapter 9. The selective β₁ agonist that has been most widely used in patients with heart failure is dobutamine. This parenteral drug produces an increase in cardiac output together with a decrease in ventricular filling pressure. Some tachycardia and an increase in myocardial oxygen consumption have been reported. Therefore, the potential for producing angina or arrhythmias in patients with coronary artery disease is significant, as is the tachyphylaxis that accompanies the use of any β stimulant. Intermittent dobutamine infusion may benefit some patients with chronic heart failure.

Dopamine has also been used in acute heart failure and may be particularly helpful if there is a need to raise blood pressure.

**INVESTIGATIONAL POSITIVE INOTROPIC DRUGS**

Istaroxime is an investigational steroid derivative that increases contractility by inhibiting Na⁺/K⁺-ATPase (like cardiac glycosides) but in addition appears to facilitate sequestration of Ca²⁺ by the SR. The latter action may render the drug less arrhythmogenic than digitalis.

Levosimendan, a drug that sensitizes the troponin system to calcium, also appears to inhibit phosphodiesterase and to cause some vasodilation in addition to its inotropic effects. Some clinical trials suggest that this drug may be useful in patients with heart failure, and the drug has been approved in some countries (not the USA).

Omecamtiv mecarbil is an investigational parenteral agent that activates cardiac myosin and prolongs systole without increasing oxygen consumption of the heart. It has been shown to reduce signs of heart failure in animal models, and a small initial phase 2 clinical trial in patients with heart failure showed increased systolic
time and stroke volume and reduced heart rate and end-systolic and diastolic volumes. A larger trial in patients with acute heart failure was disappointing, but another trial in those with chronic failure is underway.

**DRUGS WITHOUT POSITIVE INOTROPIC EFFECTS USED IN HEART FAILURE**

These agents—not positive inotropic drugs—are the first-line therapies for chronic heart failure. The drugs most commonly used are diuretics, ACE inhibitors, angiotensin receptor antagonists, aldosterone antagonists, and β blockers (Table 13–1). In acute failure, diuretics and vasodilators play important roles.

**DIURETICS**

Diuretics, especially furosemide, are drugs of choice in heart failure and are discussed in detail in Chapter 15. They reduce salt and water retention, edema, and symptoms. They have no direct effect on cardiac contractility; their major mechanism of action in heart failure is to reduce venous pressure and ventricular preload. The reduction in cardiac size, which leads to improved pump efficiency, is of major importance in systolic failure. In heart failure associated with hypertension, the reduction in blood pressure also reduces afterload. Spironolactone and eplerenone, the aldosterone antagonist diuretics (see Chapter 15), have the additional benefit of decreasing morbidity and mortality in patients with severe heart failure who are also receiving ACE inhibitors and other standard therapy. One possible mechanism for this benefit lies in accumulating evidence that aldosterone may also cause myocardial and vascular fibrosis and baroreceptor dysfunction in addition to its renal effects.

**ANGIOTENSIN-CONVERTING ENZYME INHIBITORS, ANGIOTENSIN RECEPTOR BLOCKERS, & RELATED AGENTS**

ACE inhibitors such as captopril were introduced in Chapter 11 and are discussed again in Chapter 17. These versatile drugs reduce peripheral resistance and thereby reduce afterload; they also reduce salt and water retention (by reducing aldosterone secretion) and in that way reduce preload. The reduction in tissue angiotensin levels also reduces sympathetic activity through diminution of angiotensin’s presynaptic effects on norepinephrine release. Finally, these drugs reduce the long-term remodeling of the heart and vessels, an effect that may be responsible for the observed reduction in mortality and morbidity (see Clinical Pharmacology).

Angiotensin AT₁ receptor blockers such as losartan (see Chapters 11 and 17) appear to have similar but more limited beneficial effects. Angiotensin receptor blockers should be considered in patients intolerant of ACE inhibitors because of incessant cough. In some trials, candesartan was beneficial when added to an ACE inhibitor.

Aliskiren, a renin inhibitor recently approved for hypertension, is in clinical trials for heart failure.

**VASODILATORS**

Vasodilators are effective in acute heart failure because they provide a reduction in preload (through venodilation), or reduction in afterload (through arteriolar dilation), or both. Some evidence suggests that long-term use of hydralazine and isosorbide dinitrate can also reduce damaging remodeling of the heart.

