CHAPTER 16

Heart Failure

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KEY CONCEPTS

1. Heart failure is a clinical syndrome caused by the inability of the heart to pump sufficient blood to meet the metabolic needs of the body. Heart failure can result from any disorder that reduces ventricular filling (diastolic dysfunction) and/or myocardial contractility (systolic dysfunction). The leading causes of heart failure are coronary artery disease and hypertension. The primary manifestations of the syndrome are dyspnea, fatigue, and fluid retention.

2. Heart failure is a progressive disorder that begins with myocardial injury. In response to the injury, a number of compensatory responses are activated in an attempt to maintain adequate cardiac output, including activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS), resulting in vasoconstriction and sodium and water retention, as well as ventricular hypertrophy/remodeling. These compensatory mechanisms are responsible for the symptoms of heart failure and contribute to disease progression.

3. Our current understanding of heart failure pathophysiology is best described by the neurohormonal model. Activation of endogenous neurohormones, including norepinephrine, angiotensin II, aldosterone, vasopressin, and numerous proinflammatory cytokines, plays an important role in ventricular remodeling and the subsequent progression of heart failure. Importantly, pharmacotherapy targeted at antagonizing this neurohormonal activation has slowed the progression of heart failure and improved survival.

4. Most patients with symptomatic heart failure should be routinely treated with an angiotensin-converting enzyme (ACE) inhibitor, a β-blocker, and a diuretic. The benefits of these medications on slowing heart failure progression, reducing morbidity and mortality, and improving symptoms are clearly established. Patients should be treated with a diuretic if there is evidence of fluid retention. Treatment with digoxin may also be considered to improve symptoms and reduce hospitalizations.

5. In patients with heart failure, ACE inhibitors improve survival, slow disease progression, reduce hospitalizations, and improve quality of life. The doses for these agents should be targeted at those shown in clinical trials to improve survival. When ACE inhibitors are contraindicated or not tolerated, an angiotensin II receptor blocker or the combination of hydralazine and isosorbide dinitrate are reasonable alternatives. Patients with asymptomatic left ventricular dysfunction and/or a previous myocardial infarction (stage B of the American College of Cardiologists/American Heart Association [ACC/AHA] classification scheme) should also receive ACE inhibitors, with the goal of preventing symptomatic heart failure and reducing mortality.

6. The β-blockers carvedilol, metoprolol CR/XL, and bisoprolol prolong survival, decrease hospitalizations and the need for transplantation, and cause "reverse remodeling" of the left ventricle. These agents are recommended for all patients with a reduced left ventricular ejection fraction. Therapy must be instituted at low doses, with slow upward titration to the target dose.

7. Although chronic diuretic therapy frequently is used in heart failure patients, it is not mandatory. Diuretic therapy along with sodium restriction is required only in those patients with peripheral edema and/or pulmonary congestion. Many patients will need continued diuretic therapy to maintain euvolemia after fluid overload is resolved.

8. Digoxin does not improve survival in patients with heart failure but does provide symptomatic benefits. Digoxin doses should be adjusted to achieve plasma concentrations of 0.5 to 1.0 ng/mL; higher plasma concentrations are not associated with additional benefits but may be associated with increased risk of toxicity.

9. Aldosterone antagonism with low-dose spironolactone reduces mortality in patients with New York Heart Association (NYHA) classes III and IV heart failure and thus should be strongly considered in these patients, provided that potassium and renal function can be carefully monitored. Aldosterone antagonists should also be considered soon after myocardial infarction in patients with left ventricular dysfunction and either heart failure or diabetes.

10. The combination of hydralazine and nitrates improves the composite end point of mortality, hospitalizations for heart failure, and quality of life in African Americans who receive standard therapy. The addition of hydralazine and nitrates is reasonable in patients with persistent symptoms despite optimized therapy with an ACE inhibitor (or angiotensin receptor blocker) and β-blocker.

11. No therapy for acute decompensated heart failure studied to date has been shown conclusively to influence mortality. Treatment goals are directed toward restoration of systemic oxygen transport and tissue perfusion, relief of pulmonary edema, and limitation of further cardiac damage. Maximizing oral therapy and using combinations of short-acting intravenous medica-

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tions with different cardiovascular actions are often needed to optimize cardiac output, relieve pulmonary edema, and limit myocardial ischemia. Invasive hemodynamic monitoring may be required to provide immediate feedback on treatment efficacy and adverse effects.

⑫ Pharmacists should play an important role as part of a multidisciplinary team to optimize therapy in heart failure. The pharmacist should be responsible for such activities as optimizing regimens for heart failure drug therapy (namely, ensuring that appropriate drugs at appropriate doses are used), educating patients about the importance of adherence to their heart failure regimen (including pharmacologic and dietary interventions), screening for drugs that may exacerbate or worsen heart failure, and monitoring for adverse drug effects and drug interactions.

① ② Heart failure is a progressive clinical syndrome that can result from any disorder that impairs the ability of the ventricle to fill with or eject blood, thus rendering the heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body.[1] Heart failure is the final common pathway for numerous cardiac disorders including those affecting the pericardium, heart valves, and myocardium. Diseases that adversely affect ventricular diastole (filling), ventricular systole (contraction), or both can lead to heart failure. For many years it was believed that reduced myocardial contractility, or systolic dysfunction (i.e., reduced left ventricular ejection fraction [LVEF]), was the sole disturbance in cardiac function responsible for heart failure. However, it is now recognized that large numbers of patients with the heart failure syndrome have relatively normal systolic function (i.e., normal LVEF). This is now referred to as heart failure with preserved LVEF and is believed to be primarily caused by diastolic dysfunction of the heart.[1] Recent estimates suggest 20% to 60% of patients with heart failure have preserved LVEF with disturbances in relaxation (lusitropic) properties of the heart, or diastolic dysfunction.[2] However, regardless of the etiology of heart failure, the underlying pathophysiologic process and principal clinical manifestations (fatigue, dyspnea, and volume overload) are similar and appear to be independent of the initial cause. Historically, this disorder was commonly referred to as *congestive heart failure*; the preferred nomenclature is now *heart failure* because a patient can have the clinical syndrome of heart failure without having symptoms of congestion. This chapter focuses on treatment of patients with systolic dysfunction (with or without concurrent diastolic dysfunction), whereas Chap. 20 focuses on the treatment of heart failure with preserved LVEF (diastolic dysfunction).

EPIDEMIOLOGY

Heart failure is an epidemic public health problem in the United States. Approximately 5 million Americans have heart failure with an additional 550,000 cases diagnosed each year. Unlike most other cardiovascular diseases, the incidence, prevalence, and hospitalization rates associated with heart failure are increasing and are expected to continue to increase over the next few decades as the population ages. A large majority of patients with heart failure are elderly, with multiple comorbid conditions that influence morbidity and mortality.[3,4] The incidence of heart failure doubles with each decade of life and affects nearly 10% of individuals older than age 75 years. Heart failure is more common in men than in women until age 65 years, reflecting the greater incidence of coronary artery disease in men.[4] As such, improved survival of patients after myocardial infarction is a likely contributor to the increased incidence and prevalence of heart failure.[3] Recent results from the Framingham Heart Study showed that the incidence of heart failure in men has not changed over the last 40 years, but has decreased by approximately one-third in women.[5] These differences in heart failure incidence may be a result of sex-based differences in the cause of heart failure as myocardial infarction is the leading cause in men, whereas hypertension is the leading etiology in women.

Heart failure is the most common hospital discharge diagnosis in individuals older than age 65 years. Annual hospital discharges for heart failure now total more than 1 million, a 174% increase over the last two decades.[4] Heart failure also has a tremendous economic impact, which is expected to increase markedly as the baby boom generation ages. Current estimates suggest annual expenditures for heart failure of approximately $33 billion, with the majority of these costs spent on hospitalized patients.[4] Thus, heart failure is a major medical problem, with substantial economic impact that is expected to become even more significant as the population ages.

Despite prodigious advances in our understanding of the etiology, pathophysiology, and pharmacotherapy of heart failure, the prognosis for patients with this disorder remains grim. Although the mortality rates have declined over the last 50 years, the overall 5-year survival remains approximately 50% for all patients with a diagnosis of heart failure, with mortality increasing with symptom severity.[5] For heart failure patients younger than age 65 years, 80% of men and 70% of women will die within 8 years. Death is classified as sudden in approximately 40% of patients,[1,6] implicating serious ventricular arrhythmias as the underlying cause in many patients with heart failure. Factors affecting the prognosis of patients with heart failure include, but are not limited to, age, gender, LVEF, renal function, blood pressure, heart failure etiology, and drug or device therapy. Recent models incorporating these and other factors enable clinicians to develop reliable estimates of an individual patient's prognosis.[7]

ETIOLOGY

① ② Heart failure can result from any disorder that affects the ability of the heart to contract (systolic function) and/or relax (diastolic dysfunction); Table 16–1 lists the common causes of heart failure.[8] Heart failure with impaired systolic function (i.e., reduced LVEF) is the classic, more familiar form of the disorder, but current estimates suggest up to 50% of patients with heart failure have preserved left ventricular systolic function with presumed diastolic dysfunction.[2] In contrast to systolic heart failure that is usually caused by previous myocardial infarction (MI), patients with preserved LVEF typically are elderly, female, obese, and have hypertension, atrial fibrillation, or diabetes.[2] Recent data indicate that survival

TABLE 16-1 Causes of Heart Failure

Systolic dysfunction (decreased contractility)
- Reduction in muscle mass (e.g., myocardial infarction)
- Dilated cardiomyopathies
- Ventricular hypertrophy
  - Pressure overload (e.g., systemic or pulmonary hypertension, aortic or pulmonic valve stenosis)
  - Volume overload (e.g., valvular regurgitation, shunts, high-output states)

Diastolic dysfunction (restriction in ventricular filling)
- Increased ventricular stiffness
  - Ventricular hypertrophy (e.g., hypertrophic cardiomyopathy, other examples above)
  - Infiltrative myocardial diseases (e.g., amyloidosis, sarcoidosis, endomyocardial fibrosis)
  - Myocardial ischemia and infarction
- Mitral or tricuspid valve stenosis
- Pericardial disease (e.g., pericarditis, pericardial tamponade)

Data from Colucci W, Braunwald E. Pathophysiology of heart failure. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia: Elsevier Saunders, 2005:509–538.

is similar in patients with impaired or preserved LVEF.[2] Frequently, systolic and diastolic dysfunction coexist. The common cardiovascular diseases, such as MI and hypertension, can cause both systolic and diastolic dysfunction; thus many patients have heart failure as a result of reduced myocardial contractility and abnormal ventricular filling. Heart failure with preserved LVEF is discussed in Chap. 20.

1 Coronary artery disease is the most common cause of systolic heart failure, accounting for nearly 70% of cases.[3] Myocardial infarction leads to reduction in muscle mass as a consequence of death of affected myocardial cells. The degree to which contractility is impaired will depend on the size of the infarction. In an attempt to maintain cardiac output, the surviving myocardium undergoes a compensatory remodeling, thus beginning the maladaptive process that initiates the heart failure syndrome and leads to further injury to the heart. This is discussed in greater detail in Pathophysiology below. Myocardial ischemia and infarction also affect the diastolic properties of the heart by increasing ventricular stiffness and slowing ventricular relaxation. Thus, myocardial infarction frequently results in systolic and diastolic dysfunction.

Impaired systolic function is a cardinal feature of dilated cardiomyopathies. Although the cause of reduced contractility frequently is unknown, abnormalities such as interstitial fibrosis, cellular infiltrates, cellular hypertrophy, and myocardial cell degeneration are seen commonly on histologic examination. Genetic causes of dilated cardiomyopathies may also occur.[9]

Pressure or volume overload causes ventricular hypertrophy, which attempts to return contractility to a near-normal state. If the pressure or volume overload persists, the remodeling process results in alterations in the geometry of the hypertrophied myocardial cells and is accompanied by increased collagen deposition in the extracellular matrix. Thus, both systolic and diastolic function may be impaired.[8] Examples of pressure overload include systemic or pulmonary hypertension and aortic or pulmonic valve stenosis.

Hypertension remains an important cause and/or contributor to heart failure in many patients, particularly women, the elderly, and African Americans.[1] The role of hypertension should not be underestimated because hypertension is an important risk factor for ischemic heart disease and thus is also present in a high percentage of the patients with this disorder. Volume overload may occur in the presence of valvular regurgitation, shunts, or high-output states such as anemia or pregnancy. Table 16–1 lists less-common causes of diastolic dysfunction, which include infiltrative myocardial diseases, mitral or tricuspid valve stenosis, and pericardial disease.

Because ischemic heart disease and/or hypertension contribute so significantly to the development of heart failure in the majority of patients, it is important to emphasize that heart failure is a largely preventable disorder. Thus, control of blood pressure and appropriate management of other risk factors for cardiovascular disease (e.g., smoking cessation, treatment of lipid disorders, diabetes management, dietary modification) are important strategies for clinicians to implement to reduce their patients' risk of heart failure.

PATHOPHYSIOLOGY

NORMAL CARDIAC FUNCTION

To understand the pathophysiologic processes in heart failure, a basic understanding of normal cardiac function is necessary. *Cardiac output* (CO) is defined as the volume of blood ejected per unit time (L/min) and is the product of heart rate (HR) and stroke volume (SV):

$$CO = HR \times SV$$

The relationship between CO and mean arterial pressure (MAP) is:

$$MAP = CO \times \text{systemic vascular resistance (SVR)}$$

Heart rate is controlled by the autonomic nervous system. Stroke volume, or the volume of blood ejected during systole, depends on preload, afterload, and contractility.[8] As defined by the Frank-Starling mechanism, the ability of the heart to alter the force of contraction depends on changes in preload. As myocardial sarcomere length is stretched, the number of cross-bridges between thick and thin myofilaments increases, resulting in an increase in the force of contraction. The length of the sarcomere is determined primarily by the volume of blood in the ventricle; therefore, left ventricular end-diastolic volume is the primary determinant of preload. In normal hearts, the preload response is the primary compensatory mechanism such that a small increase in end-diastolic volume results in a large increase in cardiac output. Because of the relationship between pressure and volume in the heart, left ventricular end-diastolic pressure is often used in the clinical setting to estimate preload. The hemodynamic measurement used to estimate left ventricular end-diastolic pressure is the pulmonary artery occlusion pressure (PAOP). Afterload is a more complex physiologic concept that can be viewed pragmatically as the sum of forces preventing active forward ejection of blood by the ventricle. Major components of global ventricular afterload are ejection impedance, wall tension, and regional wall geometry. In patients with left ventricular systolic dysfunction, an inverse relationship exists between afterload (or SVR) and stroke volume such that increasing afterload causes a decrease in stroke volume (Fig. 16–1). Contractility is the intrinsic property of cardiac muscle describing fiber shortening and tension development.

