a LANGE medical book

Katzung's Basic & Clinical Pharmacology

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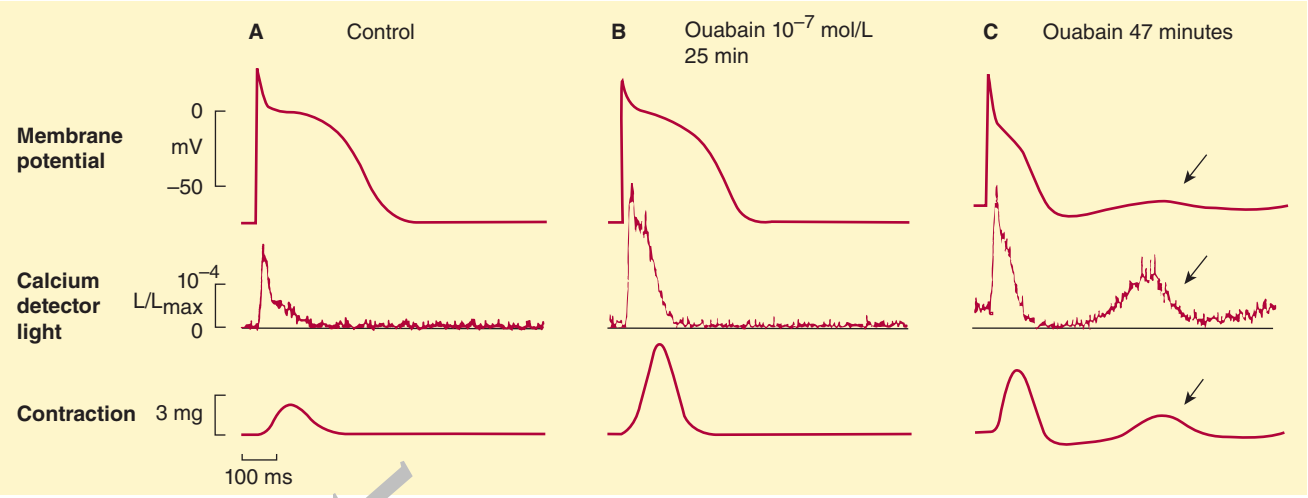

FIGURE 13–5 Effects of a cardiac glycoside, ouabain, on isolated cardiac tissue. The top tracing shows action potentials evoked during the control period (**A**), early in the "therapeutic" phase (**B**), and later, when toxicity is present (**C**). The middle tracing shows the light (L) emitted by the calcium-detecting protein aequorin (relative to the maximum possible, L_{max}) and is proportional to the free intracellular calcium concentration. The bottom tracing records the tension elicited by the action potentials. The early phase of ouabain action (**B**) shows a slight shortening of action potential and a marked increase in free intracellular calcium concentration and contractile tension. The toxic phase (**C**) is associated with depolarization of the resting potential, a marked shortening of the action potential, and the appearance of an oscillatory depolarization, calcium increment, and contraction (*arrows*). (Courtesy of P. Hess and H. Gil Wier.)

the action potential, followed by shortening (especially of 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

TABLE 13–2 Effects of digoxin on electrical properties of cardiac tissues.

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

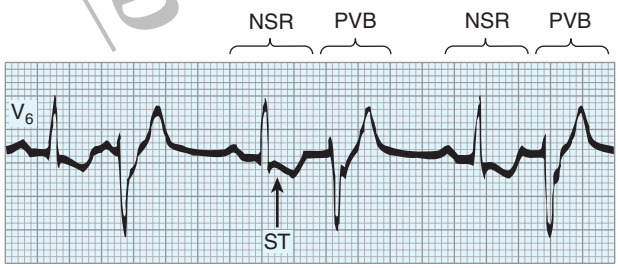

FIGURE 13–6 Electrocardiographic record showing digitalis-induced bigeminy. The complexes marked NSR are normal sinus rhythm beats; an inverted T wave and depressed ST segment are present. The complexes marked PVB are premature ventricular beats and are the electrocardiographic manifestations of depolarizations evoked by delayed oscillatory afterpotentials as shown in Figure 13–5. (Reproduced with permission from Goldman MJ: *Principles of Clinical Electrocardiography*, 12th ed. New York, NY: McGraw Hill; 1986.)

doses, cardioselective parasympathomimetic effects predominate. In fact, these atropine-blockable effects account for a significant portion of the early electrical effects of digitalis (see Table 13–2). This action involves sensitization of the baroreceptors, central vagal stimulation, and facilitation of muscarinic transmission at the nerve ending–myocyte synapse. 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 part by direct effects on the gastrointestinal tract and in part by CNS actions.