A synthetic form of the endogenous peptide brain natriuretic peptide (BNP) is approved for use in acute (not chronic) cardiac failure as nesiritide. This recombinant product increases cGMP in smooth muscle cells and reduces venous and arteriolar tone in experimental preparations. It also causes diuresis. However, large trials with this drug have failed to show an improvement in mortality or rehospitalizations. The peptide has a short half-life of about 18 minutes and is administered as a bolus intravenous dose followed by continuous infusion. Excessive hypotension is the most common adverse effect. Reports of significant renal damage and deaths have resulted in extra warnings regarding this agent, and it should be used with great caution. A newer approach to modulation of the natriuretic peptide system is inhibition of the neutral endopeptidase enzyme, neprilysin, responsible for the degradation of BNP and atrial natriuretic peptide (ANP). A dual ARB and inhibitor of neprilysin (LCZ696, sacubitril) has shown efficacy in early phase 2 trials in both heart failure and hypertension.

Plasma concentrations of endogenous BNP rise in most patients with heart failure and are correlated with severity. Measurement of plasma BNP has become a useful diagnostic or prognostic test in some centers.

Related peptides include ANP and urodilatin, a similar peptide produced in the kidney. Carperitide and ularitide, respectively, are investigational synthetic analogs of these endogenous peptides and are in clinical trials (see Chapter 15). Bosentan and pazopanib, orally active competitive inhibitors of endothelin (see Chapter 17), have been shown to have some benefits in experimental animal models with heart failure, but results in human trials have been disappointing. Bosentan is approved for use in pulmonary hypertension. It has significant teratogenic and hepatotoxic effects.

Several newer agents are thought to stabilize the RyR channel and may reduce Ca²⁺ leak from the sarcoplasmic reticulum. They are currently denoted only by code numbers (eg, JTV519, S44121). This action, if confirmed to reduce diastolic stiffness, would be especially useful in diastolic failure with preserved ejection fraction.

**BETA-ADRENOCEPTOR BLOCKERS**

Most patients with chronic heart failure respond favorably to certain β blockers in spite of the fact that these drugs can precipitate acute decompensation of cardiac function (see Chapter 10).
Studies with bisoprolol, carvedilol, metoprolol, and nebivolol showed a reduction in mortality in patients with stable severe heart failure, but this effect was not observed with another β blocker, bucindolol. A full understanding of the beneficial action of β blockade is lacking, but suggested mechanisms include attenuation of the adverse effects of high concentrations of catecholamines (including apoptosis), up-regulation of β receptors, decreased heart rate, and reduced remodeling through inhibition of the mitogenic activity of catecholamines.

**CLINICAL PHARMACOLOGY OF DRUGS USED IN HEART FAILURE**

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of chronic heart failure specify four stages in the development of heart failure (Table 13–3). Patients in stage A are at high risk because of other disease but have no signs or symptoms of heart failure. Stage B patients have evidence of structural heart disease but no symptoms of heart failure. Stage C patients have structural heart disease and symptoms of failure, and symptoms are responsive to ordinary therapy. Stage D patients have heart failure refractory to ordinary therapy, and special interventions (resynchronization therapy, transplant) are required.

Once stage C is reached, the severity of heart failure is usually described according to a scale devised by the New York Heart Association. Class I failure is associated with no limitations on ordinary activities, and symptoms that occur only with greater than ordinary exercise. Class II is characterized by slight limitation of activities, and results in fatigue and palpitations with ordinary physical activity. Class III failure results in fatigue, shortness of breath, and tachycardia with less than ordinary physical activity, but no symptoms at rest. Class IV is associated with symptoms even when the patient is at rest.

**MANAGEMENT OF CHRONIC HEART FAILURE**

The major steps in the management of patients with chronic heart failure are outlined in Tables 13–3 and 13–4. Updates to the ACC/AHA guidelines suggest that treatment of patients at high risk (stages A and B) should be focused on control of hypertension, hyperlipidemia, and diabetes, if present. Once symptoms and signs of failure are present, stage C has been entered, and active treatment of failure must be initiated.