COMPENSATORY MECHANISMS IN HEART FAILURE

2 Heart failure is a progressive disorder initiated by an event that impairs the ability of the heart to contract and/or relax. The index event may have an acute onset, as with myocardial infarction, or the onset may be slow, as with long-standing hypertension. Regardless of the index event, the decrease in the heart's pumping capacity results in the heart having to rely on compensatory responses to maintain an adequate cardiac output.[10] These compensatory responses include (a) tachycardia and increased contractility through sympathetic nervous system (SNS) activation, (b) the Frank-Starling mechanism, whereby an increase in preload results in an increase in stroke volume, (c) vasoconstriction, and (d) ventricular hypertrophy and remodeling. These compensatory responses are intended to be short-term responses to maintain circulatory homeostasis after acute reductions in blood pressure or renal perfusion. However, the

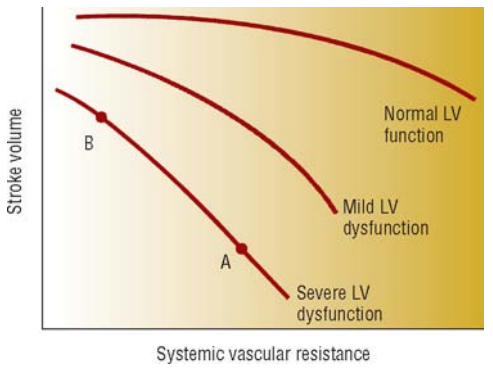

FIGURE 16-1. Relationship between stroke volume and systemic vascular resistance. In an individual with normal left ventricular (LV) function, increasing systemic vascular resistance has little effect on stroke volume. As the extent of LV dysfunction increases, the negative, inverse relationship between stroke volume and systemic vascular resistance becomes more important *(B to A)*.

TABLE 16-2 Beneficial and Detrimental Effects of the Compensatory Responses in Heart Failure

Compensatory Response	Beneficial Effects of Compensation	Detrimental Effects of Compensation
Increased preload (through Na^+ and water retention)	Optimize stroke volume via Frank-Starling mechanism	Pulmonary and systemic congestion and edema formation Increased MVO_2
Vasoconstriction	Maintain BP in face of reduced CO Shunt blood from nonessential organs to brain and heart	Increased MVO_2 Increased afterload decreases stroke volume and further activates the compensatory responses
Tachycardia and increased contractility (because of SNS activation)	Helps maintain CO	Increased MVO_2 Shortened diastolic filling time β_1-receptor downregulation, decreased receptor sensitivity Precipitation of ventricular arrhythmias Increased risk of myocardial cell death
Ventricular hypertrophy and remodeling	Helps maintain CO Reduces myocardial wall stress Decreases MVO_2	Diastolic dysfunction Systolic dysfunction Increased risk of myocardial cell death Increased risk of myocardial ischemia Increased arrhythmia risk Fibrosis

BP, blood pressure; CO, cardiac output; MVO_2, myocardial oxygen demand; SNS, sympathetic nervous system.

persistent decline in cardiac output in heart failure results in long-term activation of these compensatory responses resulting in the complex functional, structural, biochemical, and molecular changes important for the development and progression of heart failure. The beneficial and detrimental effects of these compensatory responses are described below and are summarized in Table 16–2.

Tachycardia and Increased Contractility

The change in heart rate and contractility that rapidly occurs in response to a drop in cardiac output is primarily a result of release of norepinephrine (NE) from adrenergic nerve terminals, although parasympathetic nervous system activity is also diminished. Cardiac output increases with heart rate until diastolic filling becomes compromised, which in the normal heart is at 170 to 200 beats per minute. Loss of atrial contribution to ventricular filling also can occur (atrial fibrillation, ventricular tachycardia), reducing ventricular performance even more. Because ionized calcium is sequestered into the sarcoplasmic reticulum and pumped out of the cardiac myocyte during diastole, shortened diastolic time also results in a higher average intracellular calcium concentration during diastole, increasing actin–myosin interaction, augmenting the active resistance to fibril stretch, and reducing lusitropy. Conversely, the higher average calcium concentration translates into greater filament interaction during systole, generating more tension.[8] In addition, polymorphisms in genes coding for adrenergic receptors (e.g., β_1 and α_{2c} receptors) appear to alter the response to endogenous NE and increase the risk for the development of heart failure.[11]

Increasing heart rate greatly increases myocardial oxygen demand. If ischemia is induced or worsened, both diastolic and systolic function may become impaired, and stroke volume can drop precipitously.

Fluid Retention and Increased Preload

Augmentation of preload is another compensatory response that is rapidly activated in response to decreased cardiac output. Renal perfusion in heart failure is reduced because of depressed cardiac output and redistribution of blood away from nonvital organs. The kidney interprets the reduced perfusion as an ineffective blood volume, resulting in activation of the renin–angiotensin–aldosterone system (RAAS) in an attempt to maintain blood pressure and increase renal sodium and water retention. Reduced renal perfusion and increased sympathetic tone also stimulate renin release from juxtaglomerular cells in the kidney. As shown in Fig. 16–2, renin is responsible for conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated via non–ACE-dependent pathways. Angiotensin II feeds back on the adrenal gland to stimulate aldosterone release, thereby providing an additional mechanism for sodium and water retention in the kidney. As intravascular volume increases secondary to sodium and water retention, left ventricular volume and pressure (preload) increase, sarcomeres are stretched, and the force of contraction is enhanced.[8] While the preload response is the primary compensatory mechanism in normal hearts, the chronically failing heart usually has exhausted its preload reserve.[8] As shown in Fig. 16–3, increases in preload will increase stroke volume only to a certain point. Once the flat portion of the curve is reached, further increases in preload will only lead to pulmonary or systemic congestion, a detrimental result.[8] Figure 16–3 also shows that the curve is flatter in patients with left ventricular dysfunction. Consequently, a given increase in preload in a patient with heart failure will produce a smaller increment in stroke volume than in an individual with normal ventricular function.

Vasoconstriction and Increased Afterload

Vasoconstriction occurs in patients with heart failure to help redistribute blood flow away from nonessential organs to coronary and cerebral circulations to support blood pressure, which may be reduced secondary to a decrease in cardiac output (mean arterial pressure = CO × SVR).[8] A number of neurohormones likely contribute to the vasoconstriction, including NE, angiotensin II, endothelin-1, and arginine vasopressin (AVP).[8] Vasoconstriction impedes forward ejection of blood from the ventricle, further depressing cardiac output and heightening the compensatory responses. Because the failing ventricle usually has exhausted its preload reserve (unless the patient is intravascularly depleted), its performance is exquisitely sensitive to changes in afterload (see Fig. 16–1). Thus, increases in afterload often potentiate a vicious cycle of continued worsening and downward spiraling of the heart failure state.

Ventricular Hypertrophy and Remodeling[8,10]

❸ Although the signs and symptoms of heart failure are closely associated with the items described above, the progression of heart failure appears to be independent of the patient's hemodynamic status. It is now recognized that ventricular hypertrophy and

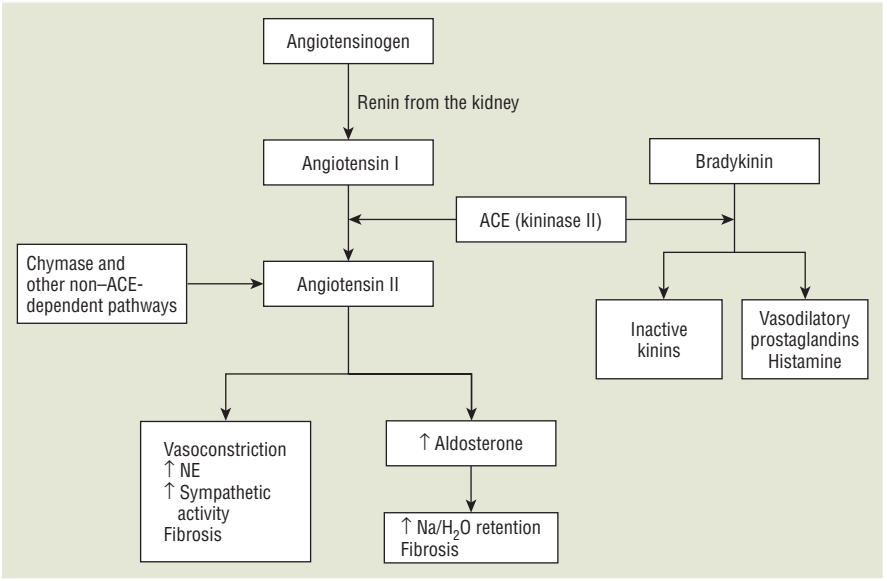

FIGURE 16-2. Physiology of the renin–angiotensin–aldosterone system. Renin produces angiotensin I from angiotensinogen. Angiotensin I is cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II has a number of physiologic actions that are detrimental in heart failure. Note that angiotensin II can be produced in a number of tissues, including the heart, independent of ACE activity. ACE is also responsible for the breakdown of bradykinin. Inhibition of ACE results in accumulation of bradykinin that, in turn, enhances the production of vasodilatory prostaglandins. (NE, norepinephrine.)

remodeling are key components in the pathogenesis of progressive myocardial failure. *Ventricular hypertrophy* is a term used to describe an increase in ventricular muscle mass. *Cardiac* or *ventricular remodeling* is a broader term describing changes in both myocardial cells and extracellular matrix that result in changes in the size, shape, structure, and function of the heart. Ventricular hypertrophy and remodeling can occur in association with any condition that causes myocardial injury including MI, cardiomyopathy, hypertension, and valvular heart disease.

Cardiac remodeling is a complex process that affects the heart at the molecular and cellular levels. Figure 16–4 shows key elements in the process. Collectively, these events result in progressive changes in myocardial structure and function such as cardiac hypertrophy, myocyte loss, and alterations in the extracellular matrix. The progression of the remodeling process leads to reductions in myocardial systolic and/or diastolic function that, in turn, result in further myocardial injury, perpetuating the remodeling process and the decline in ventricular dysfunction. Angiotensin II, NE, endothelin, aldosterone, vasopressin and numerous inflammatory cytokines, as well as substances under investigation, that are activated both systemically and locally in the heart play an important role in initiating the signal–transduction cascade responsible for ventricular remodeling. Although these mediators produce deleterious effects on the heart, their increased circulating and tissue concentrations also serve as an important reminder that heart failure is a systemic, as well as cardiac, disorder.

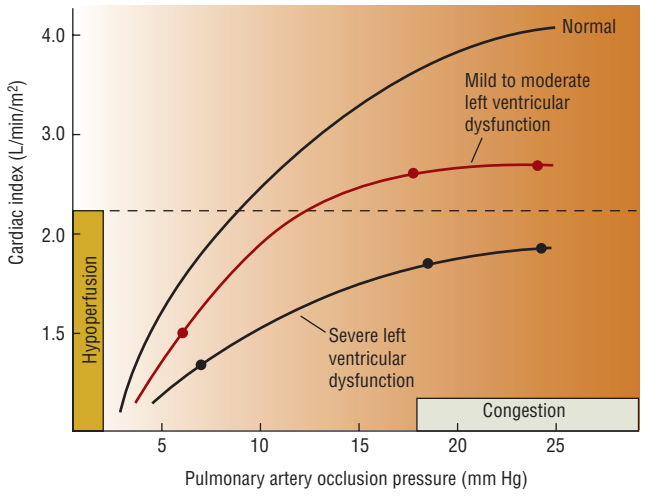

FIGURE 16-3. Relationship between cardiac output (shown as cardiac index which is cardiac output [CO]/body surface area [BSA]) and preload (shown as pulmonary artery occlusion pressure).

Pressure overload (and probably hormonal activation) associated with hypertension produces a concentric hypertrophy (increase in the ventricular wall thickness without chamber enlargement). Conversely, eccentric left ventricular hypertrophy (myocyte lengthening with increased chamber size with minimal increase in wall thickness) characterizes the hypertrophy seen in patients with systolic dysfunction or previous MI. As the myocytes undergo change, so do various components of the extracellular matrix. For example, there is evidence for collagen degradation, which may lead to slippage of myocytes, fibroblast proliferation, and increased fibrillar collagen synthesis, resulting in fibrosis and stiffening of the entire myocardium. Thus, a number of important ventricular changes that occur with remodeling include changes in the geometry of the heart from elliptical to spherical, increases in ventricular mass (from myocyte hypertrophy), and changes in ventricular composition (especially the extracellular matrix) and volumes, all of which likely contribute to the impairment of cardiac function. If the event that produces cardiac injury is acute (e.g., MI), the ventricular remodeling process begins immediately. However, it is the progressive nature of this process that results in continual worsening of the heart failure state, and thus is now the major focus for identification of therapeutic targets. In fact, it is believed that all the heart failure therapies that are associated with decreased mortality and/or slowing the progression of the disease produce this effect largely through their ability to slow or reverse the ventricular remodeling process, a process often referred to as *reverse remodeling*. Thus, although ventricular hypertrophy and remodeling may have some beneficial effects by helping maintain cardiac output, they also are believed to play an essential role in the progressive nature of heart failure.