CNS effects include vagal and chemoreceptor trigger zone stimulation. Less often, disorientation and hallucinations—especially in the elderly—and visual disturbances are noted. The latter effects may include aberrations of color perception. Gynecomastia is a rare effect reported in men taking digitalis.

C. Interactions with Potassium, Calcium, and Magnesium

Potassium and digitalis interact in two ways. First, they inhibit each other's binding to Na^+/K^+-ATPase; therefore, hyperkalemia reduces the enzyme-inhibiting actions of cardiac glycosides, whereas hypokalemia facilitates these actions. Second, increased cardiac automaticity is inhibited by hyperkalemia (see Chapter 14). Moderately increased extracellular K^+ may therefore reduce the toxic effects of digitalis.

Calcium ion facilitates the toxic actions of cardiac glycosides by accelerating the overloading of intracellular calcium stores that appears to be responsible for digitalis-induced abnormal automaticity. Hypercalcemia therefore increases the risk of a digitalis-induced arrhythmia. The effects of magnesium ion are opposite to those of calcium. These interactions mandate careful evaluation of serum electrolytes in patients with digitalis-induced arrhythmias.

OTHER POSITIVE INOTROPIC DRUGS USED IN HEART FAILURE

Major efforts are being made to find safer positive inotropic agents because cardiac glycosides have an extremely narrow therapeutic window and may not decrease mortality in chronic heart failure. Positive inotropic drugs currently available are beneficial in some patients with acute HFrEF; they are rarely beneficial, and often deleterious, in chronic failure and HFpEF.

BIPYRIDINES

Milrinone is a bipyridine compound that inhibits phosphodiesterase isozyme 3 (PDE-3). It is active orally as well as parenterally 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,** is no longer available 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 SR. 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; arrhythmias, thrombocytopenia, and liver enzyme changes have also been reported in a significant number of patients. As noted, this drug is not available in the USA. 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. **Dobutamine** is the selective β_1 agonist that has been most widely used in patients with acute decompensated heart failure. This parenteral drug can produce an increase in cardiac output together with a decrease in ventricular filling pressure. Some tachycardia and an increase in myocardial oxygen consumption often occurs. 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 when 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 Ca^{2+} 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 but not in 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 clinical trials in patients with heart failure show increased systolic time and stroke volume and reduced heart rate and end-systolic and diastolic volumes. The drug is still under study.

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 (see Table 13–1). In acute failure, diuretics and vasodilators play primary roles. The SGLT2 inhibitors are recent additions to this group.

DIURETICS

Diuretics, especially **furosemide,** are drugs of first choice in heart failure and are discussed in detail in Chapter 15. They reduce salt and water retention, reduce edema through renal effects, and reduce heart failure symptoms. They have no direct effect on cardiac contractility; their major mechanism of hemodynamic action in heart failure is to reduce venous pressure and ventricular preload. The reduction of 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 (mineralocorticoid) steroidal 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. **Finerenone** is a nonsteroidal mineralocorticoid antagonist that may be less likely to induce hyperkalemia.

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 AT_1 receptor blockers such as **losartan** (see Chapters 11 and 17) appear to have similar beneficial effects. In combination with **sacubitril, valsartan** is now approved for HFrEF. Angiotensin receptor blockers should be considered in heart failure patients intolerant of ACE inhibitors because of incessant cough.

Aliskiren, a renin inhibitor approved for hypertension, was found to have no definitive benefit 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 vasodilation by **hydralazine** and **isosorbide dinitrate** can also reduce damaging remodeling of the heart. However, treatment of acute decompensation does not reliably slow progression of chronic failure in most patients.