### TABLE 13–3 Classification and treatment of chronic heart failure.

<table>
<thead>
<tr>
<th>ACC/AHA Stage</th>
<th>NYHA Class</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Prefailure</td>
<td>No symptoms but risk factors present</td>
<td>Treat obesity, hypertension, diabetes, hyperlipidemia, etc</td>
</tr>
<tr>
<td>B</td>
<td>I</td>
<td>Symptoms with severe exercise</td>
<td>ACEI/ARB, β blocker, diuretic</td>
</tr>
<tr>
<td>C</td>
<td>II/III</td>
<td>Symptoms with marked (class II) or mild (class III) exercise</td>
<td>Add aldosterone antagonist, digoxin; CRT, hydralazine/nitrate</td>
</tr>
<tr>
<td>D</td>
<td>IV</td>
<td>Severe symptoms at rest</td>
<td>Transplant, LVAD</td>
</tr>
</tbody>
</table>

1. American College of Cardiology/American Heart Association classification.
2. New York Heart Association classification.
3. Risk factors include hypertension, myocardial infarct, diabetes.
4. For selected populations, eg, African Americans.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device.

### TABLE 13–4 Differences between systolic and diastolic heart failure.

<table>
<thead>
<tr>
<th>Variable or Therapy</th>
<th>Systolic Heart Failure</th>
<th>Diastolic Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Diuretics</td>
<td>↓ Symptoms; first-line therapy if edema present</td>
<td>Use with caution¹</td>
</tr>
<tr>
<td>ACEIs</td>
<td>↓ Mortality in chronic HF</td>
<td>May help to ↓ LVH</td>
</tr>
<tr>
<td>ARBs</td>
<td>↓ Mortality in chronic HF</td>
<td>May be beneficial</td>
</tr>
<tr>
<td>Aldosterone inhibitors</td>
<td>↓ Mortality in chronic HF</td>
<td>May be useful; currently in large RCT</td>
</tr>
<tr>
<td>Beta blockers²</td>
<td>↓ Mortality in chronic HF</td>
<td>Useful to ↓ HR, ↓ BP</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>No or small benefit³</td>
<td>Useful to ↓ HR, ↓ BP</td>
</tr>
<tr>
<td>Digoxin</td>
<td>May reduce symptoms</td>
<td>Little or no role</td>
</tr>
<tr>
<td>Nitrates</td>
<td>May be useful in acute HF⁴</td>
<td>Use with caution¹</td>
</tr>
<tr>
<td>PDE inhibitors</td>
<td>May be useful in acute HF</td>
<td>Very small study in chronic HF was positive</td>
</tr>
<tr>
<td>Positive inotropes</td>
<td>↓ Symptoms, hospitalizations</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

¹Avoid excessive reduction of filling pressures.
²Limited to certain β blockers (see text).
³Benefit, if any, may be due to BP reduction.
⁴Useful combined with hydralazine in selected patients, especially African Americans.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; HF, heart failure; HR, heart rate; LVH, left ventricular hypertrophy; PDE, phosphodiesterase; RCT, randomized controlled trial.
SODIUM REMOVAL

Sodium removal—by dietary salt restriction and a diuretic—is the mainstay in management of symptomatic heart failure, especially if edema is present. In very mild failure a thiazide diuretic may be tried, but a loop agent such as furosemide is usually required. Sodium loss causes secondary loss of potassium, which is particularly hazardous if the patient is to be given digitalis. Hypokalemia can be treated with potassium supplementation or through the addition of an ACE inhibitor or a potassium-sparing diuretic such as spironolactone. Spironolactone or eplerenone should probably be considered in all patients with moderate or severe heart failure, since both appear to reduce both morbidity and mortality.

ACE INHIBITORS & ANGIOTENSIN RECEPTOR BLOCKERS

In patients with left ventricular dysfunction but no edema, an ACE inhibitor should be the first drug used. Several large studies have shown clearly that ACE inhibitors are superior to both placebo and to vasodilators and must be considered, along with diuretics, as first-line therapy for chronic heart failure. However, ACE inhibitors cannot replace digoxin in patients already receiving the glycoside because patients withdrawn from digoxin deteriorate while on ACE inhibitor therapy.

By reducing preload and afterload in asymptomatic patients, ACE inhibitors (eg, enalapril) slow the progress of ventricular dilation and thus slow the downward spiral of heart failure. Consequently, ACE inhibitors are beneficial in all subsets of patients—from those who are asymptomatic to those in severe chronic failure. This benefit appears to be a class effect; that is, all ACE inhibitors appear to be effective.