THE NEUROHORMONAL MODEL OF HEART FAILURE AND THERAPEUTIC INSIGHTS IT PROVIDES[8,10]

❷ ❸ Over the years, several different paradigms have guided our understanding of the pathophysiology and treatment of heart failure. The early paradigm is often called the *cardiorenal model,* where the problem was viewed as excess sodium and water retention, and diuretic therapy was the main therapeutic approach. The next para-

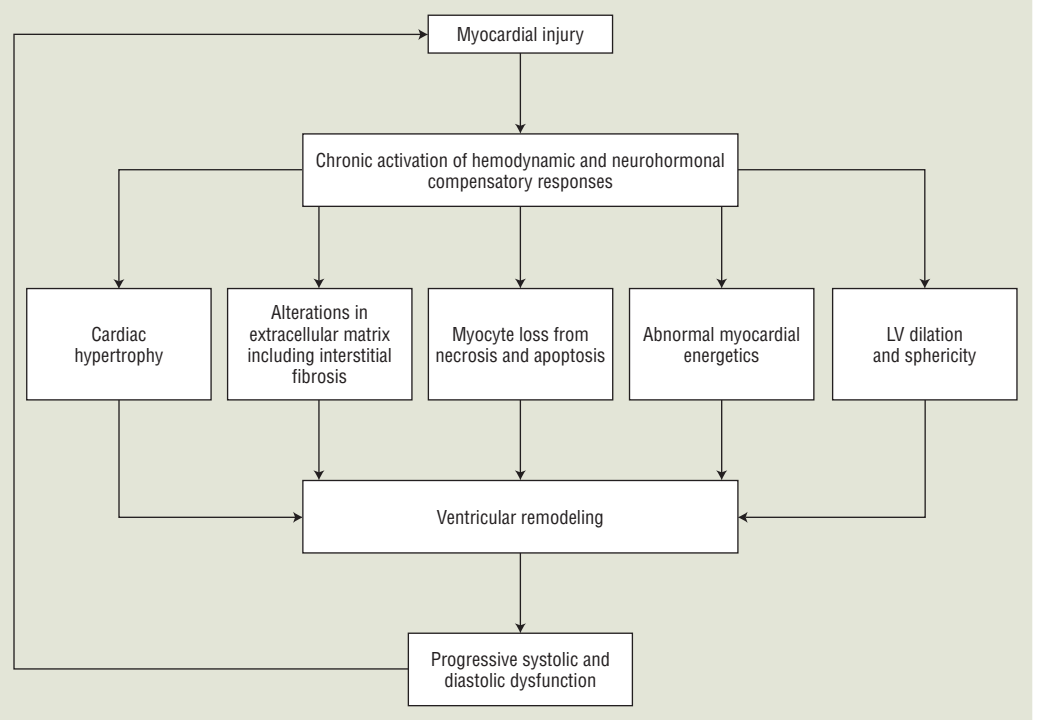

FIGURE 16-4. Key components of the pathophysiology of cardiac remodeling. Myocardial injury (e.g., myocardial infarction) results in the activation of a number of hemodynamic and neurohormonal compensatory responses in an attempt to maintain circulatory homeostasis. Chronic activation of the neurohormonal systems results in a cascade of events that affect the myocardium at the molecular and cellular levels. These events lead to the changes in ventricular size, shape, structure, and function known as ventricular remodeling. The alterations in ventricular function result in further deterioration in cardiac systolic and diastolic function which further promotes the remodeling process. (LV, left ventricle.)

digm was the *cardiocirculatory model,* which focused on impaired cardiac output (viewed as being a result of both reduced pumping capacity of the heart and systemic vasoconstriction). This paradigm focused on positive inotropes and, later, vasodilators as the primary therapies to overcome reductions in cardiac output. Although the therapeutic approaches associated with these paradigms provided some symptomatic benefits to patients with heart failure, they did little to slow progression of the disease. In fact, the detrimental effects of positive inotropic drugs on survival highlighted the inadequacy of the cardiocirculatory model to explain the progressive nature of heart failure. The first studies with ACE inhibitors were initiated with the thought that they might be effective because of their balanced (arterial and venous) vasodilation. Subsequent realization that ACE inhibitors were providing benefit beyond their vasodilating effects, followed by the positive results with β-adrenergic receptor blockers and aldosterone antagonists, has led to the current paradigm used to describe heart failure: the *neurohormonal model.* This model recognizes that there is an initiating event (e.g., MI, long-standing hypertension) that leads to decreased cardiac output and begins the "heart failure state," but then the problem moves beyond the heart, and it essentially becomes a systemic disease whose progression is mediated largely by neurohormones and autocrine/paracrine factors. Although the former paradigms still guide us to some extent in the symptomatic management of the disease (e.g., diuretics and digoxin), it is the latter paradigm that helps us understand disease progression and, more importantly, the ways to slow disease progression. In the sections that follow, important neurohormones and autocrine/paracrine factors are described with respect to their role in heart failure and its progression. The benefits of current and investigational drug therapies can be better understood through a solid understanding of the neurohormones they regulate/affect. Although the neurohormonal model provides a logical framework for our current understanding of heart failure progression and the role of various medications in attenuating this progression, it must be emphasized that this model does not completely explain heart failure progression. For example, drug therapies that target the neurohormonal perturbations in heart failure usually only slow the progressive nature of the disorder rather than completely stop it. Ongoing research will likely identify additional targets for drug therapy.

Angiotensin II[10]

Of the neurohormones and autocrine/paracrine factors that play an important role in the pathophysiology of heart failure, angiotensin II is probably the best understood. Although circulating angiotensin II produced from ACE activity is the most familiar route for generation of angiotensin II, recent evidence indicates that this hormone is synthesized directly in the myocardium through non–ACE-dependent pathways. This tissue production of angiotensin II also plays an important role in heart failure pathophysiology. Angiotensin II has multiple actions that contribute to its detrimental effects in heart failure. Angiotensin II increases systemic vascular resistance directly by promoting potent vasoconstriction and indirectly by causing release of AVP and endothelin-1. Angiotensin II also facilitates release of NE from adrenergic nerve terminals, heightening SNS activation. It promotes sodium retention through direct effects on the renal tubules and by stimulating aldosterone release. Its vasoconstriction of the efferent glomerular arteriole helps to maintain perfusion pressure in patients with severe heart failure or impaired renal function. Thus, in patients dependent on angiotensin II for maintenance of perfusion pressure, initiation of an ACE inhibitor or angiotensin receptor type I blocker (ARB) causes efferent arteriole vasodilation, decreased perfusion pressure, and decreased glomerular filtration. This explains the risk of transient impairment in renal function associated with initiation of ACE inhibitor or ARB therapy. Finally, angiotensin II, and many of the

neurohormones released in response to angiotensin II, play a central role in stimulating ventricular hypertrophy, remodeling, myocyte apoptosis (programmed cell death), oxidative stress, inflammation, and alterations in the extracellular matrix. Clinical data suggest that blocking angiotensin II-mediated effects contributes substantially to the prolonged survival of ACE inhibitor- and ARB-treated heart failure patients.[12,13] The favorable effects of ACE inhibitors and ARBs on hemodynamics, symptoms, quality of life, and survival in heart failure highlight the importance of angiotensin II in the pathophysiology of heart failure.

Norepinephrine[8,10]

Many of the detrimental effects of NE in heart failure are described above. It plays a central role in the tachycardia, vasoconstriction, and increased contractility observed in heart failure. Plasma NE concentrations are elevated in correlation with the degree of heart failure, and patients with the highest plasma NE concentrations have the poorest prognosis. In addition to the detrimental effects described, excessive SNS activation causes downregulation of β_1-receptors, with a subsequent loss of sensitivity to receptor stimulation. Evidence suggests that genetic variations in the β_1- and α_{2c}-receptors, which are targets for NE's actions, may modify the extent of receptor downregulation and increase the risk of heart failure.[11] Excess catecholamines increase the risk of arrhythmias and can cause myocardial cell loss by stimulating both necrosis and apoptosis. Finally, NE contributes to ventricular hypertrophy and remodeling. The detrimental effects of SNS activation are further highlighted by the clinical trials of chronic therapy with β-agonists, phosphodiesterase inhibitors, and other drugs that cause SNS activation, as they have been shown uniformly to increase mortality in heart failure. Conversely, β-blockers, ACE inhibitors, and digoxin all help to decrease SNS activation through various mechanisms, and are beneficial in heart failure. Thus, it is clear that NE plays a critical role in the pathophysiology of the heart failure state.

Aldosterone[14,15]

Aldosterone-mediated sodium retention and its key role in volume overload and edema has long been recognized as an important component of the heart failure syndrome. Circulating aldosterone is increased in heart failure as a consequence of stimulation of its synthesis and release from the adrenal cortex by angiotensin II and because of decreased hepatic clearance secondary to reduced hepatic perfusion. Although its enhancement of sodium retention is an important component of heart failure symptoms, recent studies indicate direct effects of aldosterone on the heart that may be even more important in heart failure pathophysiology. Chief among these is the ability of aldosterone to produce interstitial cardiac fibrosis through increased collagen deposition in the extracellular matrix of the heart. This cardiac fibrosis may decrease systolic function, and also impair diastolic function by increasing the stiffness of the myocardium. Current research shows that extraadrenal production of aldosterone in the heart, kidneys, and vascular smooth muscle also contributes to the progressive nature of heart failure through target organ fibrosis and vascular remodeling. Induction of a systemic proinflammatory state and increased oxidative stress are other important direct detrimental actions of aldosterone. Aldosterone also may increase the risk of ventricular arrhythmias through a number of mechanisms, including creation of reentrant circuits as a result of fibrosis, inhibition of cardiac NE reuptake, depletion of intracellular potassium and magnesium, and impairment of parasympathetic traffic. Recent studies demonstrate that the aldosterone antagonists spironolactone[16] and eplerenone[17] produce significant reductions in mortality in patients with heart failure, without appreciable effects on diuresis or hemodynamics, providing substantial evidence that the direct cardiac effects of aldosterone play an important role in heart failure pathophysiology.

Natriuretic Peptides[18]

The natriuretic peptide family has three members, atrial natriuretic peptide, B-type natriuretic peptide (BNP), and C-type natriuretic peptide. Atrial natriuretic peptide is stored mainly in the right atrium, whereas BNP is found primarily in the ventricles. Both are released in response to pressure or volume overload. C-type natriuretic peptide is found mainly in the brain and has very low plasma concentrations. Atrial natriuretic peptide and BNP plasma concentrations are elevated in patients with heart failure and are thought to balance the effects of the renin–angiotensin system by causing natriuresis, diuresis, vasodilation, decreased aldosterone release, decreased hypertrophy, and inhibition of the SNS and RAAS.

The development of easily performed commercial assays for BNP and the related biologically inactive peptide, N-terminal prohormone BNP, resulted in significant attention to the role of these peptides as a biomarker for prognostic, diagnostic, and therapeutic use. In patients with chronic heart failure, the degree of elevation in BNP levels is closely associated with increased mortality, risk of sudden death, symptoms, and hospital readmission. Current data indicate BNP is more sensitive than NE for predicting morbidity and mortality in heart failure patients. Accurate diagnosis of acute decompensated heart failure in acute care settings is often difficult because many of the symptoms (e.g., dyspnea) mimic those of other disorders, such as pulmonary disease or obesity. The best-established clinical application of BNP testing is in the urgent care setting where the BNP assay is useful when combined with clinical evaluation for discriminating dyspnea secondary to heart failure from other causes. The BNP assay may also be useful in the diagnosis of heart failure in the outpatient setting and used as a marker to guide titration of heart failure drug therapy. However, the usefulness of the assay in these situations remains uncertain and the results of ongoing studies may help clarify the role of BNP testing in these patients. Finally, administration of recombinant human BNP (nesiritide) for short-term management of acute heart failure resulted in hemodynamic and symptomatic improvement, further supporting the role of BNP in heart failure pathophysiology.

Arginine Vasopressin[19]

AVP is a pituitary peptide hormone that plays an important role in regulation of renal water and solute excretion. AVP secretion is directly linked to changes in plasma osmolality, thus attempting to maintain body fluid homeostasis. The physiologic effects of AVP are mediated through the V_{1a} and V_2 receptors. V_{1a} receptors are located in vascular smooth muscle and in myocytes where AVP stimulation results in vasoconstriction and increased cardiac contractility, respectively. V_2 receptors are located in the collecting duct of the kidney where AVP stimulation causes reabsorption of free water.

Plasma concentrations of AVP are elevated in patients with heart failure supporting current research that indicates AVP plays a role in the pathophysiology of heart failure. Important effects associated with increased circulating AVP concentrations include (a) increased renal free water reabsorption in the face of plasma hypoosmolality resulting in volume overload and hyponatremia; (b) increased arterial vasoconstriction which contributes to reduced cardiac output; and (c) stimulation of remodeling by cardiac hypertrophy and extracellular matrix collagen deposition.

Given the importance of AVP in heart failure, recent efforts have focused on the development of AVP antagonist drugs for treatment of acute and chronic heart failure. By blocking the AVP receptor, these agents primarily increase free water excretion (i.e., an "aquaretic" effect). The oral V_2 receptor antagonist tolvaptan increased serum sodium and urine output without affecting heart

rate, blood pressure, renal function, or other electrolytes in patients hospitalized for hyponatremia from various causes (hyponatremia due to heart failure in approximately 33% of patients).[20] In another clinical trial, the addition of oral tolvaptan to diuretic therapy in patients hospitalized for worsening heart failure had no effect on mortality or the composite end point of cardiovascular death or hospitalization for heart failure.[21] However, tolvaptan did produce short-term reductions in body weight, edema, and patient-assessed dyspnea without causing any serious adverse events.[22] These results suggest that AVP antagonists may be useful in the treatment of heart failure patients with volume overload. Unlike diuretics, they appear to reduce excess fluid volume without affecting hemodynamics, renal function, or electrolytes. Thus, these agents may offer a new therapeutic approach to currently available drug therapies.

Other Circulating Mediators[23]

In addition to neurohormones, several proinflammatory cytokines are under extensive investigation for their role in heart failure pathophysiology. Tumor necrosis factor-α (TNF-α), interleukin (IL)-6 -6), and IL-1β have all been shown to be elevated in heart failure, with a direct relationship between the degree of elevation and the severity of heart failure. Of these cytokines, TNF-α is best studied for its pathophysiologic role in heart failure. TNF-α produces multiple deleterious actions including negative inotropic effects, uncoupling α-adrenergic receptors from adenylyl cyclase (thus reducing β-receptor-mediated responses), increasing myocardial cell apoptosis, and stimulating remodeling via several mechanisms. Although these findings clearly implicate a role for TNF-α in the pathophysiology of heart failure, clinical trials evaluating anti–TNF-α therapies (e.g., etanercept and infliximab) have been disappointing, with no improvement in outcomes demonstrated.

The endothelin peptides are potent vasoconstrictors that may be involved in heart failure pathophysiology through a number of mechanisms. Endothelin-1, the best characterized of these peptides, is synthesized by endothelial and vascular smooth muscle cells with the release of endothelin-1 enhanced by NE, angiotensin II, and inflammatory cytokines. Like other peptides and hormones described earlier, endothelin-1 plasma concentrations are elevated in heart failure and are correlated directly with the severity of hemodynamic abnormality, symptoms, and mortality. Its arterial and venous constrictive effects increase preload and afterload, and its vasoconstriction of both efferent and afferent renal arterioles may decrease renal plasma flow and induce sodium retention. Endothelin-1 has direct cardiotoxic and arrhythmogenic effects and is a potent stimulator of cardiac myocyte hypertrophy. The putative role of endothelin in heart failure led to the development of a number of endothelin-receptor antagonists. Although these agents improved hemodynamics, no benefit on morbidity or mortality has been demonstrated and further clinical development is unlikely.