Nesiritide, a synthetic form of the endogenous peptide brain natriuretic peptide (BNP), is approved for use in acute (not chronic) cardiac failure. This recombinant peptide increases cGMP in smooth muscle cells and reduces venous and arteriolar tone in experimental preparations. It also causes diuresis. However, large trials in patients with heart failure have failed to show a reduction 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. Similar mixed results have been obtained with **ularitide** and **serelaxin,** two other vasodilator peptides. A newer approach to modulation of the natriuretic peptide system is inhibition of the neutral endopeptidase enzyme, **neprilysin,** which is responsible for the degradation of BNP and atrial natriuretic peptide (ANP), as well as angiotensin II, bradykinin, and other peptides. **Sacubitril** is a prodrug that is metabolized to an active neprilysin inhibitor. A combination of valsartan plus sacubitril is approved for use in HFrEF. A recent large study (PIONEER-HF) confirmed that this drug combination is superior to enalapril in reducing high-sensitivity troponin-T levels and rehospitalization of patients with acute decompensated HFrEF. Unfortunately, HFpEF is not similarly improved by this combination drug.

Plasma concentrations of *endogenous* BNP rise in most patients with heart failure and are correlated with severity. Measurement of the plasma precursor NT-proBNP is a useful diagnostic or prognostic test and has been used as a surrogate marker in clinical trials.

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 **tezosentan,** 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 Ca^{2+} leak from the SR. They are currently denoted only by code numbers (eg, TRV027, 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 despite the fact that these drugs can *precipitate* acute cardiac failure (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 endogenous catecholamines (including apoptosis), up-regulation of β receptors, decreased heart rate, and reduced remodeling through inhibition of the mitogenic activity of catecholamines.

ANTIDIABETIC DRUGS

Drugs used in type 2 diabetes have been of concern because of the association of diabetes with cardiac events. Therefore, it is of interest that two groups of these agents benefit patients with heart failure *with or without* type 2 diabetes. The gliflozins, eg, **empagliflozin** and **dapagliflozin,** are SGLT2 inhibitors that increase renal sodium excretion as well as glucose excretion (see chapter 41). They have complex effects in the heart, including inhibition of the sodium-hydrogen exchanger (NHE) and a reduction of glucose utilization for ATP production. They also slow development of chronic kidney disease. These drugs have been shown to *reduce mortality and hospitalizations for heart failure* in patients with or without type 2 diabetes. This appears to be a class effect. Empagliflozin is approved for use in both HFrEF and HFpEF; dapagliflozin is currently approved for HFrEF. **Liraglutide** and **semaglutide,** GLP-1 agonists used in diabetes (see chapter 41) and obesity (see Chapter 16), have been shown to reduce deaths from cardiovascular causes as well as the rates of myocardial infarction, nonfatal stroke, and hospitalization for heart failure. They are approved for use in HFrEF.

OTHER DRUGS

Mavacamten, an inhibitor of myosin, is approved for use in obstructive hypertrophic cardiomyopathy. This condition reduces cardiac output and is often associated with symptoms of heart failure. Mavacamten (as well as beta blockers), by slowing the contraction of the ventricles, may improve ejection and increase cardiac output. Neuroregulatory proteins appear to have cardiac as well as neural effects. The neuregulin GGF2 protein **(cimaglermin)** has been shown to benefit cardiac function in several animal models of heart failure. **Vericiguat**, a soluble guanylate cyclase stimulator, has been shown to have a small but significant benefit on death and hospitalization rates. It is approved for oral use in acute decompensated failure.

CLINICAL PHARMACOLOGY OF DRUGS USED IN HEART FAILURE

Detailed guidelines are issued by US and European expert groups (see References). 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. Patients in stage C must often be hospitalized for acute decompensation, and after discharge, they often decompensate again, requiring rehospitalization. Stage D patients have heart failure refractory to ordinary therapy, and special interventions (eg, 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 failure 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 failure is associated with symptoms even when the patient is at rest.

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

ACC/AHA Stage[1]	NYHA Class[2]	Description	Management
A	Prefailure	No symptoms but risk factors present[3]	Treat obesity, hypertension, diabetes, hyperlipidemia, etc
B	I	Symptoms with severe exercise	Diuretic, ACEI/ARB, β blocker,
C	II/III	Symptoms with marked (class II) or mild (class III) exercise	Add SGLT2I, aldosterone antagonist, digoxin; CRT, ARNI, hydralazine/nitrate[4]
D	IV	Severe symptoms at rest	Maximal medical therapy, transplant, LVAD

[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.

ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor inhibitor plus neprilysin inhibitor; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device; NYHA, New York Heart Association; SGLT2I, sodium-glucose transporter-2 inhibitor.

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

Variable or Therapy	Systolic Heart Failure	Diastolic Heart Failure
Cardiac output	Decreased	Decreased
Ejection fraction	Decreased	Normal
Diuretics	↓ Symptoms; first-line therapy if edema present	Use with caution[1]
ACEIs	↓ Mortality in chronic HF	May help to ↓ LVH
ARBs, SGLT2I	↓ Mortality in chronic HF	May be beneficial
ARNI	↓ Symptoms and NT-proBNP	↓ Symptoms and NT-proBNP
Aldosterone inhibitors	↓ Mortality in chronic HF	May be useful
Beta blockers,[2] ivabradine	Beta blocker ↓ mortality in chronic HF, ivabradine reduces hospitalizations	Useful to ↓ HR, ↓ BP
Calcium channel blockers	No or small benefit[3]	Useful to ↓ HR, ↓ BP
Digoxin	May reduce symptoms	Little or no role
Nitrates	May be useful in acute HF[4]	Use with caution[1]
PDE inhibitors	May be useful in acute HF	Very small studies in chronic HF were positive
Positive inotropes	↓ Symptoms, hospitalizations	Not recommended

[1]Avoid excessive reduction of filling pressures.

[2]Limited to certain β blockers (see text).

[3]Benefit, if any, may be due to BP reduction.

[4]Useful combined with hydralazine in selected patients, especially African Americans.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor inhibitor plus neprilysin inhibitor; BP, blood pressure; HF, heart failure; HR, heart rate; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PDE, phosphodiesterase; SGLT2I, sodium-glucose transporter 2 inhibitor.

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, arrhythmias, hyperlipidemia, and diabetes, if present. Atrial fibrillation is increasingly common in older patients and correction of this arrhythmia can be very beneficial. Once symptoms and signs of failure are present, stage C has been entered, and active treatment of failure must be initiated.

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. The use of diuretics is discussed in greater detail in Chapter 15. 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. SGLT2 inhibitors also cause natriuresis, and their benefit in heart failure maybe due, in part, to this effect.

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 both to 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 AT_1 receptor blockers (ARBs, eg, **losartan**) produce beneficial hemodynamic effects similar to those of ACE inhibitors. However, large clinical trials suggest that when used alone, ARBs are best reserved for patients who cannot tolerate ACE inhibitors (usually because of cough). In contrast, the ARB valsartan combined with the neprilysin inhibitor sacubitril **(Entresto)** has additional benefit in HFrEF and is recommended in 2016 guidelines.

BETA BLOCKERS & ION CHANNEL BLOCKERS

Beta blocker therapy in patients with heart failure is 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 of clinical trials 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 failure. On the other hand, slowing of heart rate with **ivabradine** (an I_f blocker, see Chapter 12) may be of benefit.

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 resistance to output. In these circumstances, dilation of both arterioles and veins is required. A fixed combination of hydralazine and isosorbide dinitrate is available as isosorbide dinitrate/hydralazine **(BiDil),** and this has been recommended for use in Black persons. However, as noted above, vasodilator peptides have not been shown to reduce mortality or rehospitalizations for HFrEF.

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 therapeutic effects are detected. Measurement of plasma digoxin levels is useful in patients who appear unusually resistant or sensitive; a concentration of 1 ng/mL or less is appropriate; higher concentrations may be required in patients with atrial fibrillation.

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 sometimes useful in the management of atrial arrhythmias because of its cardioselective 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 both Wolff-Parkinson-White syndrome and atrial fibrillation (see Chapter 14).

Toxicity

Despite its limited benefits and recognized hazards, digitalis is still often used inappropriately, 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, potassium concentration, 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 electrical 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.** These antibodies **(digoxin immune fab)** 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. Because the immediate cause of death in severe heart failure is often an arrhythmia, a combined biventricular pacemaker/cardioverter-defibrillator is usually implanted.

Application of a brief electric current through the myocardium during each QRS deflection of the electrocardiogram results in increased contractility, presumably by increasing Ca^{2+} release, in