The angiotensin II AT1 receptor blockers (ARBs, eg, losartan) produce beneficial hemodynamic effects similar to those of ACE inhibitors. However, large clinical trials suggest that angiotensin receptor blockers are best reserved for patients who cannot tolerate ACE inhibitors (usually because of cough).

VASODILATORS

Vasodilator drugs can be divided into selective arteriolar dilators, venous dilators, and drugs with nonselective vasodilating effects. The choice of agent should be based on the patient’s signs and symptoms and hemodynamic measurements. Thus, in patients with high filling pressures in whom the principal symptom is dyspnea, venous dilators such as long-acting nitrates will be most helpful in reducing filling pressures and the symptoms of pulmonary congestion. In patients in whom fatigue due to low left ventricular output is a primary symptom, an arteriolar dilator such as hydralazine may be helpful in increasing forward cardiac output. In most patients with severe chronic failure that responds poorly to other therapy, the problem usually involves both elevated filling pressures and reduced cardiac output. In these circumstances, dilation of both arterioles and veins is required.

In a trial in African-American patients already receiving ACE inhibitors, addition of hydralazine and isosorbide dinitrate reduced mortality. As a result, a fixed combination of these two agents has been made available as isosorbide dinitrate/hydralazine (BiDil), and this is currently recommended for use only in African Americans.

BETA BLOCKERS & ION CHANNEL BLOCKERS

Trials of β-blocker therapy in patients with heart failure are based on the hypothesis that excessive tachycardia and adverse effects of high catecholamine levels on the heart contribute to the downward course of heart failure. The results clearly indicate that such therapy is beneficial if initiated cautiously at low doses, even though acutely blocking the supportive effects of catecholamines can worsen heart failure. Several months of therapy may be required before improvement is noted; this usually consists of a slight rise in ejection fraction, slower heart rate, and reduction in symptoms. As noted above, not all β blockers have proved useful, but bisoprolol, carvedilol, metoprolol, and nebivolol have been shown to reduce mortality.

In contrast, the calcium-blocking drugs appear to have no role in the treatment of patients with heart failure. Their depressant effects on the heart may worsen heart failure. On the other hand, slowing of heart rate with ivabradine (an If blocker, see Chapter 12) may be of benefit.

DIGITALIS

Digoxin is indicated in patients with heart failure and atrial fibrillation. It is usually given only when diuretics and ACE inhibitors have failed to control symptoms. Only about 50% of patients with normal sinus rhythm (usually those with documented systolic dysfunction) will have relief of heart failure from digitalis. If the decision is made to use a cardiac glycoside, digoxin is the one chosen in most cases (and the only one available in the USA). When symptoms are mild, slow loading (digitalization) with 0.125–0.25 mg/d is safer and just as effective as the rapid method (0.5–0.75 mg every 8 hours for three doses, followed by 0.125–0.25 mg/d).

Determining the optimal level of digitalis effect may be difficult. Unfortunately, toxic effects may occur before the therapeutic end point is detected. Measurement of plasma digoxin levels is useful in patients who appear unusually resistant or sensitive; a level of 1 ng/mL or less is appropriate.

Because it has a moderate but persistent positive inotropic effect, digitalis can, in theory, reverse all the signs and symptoms of heart failure. Although the net effect of the drug on mortality is mixed, it reduces hospitalization and deaths from progressive heart failure at the expense of an increase in sudden death. It is important to note that the mortality rate is reduced in patients with serum digoxin concentrations of less than 0.9 ng/mL but increased in those with digoxin levels greater than 1.5 ng/mL.
Other Clinical Uses of Digitalis

Digitalis is useful in the management of atrial arrhythmias because of its cardioslective parasympathomimetic effects. In atrial flutter and fibrillation, the depressant effect of the drug on atrioventricular conduction helps control an excessively high ventricular rate. Digitalis has also been used in the control of paroxysmal atrial and atrioventricular nodal tachycardia. At present, calcium channel blockers and adenosine are preferred for this application. Digoxin is explicitly contraindicated in patients with Wolff-Parkinson-White syndrome and atrial fibrillation (see Chapter 14).