The role of inflammation and endothelial dysfunction has generated significant interest in the use of statins in patients with heart failure. In addition to lowering cholesterol and reducing the risk of death and other atherosclerotic vascular diseases, the proposed pleiotropic effects (e.g., antiinflammatory, improved endothelial function, promotion of angiogenesis) may be beneficial in heart failure.[24] Although some observational studies and short-term prospective clinical trials indicate beneficial effects, others have failed to demonstrate significant improvement with statin therapy. Ongoing trials to assess effects on mortality will help clarify the role of statin therapy.

FACTORS PRECIPITATING/EXACERBATING HEART FAILURE

Although significant advancements have been made in treatment, symptom exacerbations, to the point that hospitalization is required, are a common and growing problem in patients with heart failure. Hospitalization for heart failure exacerbation consumes large amounts of healthcare dollars and significantly impairs the patient's quality of life, thus there is great interest in identifying, and then remedying, factors that increase the risk of decompensation. In patients with heart failure, appropriate therapy can often maintain them in a "compensated" state, indicating that they are relatively symptom-free. However, there are many aggravating or precipitating factors that may cause a previously compensated patient to develop worsened symptoms necessitating hospitalization. Factors that may precipitate or exacerbate heart failure typically do so by one or more of the following mechanisms: (a) negative inotropic effects; (b) direct cardiotoxicity; or (c) increased sodium and/or water retention (Table 16–3). The resulting symptoms are typically those associated with volume overload, but in more severe cases hypoperfusion may also be present.

TABLE 16-3 Drugs That May Precipitate or Exacerbate Heart Failure

Negative inotropic effect
Antiarrhythmics (e.g., disopyramide, flecainide, propafenone, and others)
β-Blockers (e.g., propranolol, metoprolol, atenolol, and others)
Calcium channel blockers (e.g., verapamil, diltiazem)
Itraconazole
Terbinafine
Cardiotoxic
Doxorubicin
Daunomycin
Cyclophosphamide
Trastuzumab
Imatinib
Ethanol
Amphetamines (e.g., cocaine, methamphetamine)
Sodium and water retention
Nonsteroidal antiinflammatory drugs
Cyclooxygenase-2 inhibitors
Rosiglitazone and pioglitazone
Glucocorticoids
Androgens and estrogens
Salicylates (high dose)
Sodium-containing drugs (e.g., carbenicillin disodium, ticarcillin disodium)

Noncompliance with prescribed heart failure medications or with dietary recommendations (e.g., sodium intake and fluid restriction) are common causes of heart failure exacerbation.[25] For example, 43% of patients admitted with an acute decompensation of chronic heart failure were assessed as having dietary sodium excess, 34% had excess fluid intake (defined as >2.5 L/day), and approximately 24% had drug noncompliance that may have contributed to their decompensation (although not necessarily defined as the primary cause of decompensation).

Cardiac events may also precipitate heart failure exacerbations. Myocardial ischemia and infarction are potentially reversible causes that must be carefully considered because nearly 70% of heart failure patients have coronary artery disease. It should be noted that myocardial ischemia can either be a cause or consequence of heart failure decompensation. Revascularization should be considered in appropriate patients. Atrial fibrillation occurs in up to 30% of patients with heart failure, and is associated with increased morbidity and mortality.[26,27] Atrial fibrillation can exacerbate heart failure through rapid ventricular response and loss of atrial contribution to ventricular filling. Conversely, heart failure can precipitate atrial fibrillation by worsening atrial distension resulting from ventricular volume overload. Control of ventricular response, maintenance of sinus rhythm in appropriate patients, and prevention of thromboembolism are important elements in the treatment of heart failure patients with atrial fibrillation.

A number of noncardiac events may also be associated with heart failure decompensation. Pulmonary infections frequently cause worsening of heart failure. Many of these events would be preventable with more widespread use of the pneumococcal and influenza vaccines. Recent studies suggest that anemia occurs frequently in patients with heart failure and that it is an independent predictor of death and hospitalization for heart failure, regardless of left ventricular systolic function.[28] The exact cause of anemia in heart failure patients is uncertain but likely involves reduced response to erythropoietin, the presence of inhibitors to hematopoiesis, and/or impaired iron supply. Correction of anemia with erythropoietin analogs is associated with improved symptoms and exercise capacity but some have expressed concern that raising hemoglobin concentrations may increase the risk of thromboembolism or other cardiovascular events. Therefore, the results of ongoing clinical trials evaluating survival are needed to determine the role of this therapy in heart failure.

12 What should be evident is that many of the precipitating factors are preventable, particularly through appropriate pharmacist intervention. Specifically, patient education and counseling by a pharmacist should help to decrease the most common reason for heart failure exacerbation: noncompliance with dietary sodium and water restrictions, drug therapy, or both. Pharmacists also should be able to identify and address inadequate heart failure therapy, poorly controlled hypertension, and administration of drugs that may worsen heart failure (see Table 16–3). Use of medications such as antiarrhythmic agents and selected calcium channel blockers are important precipitants of exacerbations. It should be noted that the cyclooxygenase-2 (COX-2) inhibitor celecoxib and nonsteroidal antiinflammatory drugs (NSAIDs) have similar effects on renal function.[29] Thus, both NSAIDs and COX-2 inhibitors should be used judiciously in heart failure patients. The thiazolidinedione hypoglycemic drugs, rosiglitazone and pioglitazone, are associated with the development of weight gain and edema that may exacerbate heart failure. Current guidelines indicate these agents should not be used in patients with New York Heart Association (NYHA) class III or IV heart failure and recent evidence suggests rosiglitazone may increase the risk of myocardial infarction.[1,30,31] It can be argued that heart failure exacerbations caused by noncompliance, inadequate/inappropriate drug therapy, and poorly controlled hypertension are all preventable and amenable to pharmacist intervention. Thus the value of the pharmacist's role in careful and repeated education of patients and in monitoring of the drug regimen should not be underestimated. Attention to these factors may make an important contribution to reducing the risk of hospitalization and improving the patient's quality of life.

CLINICAL PRESENTATION[32]

SIGNS AND SYMPTOMS

2 The primary manifestations of heart failure are dyspnea and fatigue, which lead to exercise intolerance, and fluid overload, that can result in pulmonary congestion and peripheral edema. The presence of these signs and symptoms may vary considerably from patient to patient, such that some patients have dyspnea but no signs of fluid retention whereas others may have marked volume overload with few complaints of dyspnea or fatigue. However, many patients may have both dyspnea and volume overload. Clinicians should remember that symptom severity often does not correlate with the degree of left ventricle dysfunction. Patients with a low LVEF (less than 20% to 25%) may be asymptomatic, whereas patients with preserved LVEF may have significant symptoms. It is also important to note that symptoms can vary considerably over time in a given patient. Historically, signs and symptoms are classified as being a result of left ventricular (pulmonary congestion) or right ventricular failure (systemic congestion). Although most patients initially have left ventricular failure, the ventricles share a septal wall, and because left ventricular failure increases the workload of the right ventricle, both ventricles eventually fail and contribute to the heart failure syndrome. Because of the complex nature of this syndrome, it has become exceedingly more difficult to attribute a specific sign or symptom as caused by either right or left ventricular failure. Therefore, the numerous signs and symptoms associated with this disorder are collectively attributed to heart failure, rather than due to dysfunction of a specific ventricle.

CLINICAL PRESENTATION OF HEART FAILURE

General

- Patient presentation may range from asymptomatic to cardiogenic shock

Symptoms

- Dyspnea, particularly on exertion
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Exercise intolerance
- Tachypnea
- Cough
- Fatigue
- Nocturia
- Hemoptysis
- Abdominal pain
- Anorexia
- Nausea
- Bloating
- Poor appetite, early satiety
- Ascites
- Mental status changes

Signs

- Pulmonary rales
- Pulmonary edema
- S_3 gallop
- Cool extremities
- Pleural effusion
- Cheyne-Stokes respiration
- Tachycardia
- Narrow pulse pressure
- Cardiomegaly
- Peripheral edema
- Jugular venous distension
- Hepatojugular reflux
- Hepatomegaly

Laboratory Tests

- BNP >100 pg/mL
- Electrocardiogram may be normal or it could show numerous abnormalities including acute ST-T–wave changes from myocardial ischemia, atrial fibrillation, bradycardia, left ventricular hypertrophy
- Serum creatinine may be increased because of hypoperfusion. Preexisting renal dysfunction can contribute to volume overload.

- Complete blood count useful to determine if heart failure is a result of reduced oxygen-carrying capacity
- Chest radiography is useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions
- Echocardiogram assesses left ventricle size, valve function, pericardial effusion, wall motion abnormalities, and ejection fraction
- Hyponatremia, serum sodium <130 mEq/L, is associated with reduced survival and may indicate worsening volume overload and/or disease progression

Pulmonary congestion arises as the left ventricle fails and is unable to accept and eject the increased blood volume that is delivered to it. Consequently, pulmonary venous and capillary pressures rise, leading to interstitial and bronchial edema, increased airway resistance, and dyspnea. The associated signs and symptoms may include (a) dyspnea (with or without exertion), (b) orthopnea, (c) paroxysmal nocturnal dyspnea, and (d) pulmonary edema. Exertional dyspnea occurs when there is a reduction in the level of exertion that causes breathlessness. This is typically described as more breathlessness than was associated previously with a specific activity (e.g., vacuuming, stair climbing). As heart failure progresses, many patients eventually have dyspnea at rest.

Orthopnea is dyspnea that occurs with assumption of the supine position. It occurs within minutes of recumbency and is a result of reduced pooling of blood in the lower extremities and abdomen. Orthopnea is relieved almost immediately by sitting upright and typically is prevented by elevating the head with pillows. An increase in the number of pillows required to prevent orthopnea (e.g., a change from "two-pillow" to "three-pillow" orthopnea) suggests worsening heart failure. Attacks of paroxysmal nocturnal dyspnea typically occur after 2 to 4 hours of sleep; the patient awakens from sleep with a sense of suffocation. The attacks are caused by severe pulmonary and bronchial congestion, leading to shortness of breath and wheezing. The reasons these attacks occur at night are unclear but may include (a) reduced pooling of blood in the lower extremities and abdomen (as with orthopnea), (b) slow resorption of interstitial fluid from sites of dependent edema, (c) normal reduction in sympathetic activity that occurs with sleep (e.g., less support for the failing ventricle), and (d) normal depression in respiratory drive that occurs with sleep.

Rales (crackling sounds heard on auscultation) are present in the lung bases as a result of transudation of fluid into alveoli. The rales typically are bibasilar, but if heard unilaterally, they are usually right-sided. Rales are not present in most patients with chronic heart failure even though there is volume overload. This is thought to be a consequence of a compensatory increase in lymphatic drainage. Detection of rales is usually indicative of a rapid onset of worsening heart failure rather than the amount of excess fluid volume. A third heart sound, or S_3 gallop, is heard frequently in patients with left ventricular failure and may be caused by elevated atrial pressure and altered distensibility of the ventricle.

Pulmonary edema is the most severe form of pulmonary congestion, and is caused by accumulation of fluid in the interstitial spaces and alveoli. In heart failure patients, it is the result of increased pulmonary venous pressure. The patient experiences extreme breathlessness and anxiety and may cough pink, frothy sputum. Pulmonary edema can be terrifying for the patient, causing a feeling of suffocation or drowning. Patients with pulmonary edema may also report any of the above mentioned signs or symptoms of pulmonary congestion.

Systemic congestion is associated with a number of signs and symptoms. Jugular venous distension (JVD) is the simplest and most reliable sign of fluid overload. Examination of the right internal jugular vein with the patient at a 45° angle is the preferred method for assessing JVD. The presence of JVD more than 4 cm above the sternal angle suggests systemic venous congestion. In patients with mild systemic congestion, JVD may be absent at rest, but application of pressure to the abdomen will cause an elevation of JVD (hepatojugular reflux).

Peripheral edema is a cardinal finding in heart failure. Edema usually occurs in dependent parts of the body, and thus is seen as ankle or pedal edema in ambulatory patients, although it may be manifested as sacral edema in bedridden patients. Adults typically have a 10-lb fluid weight gain before trace peripheral edema is evident; therefore, patients with acute decompensated heart failure may have no clinical evidence of systemic congestion except weight gain. Consequently, body weight is the best short-term end point for evaluating fluid status. Nonfluid weight gain or loss of muscle mass as a result of cardiac cachexia are potential confounders for long-term use of weight as a marker for fluid status. Ascites is another common sign of systemic congestion.

Heart failure patients may exhibit signs and symptoms of low cardiac output alone or in addition to volume overload. The primary complaint associated with such poor perfusion is fatigue. Patients may also complain of poor appetite or early satiety because of limited perfusion of the gastrointestinal tract. Conversely, patients with such gastrointestinal complaints may simply be experiencing gut edema. More subjective measures of low cardiac output include worsening renal function, cool extremities, and narrow pulse pressure.

DIAGNOSIS[1]

No single test is available to confirm the diagnosis of heart failure. Because the syndrome of heart failure can be caused or worsened by multiple cardiac and noncardiac disorders, accurate diagnosis is essential for development of therapeutic strategies. Heart failure is often initially suspected in a patient based on their symptoms. These will often include dyspnea, exercise intolerance, fatigue, and/or fluid retention. However, it must be emphasized that signs and symptoms lack sensitivity for diagnosing heart failure since these symptoms are frequently found with many other disorders. Even in patients with known heart failure, there is poor correlation between the presence or severity of symptoms and hemodynamic abnormality.

A complete history and physical examination targeted at identifying cardiac or noncardiac disorders or behaviors that may cause or hasten heart failure development or progression are essential in the initial evaluation of a symptomatic patient. A careful medication history should also be obtained with a focus on use of ethanol, tobacco, illicit drugs (e.g., cocaine or methamphetamine), vitamins and supplements (including herbal or "natural" supplements), NSAIDs, and antineoplastic agents (anthracyclines, cyclophosphamide, trastuzumab, imatinib). Particular attention should be paid to cardiovascular risk factors and to other disorders that can cause or exacerbate heart failure. Because coronary artery disease is the cause of heart failure in nearly 70% of patients, careful attention and evaluation of the possibility of coronary disease is essential, especially in men. If coronary artery disease is detected, appropriate revascularization procedures may then be considered. The patient's volume status should be documented by assessing the body weight, JVD, and presence or absence of pulmonary congestion and peripheral edema. Laboratory testing may assist in identification of disorders that cause or worsen heart failure. The initial evaluation should include a complete blood count, serum electrolytes (including calcium and magnesium), tests of renal and hepatic function, urinalysis, lipid profile, hemoglobin A_{1c}, thyroid function tests, chest radiography, and 12-lead electrocardiogram (ECG). There are no specific ECG findings associated with heart failure, but findings may help detect coronary artery disease or conduction abnormali-

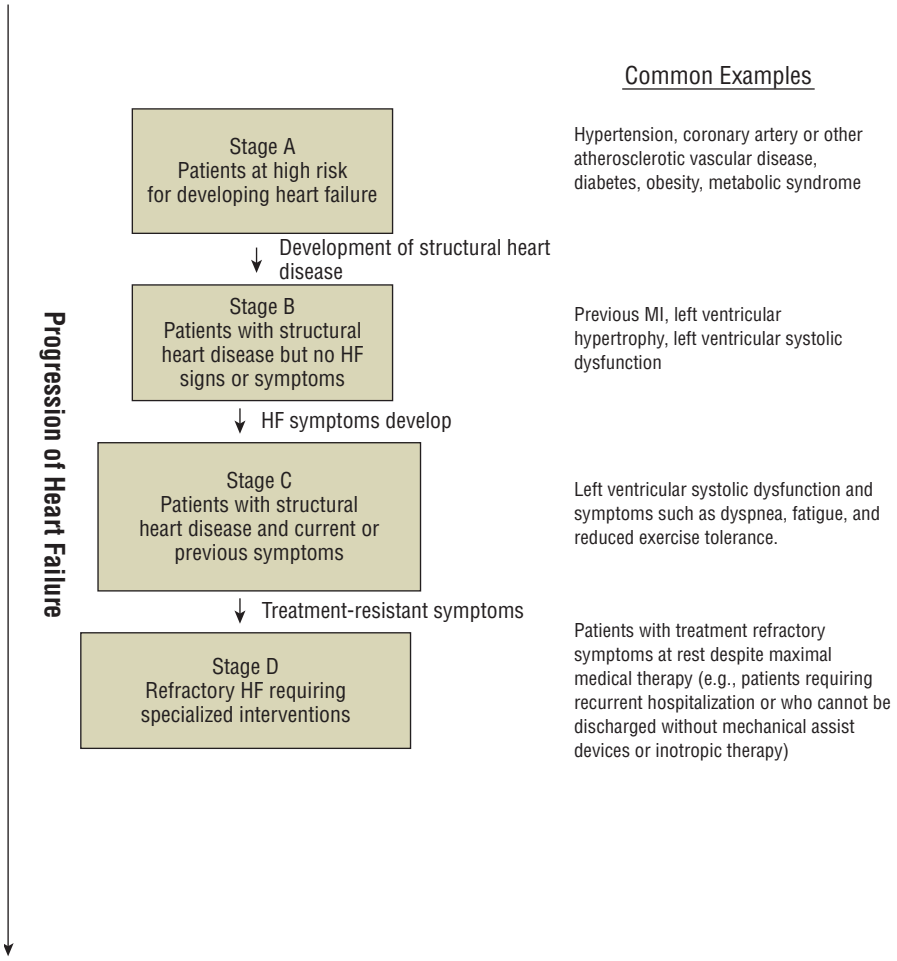

FIGURE 16-5. ACC/AHA heart failure staging system. (HF, heart failure; MI, myocardial infarction.) *(Adapted with permission from Circulation 2005;112:154–234.)*

ties that could affect prognosis and guide treatment decisions. Measurement of BNP may also assist in differentiating dyspnea caused by heart failure from other causes.[18]

Although the history, physical examination, and laboratory tests can provide important clues to the underlying cause of heart failure, the echocardiogram is the single most useful test in the evaluation of a patient with heart failure. The echocardiogram is used to evaluate abnormalities in the pericardium, myocardium, or heart valves and to quantify the LVEF to determine if systolic or diastolic dysfunction is present.

TREATMENT

Chronic Heart Failure

■ DESIRED OUTCOMES

The goals of therapy in management of chronic heart failure are to improve the patient's quality of life; relieve or reduce symptoms; prevent or minimize hospitalizations for exacerbations of heart failure; slow progression of the disease process; and prolong survival. Although these goals are still important, identification of risk factors for heart failure development and recognition of its progressive nature have led to increased emphasis on preventing the development of this disorder. With this in mind, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the evaluation and management of chronic heart failure use a staging system that recognizes not only the evolution and progression of the disorder, but also emphasizes risk factor modification and preventive treatment strategies.[1] The system is comprised of four stages (Fig. 16–5). This staging system differs from the NYHA functional classification (Table 16–4) with which most clinicians are familiar. The NYHA system is primarily intended to classify *symptomatic* heart failure according to the clinician's subjective evaluation and does not recognize preventive measures or the progression of the disorder. A patient's symptoms can change frequently over a short period of time as a result of changes in, medications, diet, or intercurrent illnesses. For example, a patient with NYHA class IV symptoms with marked volume overload could rapidly improve to class II or III with aggressive diuretic therapy. In spite of these limitations, this system can be useful for monitoring patients and is widely used in heart failure studies. In contrast, and consistent with the progressive nature of heart failure, a patient's ACC/AHA heart failure stage could not improve (e.g., go from stage C to stage B) even though the

TABLE 16-4 New York Heart Association Functional Classification

Functional class	
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III	Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less-than-ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

patient's symptoms could fluctuate from NYHA class IV to class I. In addition, the ACC/AHA staging system provides a more comprehensive framework for evaluation, prevention, and treatment of heart failure.

GENERAL MEASURES

The complexity of the heart failure syndrome necessitates a comprehensive approach to management that includes accurate diagnosis, identification and treatment of risk factors (e.g., diabetes, hypertension, coronary artery disease), elimination or minimization of precipitating factors, appropriate pharmacologic and nonpharmacologic therapy, and close monitoring and followup.

The first step in management of chronic heart failure is to determine the etiology (see Table 16–1) and/or any precipitating factors. Treatment of underlying disorders, such as hyperthyroidism, may obviate the need for treatment of heart failure. Patients with valvular diseases may derive significant benefit from valve replacement or repair. Revascularization or antiischemic therapy in patients with coronary disease may reduce heart failure symptoms. Drugs that aggravate heart failure (see Table 16–3) should be discontinued if possible.

Restriction of physical activity reduces cardiac workload and is recommended for virtually all patients with acute congestive symptoms. However, once the patient's symptoms have stabilized and excess fluid is removed, restrictions on physical activity are discouraged. In fact, current guidelines indicate that exercise training programs in stable heart failure patients improve exercise tolerance, functional capacity, and may slow heart failure progression.[1]

Because a major compensatory response in heart failure is sodium and water retention, restriction of dietary sodium and fluid intake are important nonpharmacologic interventions. Mild (<3 g per day) to moderate (<2 g per day) sodium restriction, in conjunction with daily measurement of weight, should be implemented to minimize volume retention and allow use of lower and safer diuretic doses. The typical American diet contains 3 to 6 g of sodium per day so most patients would need to reduce their intake by approximately 50%. This can often be accomplished by not adding salt to prepared foods and eliminating foods high in sodium (e.g., salt-cured meats, salted snack foods, pickles, soups, delicatessen meats, and processed foods). In patients with hyponatremia (serum Na <130 mEq/L) or those with persistent volume retention despite high diuretic doses and sodium restriction, daily fluid intake should be limited to 2 L per day from all sources.

Other important general measures include patient and family counseling on the signs and symptoms of heart failure, detailed instructions on the importance of appropriate medication use and compliance, and the need for close monitoring and followup to reinforce compliance and minimize the risk of heart failure exacerbations and subsequent hospitalization.

GENERAL APPROACH TO TREATMENT

4 Current ACC/AHA treatment guidelines are organized around the four identified stages of heart failure and the treatment recommendations are summarized below (Figs. 16–6 and 16–7).[1] This staging system emphasizes the progressive nature of the disorder and targets treatment to prevent and/or slow the progression of heart failure. Clinicians are reminded that, in addition to the ACC/AHA, other cardiology professional societies have developed guidelines for evaluation and treatment of heart failure. The Heart Failure Society of America (HFSA) issued practice guidelines in 2006.[33] The HFSA and ACC/AHA guidelines are very similar with regard to care and treatment of patients with chronic heart failure. In addition, the HFSA guidelines provide a thorough discussion of other areas including acute decompensated heart failure, heart failure with preserved LVEF, and management of patients with heart failure and a number of comorbid diseases. The HFSA guidelines will be periodically updated on the HFSA website (*www.hfsa.org*). Finally, the European Society of Cardiology published guidelines for the management of both acute[34] and chronic heart failure.[35] Although minor differences exist between the recommendations in the American and European guidelines, they are in general agreement in their overall approach. Clinicians caring for patients with heart failure should be familiar with these guidelines but should also remember that these are only *guidelines* and that management and treatment must be individualized for each patient.

Treatment of Stage A Heart Failure (See Fig. 16–6)

Patients in stage A do not have structural heart disease or heart failure symptoms but are at high risk for developing heart failure because of the presence of risk factors. The emphasis here is on identification and modification of these risk factors to prevent the development of structural heart disease and subsequent heart failure. Commonly encountered risk factors include hypertension, diabetes, obesity, metabolic syndrome, smoking, and coronary artery disease. Although each of these disorders individually increases risk, they frequently coexist in many patients and act synergistically to foster the development of heart failure. Effective control of blood pressure reduces the risk of developing heart failure by approximately 50%, thus current hypertension treatment guidelines should be followed.[36] Control of hyperglycemia reduces the risk of end-organ damage and the risk of developing heart failure. Appropriate management of coronary disease and its associated risk factors is also important, including treatment of hyperlipidemia according to published guidelines and smoking cessation.[37] Although treatment must be individualized, ACE inhibitors or ARBs should be strongly considered for antihypertensive therapy in patients with multiple vascular risk factors.[1] Diuretics and β-blockers may also useful in this setting.

Treatment of Stage B Heart Failure (See Fig. 16–6)

Patients in stage B have structural heart disease, but do not have heart failure symptoms. This group includes patients with left ventricular hypertrophy, recent or remote MI, valvular disease, or reduced LVEF (less than 40%). These individuals are at risk for developing heart failure and treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process. In addition to the treatment measures outlined in stage A, ACE inhibitors and β-blockers are important components of therapy. Patients with a previous MI should receive both ACE inhibitors and β-blockers, regardless of the LVEF.[1] Similarly, patients with a reduced LVEF should also receive both these agents, whether or not they have had a MI.[1] ARBs are an effective alternative in patients intolerant to ACE inhibitors.[1]

Treatment of Stage C Heart Failure (See Fig. 16–7)

4 5 6 7 Patients with structural heart disease and previous or current heart failure symptoms are classified in stage C. In addition to treatments in stages A and B, most patients in stage C should be routinely treated with three medications: a diuretic, an ACE inhibitor, and a β-blocker (see Drug Therapies for Routine Use below). The benefits of these medications on slowing heart failure progression, reducing morbidity and mortality, and improving symptoms are clearly established. Aldosterone receptor antagonists, ARBs, digoxin, and hydralazine-isosorbide dinitrate are also useful in selected patients. Nonpharmacologic therapy with devices such as an implantable cardiac-defibrillator (ICD) or cardiac resynchroni-

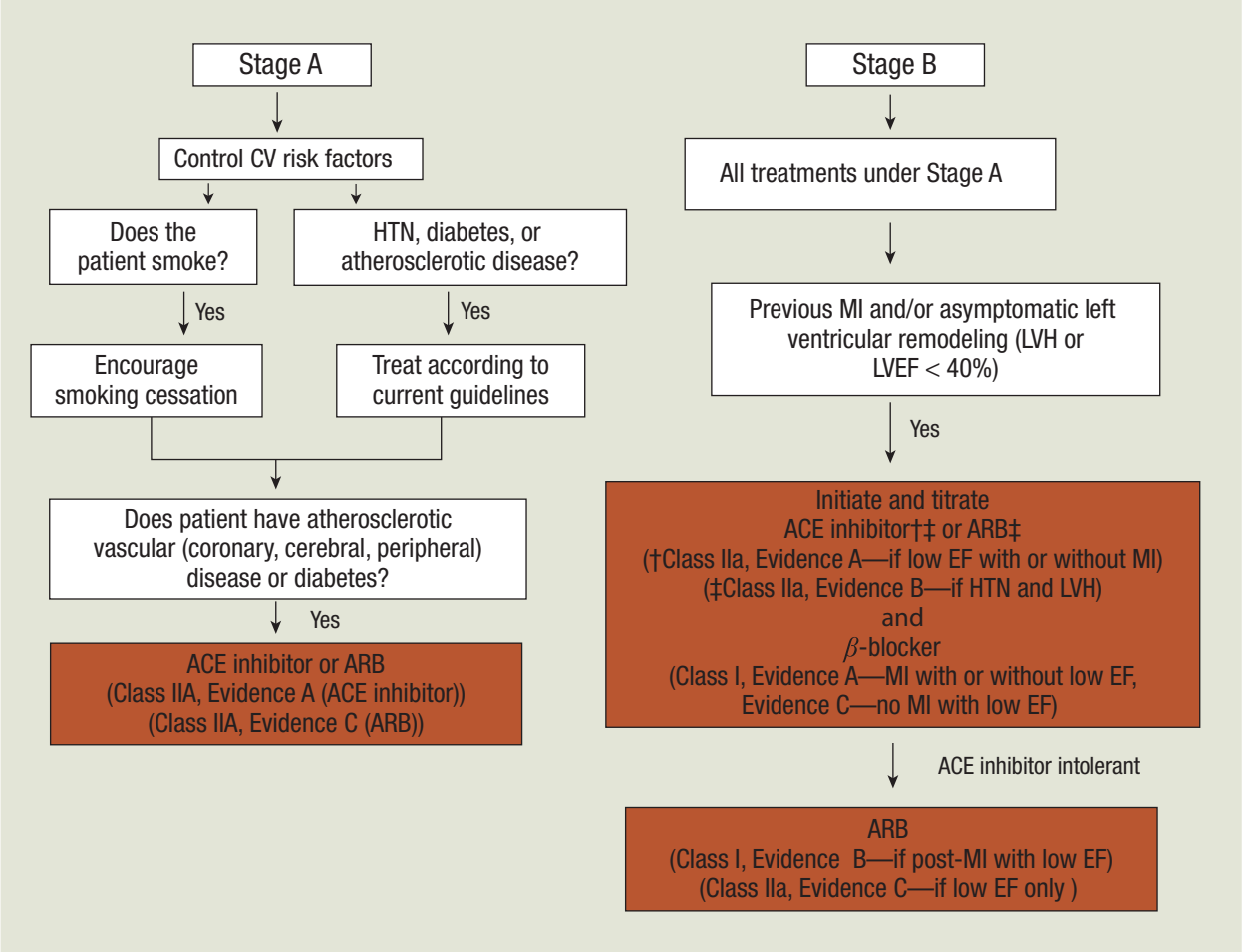

FIGURE 16-6. Treatment algorithm for patients with ACC/AHA stages A and B heart failure. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CV, cardiovascular; EF, ejection fraction; HTN, hypertension; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction.) *(Adapted with permission from Circulation 2005;112:154–234.)*

zation therapy (CRT) with a biventricular pacemaker is also indicated in certain patients in stage C (see Nonpharmacologic Therapy below). Other general measures are also important, including moderate sodium restriction, daily weight measurement, immunization against influenza and pneumococcus, modest physical activity, and avoidance of medications that can exacerbate heart failure. Recent evidence suggests that careful followup and patient education that reinforces dietary and medication compliance can prevent clinical deterioration and reduce hospitalization.[1]

Treatment of Stage D Heart Failure

Stage D heart failure includes patients with symptoms at rest that are refractory despite maximal medical therapy. This includes patients who undergo recurrent hospitalizations or who cannot be discharged from the hospital without special interventions. These individuals have the most advanced form of heart failure and should be considered for specialized therapies including mechanical circulatory support, continuous intravenous positive inotropic therapy, cardiac transplantation, or hospice care. The approach to treatment of patients with stage D heart failure is discussed in more detail in Acute Decompensated Heart Failure below.