Toxicity

In spite of its limited benefits and recognized hazards, digitalis is still heavily used and toxicity is common. Therapy for toxicity manifested as visual changes or gastrointestinal disturbances generally requires no more than reducing the dose of the drug. If cardiac arrhythmia is present, more vigorous therapy may be necessary. Serum digitalis level and the electrocardiogram should always be monitored during therapy of significant digitalis toxicity. Electrolytes should be monitored and corrected if abnormal. Digitalis-induced arrhythmias are frequently made worse by cardioversion; this therapy should be reserved for ventricular fibrillation if the arrhythmia is digitalis-induced.

In severe digitalis intoxication, serum potassium will already be elevated at the time of diagnosis (because of potassium loss from the intracellular compartment of skeletal muscle and other tissues). Automaticity is usually depressed, and antiarrhythmic agents may cause cardiac arrest. Treatment should include prompt insertion of a temporary cardiac pacemaker and administration of digitalis antibodies (digoxin immune fab). These antibodies recognize cardiac glycosides from many plants in addition to digoxin. They are extremely useful in reversing severe intoxication with most glycosides. As noted previously, they may also be useful in eclampsia and preeclampsia.

CARDIAC RESYNCHRONIZATION & CARDIAC CONTRACTILITY MODULATION THERAPY

Patients with normal sinus rhythm and a wide QRS interval, eg, greater than 120 ms, have impaired synchronization of right and left ventricular contraction. Poor synchronization of ventricular contraction results in diminished cardiac output. Resynchronization, with left ventricular or biventricular pacing, has been shown to reduce mortality in patients with chronic heart failure who were already receiving optimal medical therapy.

Repeated application of a brief electric current through the myocardium during the QRS deflection of the electrocardiogram results in increased contractility, presumably by increasing Ca²⁺ release, in the intact heart. Preliminary clinical studies of this cardiac contractility modulation therapy are underway.

MANAGEMENT OF DIASTOLIC HEART FAILURE

Most clinical trials have been carried out in patients with systolic dysfunction, so the evidence regarding the superiority or inferiority of drugs in heart failure with preserved ejection fraction is meager. Most authorities support the use of the drug groups described above (Table 13–4), and the SENIORS 2009 study suggests that the β blocker nebivolol is effective in both systolic and diastolic failure. Control of hypertension is particularly important, and revascularization should be considered if coronary artery disease is present. Tachycardia limits filling time; therefore, brady-cardic drugs may be particularly useful, at least in theory.

MANAGEMENT OF ACUTE HEART FAILURE

Acute heart failure occurs frequently in patients with chronic failure. Such episodes are usually associated with increased exertion, emotion, excess salt intake, nonadherence to medical therapy, or increased metabolic demand occasioned by fever, anemia, etc. A particularly common and important cause of acute failure—with or without chronic failure—is acute myocardial infarction. Measurements of arterial pressure, cardiac output, stroke work index, and pulmonary capillary wedge pressure are particularly useful in patients with acute myocardial infarction and acute heart failure. Patients with acute myocardial infarction are often treated with emergency revascularization using either coronary angioplasty and a stent, or a thrombolytic agent. Even with revascularization, acute failure may develop in such patients.

Intravenous treatment is the rule in drug therapy of acute heart failure. Among diuretics, furosemide is the most commonly used. Dopamine or dobutamine are positive inotropic drugs with prompt onset and short durations of action; they are most useful in patients with failure complicated by severe hypotension. Levosimendan has been approved for use in acute failure in Europe, and noninferiority has been demonstrated against dobutamine. Vasodilators in use in patients with acute decompensation include nitroprusside, nitroglycerine, and nesiritide. Reduction in afterload often improves ejection fraction, but improved survival has not been documented. A small subset of patients in acute heart failure will have dilutional hyponatremia, presumably due to increased vasopressin activity. A V₁ₙ and V₂ receptor antagonist, conivaptan, is approved for parenteral treatment of euclidean hyponatremia. Several clinical trials have indicated that this drug and related V₂ antagonists (tolvaptan) may have a beneficial effect in some patients with acute heart failure and hyponatremia. Thus far, vasopressin antagonists do not seem to reduce mortality. Clinical trials are underway with the myosin activator, omecamtiv mecarbil.
### SUMMARY Drugs Used in Heart Failure