■ NONPHARMACOLOGIC THERAPY

Sudden cardiac death, primarily as a consequence of ventricular tachycardia and fibrillation, is responsible for 40% to 50% of the mortality in heart failure patients. In general, patients in the earlier stages of heart failure with milder symptoms are more likely to die from sudden death, whereas death from pump failure is more frequent in those with advanced heart failure. Many of these patients have complex and frequent ventricular ectopic beats, although it remains unknown whether these ectopic beats contribute to the risk of malignant arrhythmias or merely serve as markers for individuals at higher risk for sudden death. Drugs that attenuate disease progression such as β-blockers and aldosterone antagonists reduce the risk of sudden death. However, empiric treatment with class I antiarrhythmic agents, although they can suppress ventricular ectopic beats, adversely affect survival.[38] The role of the ICD compared to amiodarone for primary prevention of sudden death was evaluated in Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Placement of an ICD was superior to amiodarone or placebo for reducing mortality in patients with NYHA class II or III heart failure and LVEF ≤35%, regardless of the etiology of heart failure.[39] Importantly, this study also found that amiodarone had no benefit compared to placebo and thus this drug, because of its multiple adverse effects, drug interactions, and lack of effect on mortality, should not be used for primary prevention of sudden death. However, because of the neutral effects of amiodarone on survival, it is often used in heart failure patients with atrial fibrillation to maintain sinus rhythm and/or to prevent ICD discharges. In cardiac arrest survivors with a reduced LVEF, the ICD is superior to antiarrhythmic drug therapy for improving survival.[40] Thus, the ACC/AHA guidelines recommend the ICD for both primary and secondary prevention to improve survival in patients with current or previous heart failure symptoms and reduced LVEF. Chapter 19 thoroughly reviews ICD therapy.

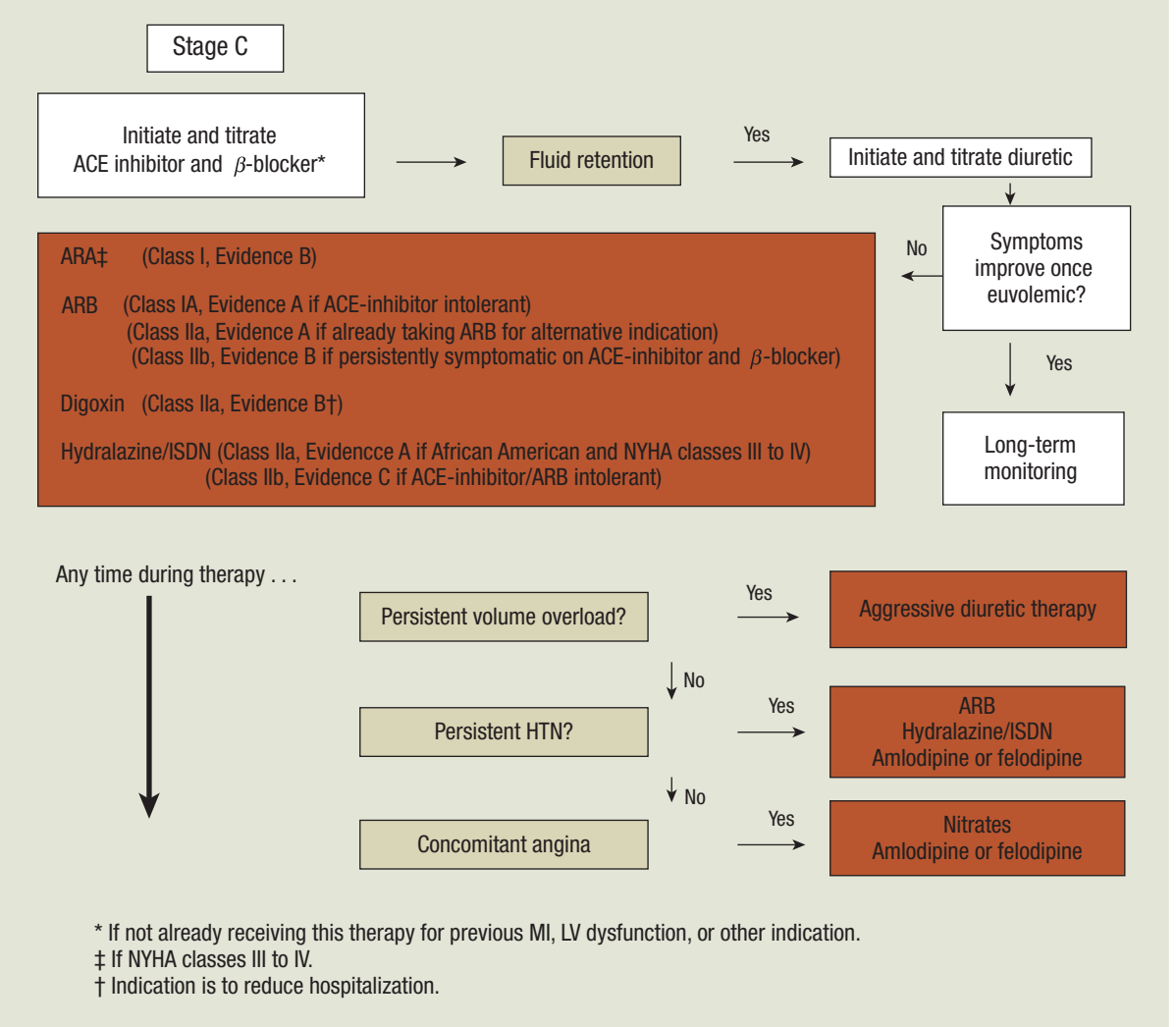

FIGURE 16-7. Treatment algorithm for patients with ACC/AHA stage C heart failure. (ACE, angiotensin-converting enzyme; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; HTN, hypertension; ISDN, isosorbide dinitrate; LV, left ventricle; MI, myocardial infarction.) *(Adapted with permission from Circulation 2005;112:154–234.)*

Recent studies demonstrate that CRT offers a promising approach to selected patients with chronic heart failure.[41,42] Delayed electrical activation of the left ventricle, characterized on the ECG by a QRS duration that exceeds 120 msec, occurs in approximately one-third of patients with moderate to severe systolic heart failure. Because the left and right ventricles normally activate simultaneously, this delay results in asynchronous contraction of the ventricles, which contributes to the hemodynamic abnormalities of heart failure. Implantation of a specialized biventricular pacemaker to restore synchronous activation of the ventricles can improve ventricular contraction and hemodynamics. Recent trials show improvements in exercise capacity, NYHA classification, quality of life, hemodynamic function, hospitalizations, and mortality with CRT.[41,42] A CRT is currently indicated only in NYHA classes III to IV patients receiving optimal medical therapy and with a QRS duration ≥120 msec and LVEF ≤35%. Combined CRT and ICD devices are available and can be used if the patient meets the indications for both devices.

■ PHARMACOLOGIC THERAPY

Drug Therapies for Routine Use

❹ ❺ ❻ ❼ ❽ ❾ Figure 16–7 is a treatment algorithm for management of patients with reduced LVEF and current or prior heart failure symptoms (i.e., stage C). In general, these patients should receive combined therapy with an ACE inhibitor or ARB and a β-blocker, plus a diuretic if there is evidence of fluid retention. Initiation of digoxin therapy can be considered at any time for symptom reduction, to decrease hospitalizations, or slow ventricular response in patients with concomitant atrial fibrillation. An aldosterone receptor antagonist should also be considered in selected patients.[1]

❼ **Diuretics**[43,44] The compensatory mechanisms in heart failure stimulate excessive sodium and water retention, often leading to pulmonary and systemic congestion. Diuretic therapy, in addition to sodium restriction, is recommended in all patients with clinical evidence of fluid retention. Once fluid overload has been resolved, many patients require chronic diuretic therapy to maintain euvolemia. Among the drugs used to manage heart failure, diuretics are the most rapid in producing symptomatic benefits. Because diuretics do not alter disease progression or prolong survival, they are not considered mandatory therapy. Thus patients who do not have fluid retention would not require diuretic therapy.

The primary goal of diuretic therapy is to reduce symptoms associated with fluid retention, improve exercise tolerance and quality of life, and reduce hospitalizations from heart failure. They accomplish this by decreasing pulmonary and peripheral edema through reduction of preload. Although preload is a determinant of

cardiac output, the Frank-Starling curve (see Fig. 16–3) shows that patients with congestive symptoms have reached the flat portion of the curve. A reduction in preload improves symptoms but has little effect on the patient's stroke volume or cardiac output until the steep portion of the curve is reached. However, diuretic therapy must be used judiciously because overdiuresis can lead to a reduction in cardiac output and symptoms of dehydration.

Diuretic therapy is usually initiated in low doses in the outpatient setting, with dosage adjustments based on symptom assessment and daily body weight. Change in body weight is a sensitive marker of fluid retention or loss, and it is recommended that patients monitor their status by taking daily morning body weights. Patients who gain a pound per day for several consecutive days, or 3 to 5 lb in a week, should contact their healthcare provider for instructions (which often will be to increase the diuretic dose temporarily). Such action often will allow patients to prevent a decompensation that requires hospitalization. One study demonstrated a significant reduction in emergency department visits with a protocol that directed patients to self-adjust their diuretic dose based on changes in heart failure symptoms and daily body weight.[45] Hypotension or worsening renal function (e.g., increases in serum creatinine) may be indicative of volume depletion and necessitate a reduction in the diuretic dose. Assessing for volume depletion is particularly important before ACE inhibitor or β-blocker initiation or dose up-titration as overdiuresis may predispose patients to hypotension and other adverse effects with increases in ACE inhibitor or β-blocker doses.

Thiazide Diuretics. Thiazide diuretics such as hydrochlorothiazide block sodium and chloride reabsorption in the distal convoluted tubule (approximately 5% to 8% of filtered sodium). Consequently, the thiazides are relatively weak diuretics and infrequently are used alone in heart failure. However, as reviewed in Treatment: Acute Decompensated Heart Failure below, under Diuretic Resistance, thiazides or the thiazide-like diuretic metolazone can be used in combination with loop diuretics to promote a very effective diuresis. In addition, thiazide diuretics may be preferred in patients with only mild fluid retention and elevated blood pressure because of their more persistent antihypertensive effects compared to loop diuretics.

Loop Diuretics. Loop diuretics are usually necessary to restore and maintain euvolemia in heart failure. They act by inhibiting a Na-K-^{2}Cl transporter in the thick ascending limb of the loop of Henle, where 20% to 25% of filtered sodium normally is reabsorbed. Because loop diuretics are highly bound to plasma proteins, they are not highly filtered at the glomerulus. They reach the tubular lumen by active transport via the organic acid transport pathway. Competitors for this pathway (probenecid or organic by-products of uremia) can inhibit delivery of loop diuretics to their site of action and decrease effectiveness. Loop diuretics also induce a prostaglandin-mediated increase in renal blood flow, which contributes to their natriuretic effect. Coadministration of NSAIDs blocks this prostaglandin-mediated effect and can diminish diuretic efficacy. Excessive dietary sodium intake may also reduce the efficacy of loop diuretics. Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary to obtain adequate delivery of the drug to the site of action.

Heart failure is one of the disease states in which the maximal response to loop diuretics is reduced. This is believed to result from a decrease in the rate of diuretic absorption and/or increased proximal or distal tubule reabsorption of sodium, possibly due to increased activity of the Na-K-^{2}Cl transporter.[43] As a consequence, doses above the recommended ceiling doses produce no additional diuresis. Thus, once the ceiling dose is reached, it is recommended to give the diuretic more frequently for additional effect rather than to give progressively higher doses. The appropriate chronic dose is that which maintains the patient at a stable dry weight without symptoms of dyspnea. Table 16–5 lists ranges of doses of loop diuretics and recommended ceiling doses.

TABLE 16-5 Loop Diuretics–Use in Heart Failure

	Furosemide	Bumetanide	Torsemide
Usual daily dose (oral)	20–160 mg/day	0.5–4 mg/day	10–80 mg/day
Ceiling dose[a]			
Normal renal function	80–160 mg	1–2 mg	20–40 mg
CL_{cr} - 20–50 mL/min	160 mg	2 mg	40 mg
CL_{cr} <20 mL/min	400 mg	8–10 mg	100 mg
Bioavailability	10%–100% average: 50%	80%–90%	80%–100%
Affected by food	Yes	Yes	No
Half-life	0.3–3.4 h	0.3–1.5 h	3–4 h

CL_{cr}, creatine clearance.
[a]Ceiling dose: single dose above which additional response is unlikely to be observed.
Adapted from Am J Med Sci 2000;319:38–50.

5 ACE Inhibitors ACE inhibitors are the cornerstone of pharmacotherapy for patients with heart failure. By blocking the conversion of angiotensin I to angiotensin II by ACE, the production of angiotensin II and, in turn, aldosterone is decreased, but not completely eliminated.[13] This decrease in angiotensin II and aldosterone attenuates many of the deleterious effects of these neurohormones, including ventricular remodeling, myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy, norepinephrine release, vasoconstriction, and sodium and water retention.[13] Thus, ACE inhibitor therapy plays an important role in preventing RAAS-mediated progressive worsening of myocardial function. The endogenous vasodilator bradykinin, which is inactivated by ACE, is also increased by ACE inhibitors, along with the release of vasodilatory prostaglandins and histamine.[13] The precise contribution of the effects of ACE inhibitors on bradykinin and vasodilatory prostaglandins is unclear. However, the persistence of clinical benefits with ACE inhibitors despite angiotensin II and aldosterone levels returning to pretreatment levels suggests this is a potentially important effect.[13]

Numerous placebo-controlled clinical trials involving more than 7,000 patients with reduced LVEF have documented the favorable effects of ACE inhibitor therapy on symptoms, NYHA functional classification, clinical status, exercise tolerance, and quality of life.[13] When compared with placebo, patients treated with ACE inhibitors have fewer treatment failures, hospitalizations, and increases in diuretic dosages.[13]

More importantly, these trials show that ACE inhibitors improve survival by 20% to 30% compared to placebo.[13] In addition, the Studies of Left Ventricular Dysfunction (SOLVD) Prevention and Treatment trials indicate the survival benefit is maintained long-term (12 years) in patients who were treated with enalapril.[46] In addition to improving survival, ACE inhibitors also reduce the combined risk of death or hospitalization, slow the progression of heart failure, and reduce the rates of reinfarction.[13] The benefits of ACE inhibitor therapy are independent of the etiology of heart failure (ischemic versus nonischemic) and are observed in patients with mild, moderate, or severe symptoms.

The most common cause of heart failure is ischemic heart disease, where MI results in loss of myocytes, followed by ventricular dilation and remodeling. Captopril, ramipril, and trandolapril all benefit post-MI patients, whether they are initiated early (within 36 hours) and continued for 4 to 6 weeks or started later and administered for several years.[13] Collectively, these studies indicate that ACE inhibitors after MI improve overall survival, decrease development of severe heart failure, and reduce reinfarction and heart failure hospitalization rates.[13] The benefit occurs within the first few days

of therapy and persists during long-term treatment. The effects are most pronounced in higher-risk patients, such as those with symptomatic heart failure or reduced LVEF, with 20% to 30% reductions in mortality reported in these patients.[13] Post-MI patients without heart failure symptoms or decreases in LVEF (stage B) should also receive ACE inhibitors to prevent the development of heart failure and to reduce mortality.[1,13,47]

In addition to their benefits in patients with established heart failure, ACE inhibitors also are effective for preventing the development of heart failure and reducing cardiovascular risk. Enalapril decreases the risk of hospitalization for worsening heart failure and reduces the composite end point of death and heart failure hospitalization in patients with asymptomatic left ventricular dysfunction.[48] The development of diabetes mellitus, an important risk factor for cardiovascular disease that also increases morbidity and mortality in heart failure patients, is reduced by enalapril in patients with chronic heart failure.[49] In patients with established atherosclerotic vascular disease (e.g., coronary, cerebral, or peripheral circulations) and normal LVEF, ACE inhibitors reduce the development of new-onset heart failure and diabetes, cardiovascular death, overall mortality, MI, and stroke.[50]

The clear benefit of ACE inhibitors is evident in the Joint Commission for Accreditation of Healthcare Organizations (JCAHO) and Centers for Medicare and Medicaid Services (CMS) selection of ACE inhibitor use in patients with heart failure and decreased LVEF as a key quality measure. Despite the overwhelming benefit demonstrated with these agents, there is substantial evidence that they are underused and underdosed.[51,52] These data indicate that significant numbers of heart failure patients do not receive ACE inhibitors, and of those who are receiving these agents, many are taking lower-than-recommended doses.[52] Also, for patients receiving an ACE inhibitor at hospital discharge, use significantly decreases over time and patients who were not prescribed ACE inhibitors at discharge were unlikely to have therapy initiated in the outpatient setting.[51] The most common reasons cited for underuse or underdosing are concerns about safety and adverse reactions to ACE inhibitors, especially in patients with underlying renal dysfunction or hypotension. The use of ACE inhibitors in patients with renal insufficiency is particularly relevant because it is present in 25% to 50% of heart failure patients and is associated with an increased risk of mortality.[53] Several recent studies in different patient populations, including post-MI patients with decreased left ventricular function and patients with stable coronary artery disease and preserved left ventricular function, indicate that ACE inhibitors may be more effective in those patients with renal insufficiency.[54–56] Because many heart failure patients have concomitant disorders (e.g., diabetes, hypertension, previous MI) that also may be favorably affected by ACE inhibitors, renal dysfunction should not be an absolute contraindication to ACE inhibitor use in patients with left ventricular dysfunction. However, these patients should be monitored carefully for the development of worsening renal function and/or hyperkalemia with special attention to risk factors associated with this complication of ACE inhibitor therapy.[1]

An important practical consideration is determining the proper dose of an ACE inhibitor. The ability to achieve target doses shown to be effective in clinical trials is often limited by hypotension and/or a decline in renal function. Clinical trials establishing the efficacy of these agents titrated drug doses to a predetermined target rather than according to therapeutic response. Although data on the dose-dependent effects of ACE inhibitors in patients with heart failure are limited, higher doses may reduce the risk of hospitalization compared to lower doses, but there do not appear to be significant differences in mortality.[57] In many positive trials of other heart failure therapies (e.g., β-blockers, aldosterone antagonists), intermediate ACE inhibitor doses were generally used as background therapy. These results emphasize that clinicians should attempt to use ACE inhibitor doses proven beneficial in clinical trials, but if these doses are not tolerated, lower doses can be used with the knowledge that there are likely only small differences in mortality outcomes between the high and low doses. Also, initiation of β-blocker therapy should not be delayed until target ACE inhibitor doses are achieved as the addition of a β-blocker is proven to reduce mortality, whereas that is not the case with increasing ACE inhibitor doses.

In summary, the evidence that ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in patients with heart failure and reduced LVEF (stage C) is unequivocal. Current guidelines indicate these patients should receive ACE inhibitors, unless contraindications are present.[1] Moreover, ACE inhibitors should also be used to prevent the development of heart failure in at-risk patients (i.e., stages A and B).[1]

6 β-Blockers There is overwhelming evidence from multiple randomized, placebo-controlled clinical trials that β-blockers reduce morbidity and mortality in patients with heart failure. As such, the ACC/AHA guidelines on the management of heart failure recommend that β-blockers should be used in all stable patients with heart failure and a reduced left ventricular ejection fraction in the absence of contraindications or a clear history of β-blocker intolerance.[1] Patients should receive a β-blocker even if their symptoms are mild or well controlled with diuretic and ACE inhibitor therapy. Importantly, it is not essential that ACE inhibitor doses be optimized before a β-blocker is started because the addition of a β-blocker is likely to be of greater benefit than an increase in ACE inhibitor dose.[1] β-Blockers are also recommended for asymptomatic patients with a reduced left ventricular ejection fraction (stage B) to decrease the risk of progression to heart failure.

β-Blockers have been studied in more than 20,000 patients with heart failure in placebo-controlled trials. Three β-blockers have been shown to significantly reduce mortality compared to placebo: carvedilol, metoprolol controlled-release/extended-release (CR/XL), and bisoprolol. Each was studied in a large population with the primary end point of mortality. Carvedilol was the first β-blocker shown to improve survival in heart failure. In the U.S. Carvedilol Heart Failure Study, 1,094 patients were randomized to carvedilol or placebo in addition to standard therapy, including an ACE inhibitor, digoxin, and diuretic. The study was stopped early because of a 65% reduction in the risk of death with carvedilol.[58] Nearly 4,000 patients were randomized to metoprolol CR/XL (Toprol-XL) or placebo in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), the largest β-blocker mortality trial to date.[59] This trial was also stopped early because of a significant survival benefit with β-blockade. Specifically, metoprolol was associated with a 34% reduction in total mortality, a 41% reduction in sudden death, and a 49% reduction in death from worsening heart failure. Bisoprolol was studied in more than 2,600 patients enrolled in the Cardiac Insufficiency Bisoprolol Study (CIBIS) II.[60] The study was also stopped prematurely because of a 34% reduction in total mortality with bisoprolol compared to placebo. Bisoprolol was also associated with a 44% reduction in sudden death and a 26% reduction in death because of worsening heart failure. Multiple post-hoc subgroup analyses of data from the MERIT-HF and CIBIS II trials suggest that the benefits of β-blockade occur regardless of heart failure etiology or disease severity.

The majority of participants in MERIT-HF and CIBIS II had either class II or class III heart failure, and β-blockers became standard therapy in patients with class II or III disease after these trials were published. However, the efficacy and safety of β-blockers in patients with class IV heart failure were unclear until publication of the Carvedilol, Prospective, Randomized, Cumulative Survival (COPERNICUS) trial.[61] This trial randomized nearly 2,300 clinically stable patients who had symptoms at rest or with minimal exertion

to carvedilol or placebo. Like the other studies, COPERNICUS was stopped prematurely after carvedilol produced a 35% relative reduction in mortality. Carvedilol was well tolerated in this population, with fewer participants receiving carvedilol compared to placebo requiring permanent discontinuation of study medication.

Data supporting the use of β-blockers in asymptomatic patients with left ventricular systolic dysfunction (stage B) come from a study of carvedilol in post-MI patients with a decreased LVEF.[62] While the primary end point of all-cause mortality or hospital admission for cardiovascular problems was similar in the carvedilol and placebo groups, carvedilol significantly reduced all-cause mortality alone compared to placebo. Cardiovascular mortality and nonfatal MI were also lower among carvedilol-treated patients.

In addition to improving survival, β-blockers improve multiple other end points. All the large clinical trials demonstrated 15% to 20% reductions in all-cause hospitalization and 25% to 35% reductions in hospitalizations for worsening heart failure with β-blocker therapy.[60,63,64] Studies also show consistent improvements in left ventricular systolic function with β-blockers, with increases in LVEF of 5 to 10 units (e.g., from an ejection fraction of 20% to 25% or 30%) after several weeks to months of therapy. β-Blockers have also been shown to decrease ventricular mass, improve the sphericity of the ventricle, and reduce systolic and diastolic volumes (left ventricular end-systolic volume and left ventricular end-diastolic volume).[65,66] These effects are often collectively called *reverse remodeling,* referring to the fact that they return the heart toward more normal size, shape, and function.

The effects of β-blockers on symptoms and exercise tolerance varies among studies. Many studies show improvements in NYHA functional class, patient symptom scores, or quality-of-life assessments (such as the Minnesota Living with Heart Failure Questionnaire), and exercise performance, as assessed by the 6-minute walk test.[63–65] Other investigators find significant reductions in mortality with β-blockers but no significant improvement in symptoms.[67] As such, it is important to educate patients that β-blocker therapy is expected to positively influence disease progression and survival even if there is little to no symptomatic improvement.

The majority of participants in β-blocker trials were on ACE inhibitors at baseline as the benefits of ACE inhibitors were proven prior to β-blocker trials. Whether the strategy of starting a β-blocker prior to an ACE inhibitor is safe and effective has been debated. This issue was addressed in CIBIS III, in which patients with mild to moderate symptoms were randomized to initial therapy with either bisoprolol or enalapril.[68] The two strategies produced similar rates of death or hospitalization. However, the trial failed to satisfy the prespecified statistical criterion for noninferiority of initial therapy with a β-blocker compared to an ACE inhibitor. In the absence of more compelling evidence, ACE inhibitors should be started first in most patients. Initiating a β-blocker first may be advantageous for patients with evidence of excessive SNS activity (e.g., tachycardia) and may also be appropriate for patients whose renal function or potassium concentrations preclude starting an ACE inhibitor at that time. However, the risk for decompensation during β-blocker initiation may be greater in the absence of preexisting ACE inhibitor therapy, and careful monitoring is essential.

The mechanism by which β-blockers exert their therapeutic benefit is unclear. β-Blockers antagonize the detrimental effects of the SNS described earlier in the chapter. To this end, potential mechanisms to explain the favorable effects of β-blockers in heart failure include antiarrhythmic effects, attenuating or reversing ventricular remodeling, decreasing myocyte death from catecholamine-induced necrosis or apoptosis, preventing fetal gene expression, improving left ventricular systolic function, decreasing heart rate and ventricular wall stress thereby reducing myocardial oxygen demand, and inhibiting plasma renin release.[1]

Components that are critical for successful β-blocker therapy include appropriate patient selection, drug initiation and titration, and patient education. β-Blockers should be initiated in stable patients who have no or minimal evidence of fluid overload.[1] Although β-blockers are typically started in the outpatient setting, there are data indicating that initiation of a β-blocker prior to discharge in patients who are hospitalized for decompensated heart failure increases β-blocker usage compared with outpatient initiation without increasing the risk of serious adverse effects.[69] However, β-blockers should not be started in patients who are hospitalized in the intensive care unit or recently required intravenous inotropic support. In unstable patients, other heart failure therapy should be optimized and then β-blocker therapy reevaluated once stability is achieved.

Initiation of a β-blocker at normal doses in patients with heart failure may to lead to symptomatic worsening or acute decompensation owing to the drug's negative inotropic effect. For this reason, β-blockers are listed as drugs that may exacerbate or worsen heart failure (see Table 16–3). To minimize the likelihood for acute decompensation, β-blockers should be started in very low doses with slow upward dose titration. Table 16–6 describes the starting and target doses. Of note, the smallest commercially available tablet of bisoprolol is a scored 5-mg tablet. Because the recommended starting dose of 1.25 mg/day is not readily available, bisoprolol is the least commonly used of the three agents and, in fact, is not approved by the Food and Drug Administration (FDA) for use in heart failure. Thus, therapy is generally limited to either carvedilol or metoprolol CR/XL, and there is no compelling evidence that one drug is superior to the other. A controlled-release formulation of carvedilol (carvedilol CR) that allows once-daily dosing was recently FDA-approved, and pharmacokinetic studies demonstrate similar degrees of drug exposure with the controlled- and immediate-release formations of the drug.[70] Carvedilol CR should be considered in patients with difficulty maintaining adherence to the immediate-release formulation.