<table>
<thead>
<tr>
<th>Subclass, Drug</th>
<th>Mechanism of Action</th>
<th>Effects</th>
<th>Clinical Applications</th>
<th>Pharmacokinetics, Toxicities, Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIURETICS</strong></td>
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<tr>
<td>Furosemide</td>
<td>Loop diuretic: Decreases NaCl and KCl reabsorption in thick ascending limb of the loop of Henle in the nephron (see Chapter 15)</td>
<td>Increased excretion of salt and water • reduces cardiac preload and afterload • reduces pulmonary and peripheral edema</td>
<td>Acute and chronic heart failure • severe hypertension • edematous conditions</td>
<td>Oral and IV • duration 2–4 h • Toxicity: Hypovolemia, hypokalemia, orthostatic hypotension, ototoxicity, sulfonamide allergy</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Decreases NaCl reabsorption in the distal convoluted tubule</td>
<td>Same as furosemide, but much less efficacious</td>
<td>Mild chronic failure • mild-moderate hypertension • hypercalcemia • has not been shown to reduce mortality</td>
<td>Oral only • duration 10–12 h • Toxicity: Hyponatremia, hypokalemia, hyperglycemia, hyperuricemia, hyperlipidemia, sulfonamide allergy</td>
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<tr>
<td>Three other loop diuretics:</td>
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<td>Bumetanide and torsemide</td>
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<td>Ethacrynic acid</td>
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<tr>
<td>Many other thiazides:</td>
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<td>All basically similar to</td>
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<td>hydrochlorothiazide, differing</td>
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<td>only in pharmacokinetics</td>
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<tr>
<td><strong>ALDOSTERONE ANTAGONISTS</strong></td>
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<tr>
<td>Spironolactone</td>
<td>Blocks cytoplasmic aldosterone receptors in collecting tubules of nephron • possible membrane effect</td>
<td>Increased salt and water excretion • reduces remodeling</td>
<td>Chronic heart failure • aldosteronism (cirrhosis, adrenal tumor) • hypertension • has been shown to reduce mortality</td>
<td>Oral • duration 24–72 h (slow onset and offset) • Toxicity: Hyperkalemia, antiandrogen actions</td>
</tr>
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<td>Eplerenone: Similar to</td>
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<td>spironolactone; more selective</td>
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<td>antialdosterone effect; no</td>
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<td>significant antiandrogen</td>
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<td>action; has been shown to</td>
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<td>reduce mortality</td>
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<tr>
<td><strong>ANGIOTENSIN ANTAGONISTS</strong></td>
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<tr>
<td>Angiotensin-converting enzyme</td>
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<tr>
<td>(ACE) inhibitors:</td>
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<tr>
<td>Captopril</td>
<td>Inhibits ACE • reduces All formation by inhibiting conversion of AI to All</td>
<td>Arteriolar and venous dilation • reduces aldosterone secretion • reduces cardiac remodeling</td>
<td>Chronic heart failure • hypertension • diabetic renal disease • has been shown to reduce mortality</td>
<td>Oral • half-life 2–4 h but given in large doses so duration 12–24 h • Toxicity: Cough, hyperkalemia, angio-neurotic edema • Interactions: Additive with other angiotensin antagonists</td>
</tr>
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<tr>
<td>Angiotensin receptor blockers</td>
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<tr>
<td>(ARBs):</td>
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<tr>
<td>Losartan</td>
<td>Antagonize All effects at AT₇ receptors</td>
<td>Like ACE inhibitors</td>
<td>Like ACE inhibitors • used in patients intolerant to ACE inhibitors • has been shown to reduce mortality</td>
<td>Oral • duration 6–8 h • Toxicity: Hyperkalemia; angio-neurotic edema • Interactions: Additive with other angiotensin antagonists</td>
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<tr>
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<tr>
<td>Enalapril, many other ACE</td>
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<tr>
<td>inhibitors: Like captopril</td>
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<tr>
<td>Candesartan, many other ARBs:</td>
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<tr>
<td>Like losartan</td>
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<tr>
<td><strong>BETA BLOCKERS</strong></td>
<td></td>
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</tr>
<tr>
<td>Carvedilol</td>
<td>Competitively blocks β receptors (see Chapter 10)</td>
<td>Slows heart rate • reduces blood pressure • poorly understood effects</td>
<td>Chronic heart failure: To slow progression • reduce mortality in moderate and severe heart failure • many other indications in Chapter 10</td>
<td>Oral • duration 10–12 h • Toxicity: Bronchospasm, bradycardia, atrioventricular block, acute cardiac decompensation • see Chapter 10 for other toxicities and interactions</td>
</tr>
<tr>
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<tr>
<td>Metoprolol, bisoprolol, nebivolol: Select group of β blockers that have been shown to reduce heart failure mortality</td>
<td></td>
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</tr>
<tr>
<td><strong>CARDIAC GLYCOSIDE</strong></td>
<td></td>
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</tr>
<tr>
<td>Digoxin (other glycosides are</td>
<td>Na⁺/K⁺-ATPase inhibition results in reduced Ca²⁺ expulsion and increased Ca²⁺ stored in sarcoplasmic reticulum</td>
<td>Increases cardiac contractility • cardiac parasympathomimetic effect (slowed sinus heart rate, slowed atrioventricular conduc- tion)</td>
<td>Chronic symptomatic heart failure • rapid ventricular rate in atrial fibrillation • has not been shown to reduce mortality</td>
<td>Oral, parenteral • duration 36–40 h • Toxicity: Nausea, vomiting, diarrhea • cardiac arrhythmias</td>
</tr>
<tr>
<td>outside the USA)</td>
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</tbody>
</table>

(continued)
### Subclass, Drug

#### VASODILATORS

**Venodilators:**
- **Isosorbide dinitrate**
  - Releases nitric oxide (NO) • activates guanylyl cyclase (see Chapter 12)
  - Venodilation • reduces preload and ventricular stretch
  - Acute and chronic heart failure • angina
  - Oral • duration 4–6 h • Toxicity: Postural hypotension, tachycardia, headache • Interactions: Additive with other vasodilators and synergistic with phosphodiesterase type 5 inhibitors

**Arteriolar dilators:**
- **Hydralazine**
  - Probably increases NO synthesis in endothelium (see Chapter 11)
  - Reduces blood pressure and afterload • results in increased cardiac output
  - Hydralazine plus nitrates have reduced mortality
  - Oral • duration 8–12 h • Toxicity: Tachycardia, fluid retention, lupus-like syndrome

**Combined arteriolar and venodilator:**
- **Nitroprusside**
  - Releases NO spontaneously • activates guanylyl cyclase
  - Marked vasodilation • reduces preload and afterload
  - Acute cardiac decompensation • hypertensive emergencies (malignant hypertension)
  - IV only • duration 1–2 min • Toxicity: Excessive hypotension, thiocyanate and cyanide toxicity • Interactions: Additive with other vasodilators

#### BETA-ADRENOCEPTOR AGONISTS

- **Dobutamine**
  - Beta1-selective agonist • increases cAMP synthesis
  - Increases cardiac contractility, output
  - Acute decompensated heart failure • intermittent therapy in chronic failure reduces symptoms
  - IV only • duration a few minutes • Toxicity: Arrhythmias • Interactions: Additive with other sympathomimetics

- **Dopamine**
  - Dopamine receptor agonist • higher doses activate β and α adrenoceptors
  - Increases renal blood flow • higher doses increase cardiac force and blood pressure
  - Acute decompensated heart failure • shock
  - IV only • duration a few minutes • Toxicity: Arrhythmias • Interactions: Additive with sympathomimetics

#### BIPYRIDINES

- **Milrinone**
  - Phosphodiesterase type 3 inhibitor • decreases cAMP breakdown
  - Vasodilator; lower peripheral vascular resistance • also increases cardiac contractility
  - Acute decompensated heart failure • increases mortality in chronic failure
  - IV only • duration 3–6 h • Toxicity: Arrhythmias • Interactions: Additive with other arrhythmogenic agents

#### NATRIURETIC PEPTIDE

- **Nesiritide**
  - Activates BNP receptors, increases cGMP
  - Vasodilation • diuresis
  - Acute decompensated failure • has not been shown to reduce mortality
  - IV only • duration 18 minutes • Toxicity: Renal damage, hypotension, may increase mortality
The patient has a low ejection fraction with systolic heart failure. He was placed on a low-sodium diet and treated with a diuretic (furosemide, 40 mg twice daily). On this therapy, he was less short of breath on exertion and could also lie flat without dyspnea. An angiotensin-converting enzyme (ACE) inhibitor was added (enalapril, 20 mg twice daily), and over the next few weeks, he continued to feel better. Because of continued shortness of breath on exercise, digoxin at 0.25 mg/d was added with a further improvement in exercise tolerance. Addition of a β blocker and eplerenone is being considered.