β-Blocker doses should be doubled no more often than every 2 weeks, as tolerated, until the target or maximally tolerated dose is reached. Target doses are those associated with reductions in mortality in placebo-controlled clinical trials. It is important to make every effort to titrate doses up to target whenever possible in order to provide maximal survival benefits. In addition, there is evidence that response to β-blockers is dose dependent, with greater reductions in hospitalization rates and improvements in LVEF at higher doses. However, even low doses appear to prolong survival compared to placebo, and thus, any dose of β-blocker is likely to provide some benefit.[71] Data with metoprolol suggest that heart rate may serve as a guide to the degree of β-blockade and that lower β-blocker doses might be considered reasonable if the reduction in heart rate indicates a good response to β-blocker therapy.[71]

Good communication between the patient and healthcare provider(s) is particularly important for successful therapy. Patients

TABLE 16-6 Initial and Target Doses for β-Blockers Used in Treatment of Heart Failure

Drug	Initial Dose[a]	Target Dose
Bisoprolol[b]	1.25 mg daily	10 mg daily
Carvedilol[b]	3.125 mg bid	25 mg bid[c]
Metoprolol succinate CR/XL[b]	12.5-25 mg daily[d]	200 mg daily

[a] Doses should be doubled approximately every 2 weeks, or as tolerated by the patient, until the highest tolerated or target dose is reached.
[b] Regimens proven in large trials to reduce mortality.
[c] Target dose for patients who weigh >85 kg is 50 mg bid.
[d] In Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), the majority of class II patients were given 25 mg daily, whereas the majority of class III patients were given 12.5 mg daily as their starting dose.

should understand that dose up-titration is a long, gradual process and that achieving the target dose is important to maximize the benefits of therapy. Patients should also be aware that response to therapy may be delayed and that heart failure symptoms may actually worsen during the initiation period. In the event of worsening symptoms, patients who understand the potential benefits of long-term β-blocker therapy may be more likely to continue treatment.

In summary, the data provide clear evidence that β-blockers slow disease progression, decrease hospitalizations, and improve survival in heart failure. β-Blockers have also been shown to improve quality of life in many patients with heart failure, although this is not a universal finding. Based on these data, β-blockers are recommended as standard therapy for all patients with systolic dysfunction, regardless of the severity of their symptoms. Clinical trial experience shows that target β-blocker doses can be achieved in the majority of patients provided that appropriate initiation, titration, and education are implemented.

Drug Therapies to Consider for Selected Patients

5 Angiotensin II Receptor Blockers The use of ARBs in heart failure has generated great interest and controversy.[72] The crucial role of the RAAS in heart failure development and progression is well established, as are the benefits of inhibiting this system with ACE inhibitors. Although ACE inhibitors decrease angiotensin II production in the short-term, these agents do not completely suppress generation of this hormone. With chronic administration of ACE inhibitors, *ACE escape,* characterized by increases in circulating angiotensin II and aldosterone, often occurs.[12,73] In addition, angiotensin II can be formed in a number of tissues, including the heart, through non–ACE-dependent pathways (e.g., chymase, cathepsin, and kallikrein).[12] Therefore, blockade of the detrimental effects of angiotensin II by ACE inhibition is incomplete. In addition, troublesome adverse effects of ACE inhibitors such as cough are linked to accumulation of bradykinin.[13] The ARBs block the angiotensin II receptor subtype 1 (AT_1), preventing the deleterious effects of angiotensin II, regardless of its origin. Because ARBs do not inhibit the ACE enzyme, these agents do not appear to affect bradykinin.[12,73] By inhibiting both the formation of angiotensin II and its effects on the AT_1 receptor, combination therapy with an ACE inhibitor plus an ARB offers a theoretical advantage over either agent used alone through more complete blockade of the deleterious effects of angiotensin II. Also, by directly blocking AT_1 receptors, ARBs would allow unopposed stimulation of AT_2 receptors, causing vasodilation and inhibition of ventricular remodeling.[12] Because bradykinin-related adverse effects of ACE inhibitors such as angioedema and cough lead to drug discontinuation in some patients, the potential for an ARB to produce similar clinical benefits with fewer side effects is of great interest. Whether ARBs add incremental benefit to current established therapies or are superior (or equivalent) to ACE inhibitors is the focus of several clinical trials.[72]

Although a number of ARBs are currently available, the primary clinical trials supporting the use of these agents in heart failure used either valsartan or candesartan.[72] The Valsartan Heart Failure Trial (Val-HeFT) evaluated whether the addition of valsartan to standard background heart failure therapy (which included an ACE inhibitor in 93% and a β-blocker in 35% of patients) improved survival.[74] The addition of valsartan had no effect on all-cause mortality but produced a 13% reduction in morbidity and mortality (principally as a result of reductions in heart failure hospitalizations). Subgroup analysis showed that the benefits were greatest in those patients not receiving background ACE inhibitor therapy. Based on these results, valsartan is now approved for use in patients with NYHA classes II to IV heart failure. The Valsartan in Acute Myocardial Infarction (VALIANT) trial compared the effect of valsartan, captopril, and the combination of the two agents in post-MI patients with symptomatic heart failure, reduced left ventricular systolic function, or both, in a noninferiority trial design.[47] The primary end point of total mortality occurred in 19.3% of patients receiving valsartan and captopril, 19.5% of captopril-treated patients, and 19.9% of the valsartan group. Thus, in this high-risk post-MI population, valsartan was as effective as captopril in reducing the risk of death, but combination therapy only increased the risk of adverse effects and did not improve survival compared to monotherapy with either agent. Based on these findings, valsartan is now approved for use in post-MI patients with left ventricular failure or left ventricular dysfunction.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trials were designed as three studies to compare candesartan with placebo in patients with symptomatic heart failure (Table 16–7).[75] Both the CHARM-Added (patients receiving background ACE-inhibitor therapy)[76] and CHARM-Alternative (patients intolerant of ACE-inhibitor therapy)[77] trials found significant reductions in the primary end point of cardiovascular death or hospitalization for heart failure in patients receiving candesartan, although the benefit was modest in CHARM-Added. No significant benefit of candesartan was observed in CHARM-Preserved (patients with LVEF >40%).[78] Overall, candesartan was well tolerated but its use was associated with an increased risk of hypotension, hyperkalemia, and renal dysfunction. On the basis of these results, candesartan is now approved for use in heart failure.

Although ACE inhibitors remain first-line therapy in patients with stage C heart failure and reduced LVEF, the current ACC/AHA guidelines recommend the use of ARBs in patients who are unable to tolerate ACE inhibitors.[1] Similarly, ARBs are alternatives to ACE inhibitors in patients with stages A and B heart failure.[1] Cough and angioedema are the most common causes of ACE inhibitor intolerance. Caution should be exercised when ARBs are used in patients with angioedema from ACE inhibitors as some cross-reactivity has been reported.[77,79] ARBs are not an alternative in patients with hypotension, hyperkalemia, or renal insufficiency secondary to ACE inhibitors because they are as likely to cause these adverse effects. Also, the combined use of ACE inhibitors, ARBs, and aldosterone

TABLE 16-7 Clinical Trials of Candesartan in Heart Failure

Trial	Drug	Patient Population	Primary End Point	Results (%)		Adjusted Hazard Ratio	*P* Value
				Drug	*Placebo*		
CHARM-Added	Candesartan vs. placebo	Symptomatic HF and EF ≤40% on ACE inhibitors	CV death or hospital admission for HF	37.9	42.3	0.85	0.01
CHARM-Alternative	Candesartan vs. placebo	Symptomatic HF and EF ≤40%, ACE-inhibitor intolerant	CV death or hospital admission for HF	33.0	40.0	0.70	<0.0001
CHARM-Preserved	Candesartan vs. placebo	Symptomatic HF and EF ≤40%	CV death or hospital admission for HF	22.0	24.3	0.86	0.051
CHARM-Overall	Candesartan vs. placebo	Combined from above 3 trials	All-cause mortality	23.0	25	0.90	0.032

ACE, angiotensin-converting enzyme; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity trial; CV, cardiovascular; EF, ejection fraction; HF, heart failure.

antagonists is not recommended because of the increased risk of renal dysfunction and hyperkalemia.[1] The specific drugs and doses proven to be effective in clinical trials should be used.

The role of ARBs as an adjunct to ACE inhibitors remains controversial. The CHARM-Added trial found the addition of candesartan to ACE inhibitor and β-blocker therapy produced incremental reductions in cardiovascular death and hospitalizations for heart failure, but did not improve overall survival.[76] In contrast, neither the VALIANT nor the Val-HeFT trials found additional benefit from the addition of valsartan to ACE-inhibitor treatment.[47,74] These results suggest the addition of an ARB to optimal heart failure therapy (ACE inhibitors, β-blockers, diuretics, etc.) offers, at best, marginal benefits with increased risk of adverse effects. The current guidelines indicate that the addition of an ARB can be considered in patients who remain symptomatic despite receiving conventional heart failure pharmacotherapy. Some clinicians suggest that the addition of an aldosterone antagonist to ACE inhibitor and β-blocker therapy is preferred over that of an ARB. The proven survival benefit of aldosterone antagonists in patients with NYHA classes III to IV heart failure (Randomized Aldactone Evaluation Study [RALES] trial) and in post-MI patients with left ventricular systolic dysfunction (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS] trial), as discussed in the following section, supports this approach.[16,17]

9 Aldosterone Antagonists Spironolactone and eplerenone are aldosterone antagonists that work by blocking the mineralocorticoid receptor, the target site for aldosterone. In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion. Although the diuretic effects with low doses of aldosterone antagonists are minimal, the potassium-sparing effects can have significant consequences as discussed below. In the heart, aldosterone antagonists inhibit cardiac extracellular matrix and collagen deposition, thereby attenuating cardiac fibrosis and ventricular remodeling.[80] Spironolactone also interacts with androgen and progesterone receptors, which may lead to gynecomastia and other sexual side effects in some patients. Such adverse effects are less frequent with eplerenone owing to its low affinity for the progesterone and androgen receptors.

Evidence that ACE inhibitors incompletely suppress aldosterone provided the impetus for examining the benefits of adding an aldosterone antagonist to ACE inhibitor therapy.[81] RALES randomized more than 1,600 patients with current or recent class IV heart failure to aldosterone blockade with spironolactone 25 mg/day or placebo.[16] Patients were also treated with standard therapy, usually including an ACE inhibitor, loop diuretic, and digoxin. Those with a serum creatinine concentration above 2.5 mg/dL or a serum potassium concentration above 5 mEq/L were excluded. The study was stopped prematurely after an average followup of 24 months because of a significant 30% reduction in the primary end point of total mortality with spironolactone. Spironolactone reduced mortality as a consequence of both progressive heart failure and sudden cardiac death. Spironolactone also produced a 35% reduction in hospitalizations for worsening heart failure and significant symptomatic improvement, as assessed by changes in NYHA functional class. The low dose of spironolactone was well tolerated in RALES. The most common adverse effect was gynecomastia, which occurred in 10% of men on spironolactone, compared to 1% of men on placebo, and led to treatment discontinuation in 2% of patients. There were statistically (but not clinically) significant increases in serum creatinine (by 0.05 to 0.10 mg/dL) and potassium concentrations (by 0.30 mEq/L) with spironolactone. The incidence of serious hyperkalemia (>6 mEq/L) was minimal and did not differ between spironolactone- and placebo-treated groups.

More recently, the EPHESUS trial evaluated the effect of selective antagonism of the mineralocorticoid receptor with eplerenone in patients with left ventricular dysfunction after MI.[17] To be eligible for study participation, patients had to have either evidence of heart failure or diabetes. More than 6,600 patients were randomized within 3 to 14 days of MI to eplerenone, titrated to 50 mg/day, or placebo in addition to standard therapy, which usually included an ACE inhibitor, β-blocker, aspirin, and diuretics. As occurred in RALES, patients with serum creatinine concentrations greater than 2.5 mg/dL or serum potassium concentrations greater than 5 mEq/L were excluded. Treatment with eplerenone was associated with a significant 15% relative reduction in the risk for death from any cause and a 15% reduction in the risk of hospitalization from heart failure. Serious hyperkalemia occurred in 5.5% of eplerenone-treated patients and 3.9% of placebo-treated patients. Eplerenone was not associated with gynecomastia.

The benefits of aldosterone antagonists in heart failure are not just a result of the inhibition of aldosterone's actions in the heart resulting in inhibition of aldosterone-mediated cardiac fibrosis and ventricular remodeling. Recent evidence points to an important role of aldosterone antagonists in attenuating the systemic proinflammatory state and oxidative stress caused by aldosterone.[14,80] And while spironolactone historically has been viewed as a diuretic, this is believed to contribute little to its benefits in heart failure, in part, because the doses used have minimal diuretic effect.[16] Thus, as with ACE inhibitors and β-blockers, the data on aldosterone antagonists also support the neurohormonal model of heart failure.

The clinical trial data suggest that the use of aldosterone antagonists in heart failure is associated with minimal risk. However, data from clinical practice suggest otherwise. In particular, an observational study of approximately 1.3 million elderly patients in the Ontario Drug Benefit Program found that the spironolactone prescription rate increased approximately fourfold immediately after the publication of RALES.[82] The increase in the prescription rate was accompanied by nearly threefold increases in the rate of hospital admissions and the rate of death related to hyperkalemia. Further evidence of spironolactone-induced hyperkalemia comes from small case series showing that 25% to 35% of patients treated outside the controlled clinical trial setting develop hyperkalemia (>5 mEq/L) and that 10% to 12% develop serious hyperkalemia.[83,84]

Potential factors contributing to the high incidence of hyperkalemia in clinical practice include the initiation of aldosterone antagonists in patients with impaired renal function or high potassium concentrations and the failure to decrease or stop potassium supplements when starting aldosterone antagonists. Other risk factors for hyperkalemia include diabetes, older age, inadequate laboratory monitoring, and concomitant use of high-dose ACE inhibitors, β-blockers, NSAIDs, or cyclooxygenase-2 inhibitors. The ACC/AHA recently recommended strategies to minimize the risk for hyperkalemia with aldosterone antagonists in heart failure.[1] Table 16–8 summarizes these strategies. Chief among these recommendations is to avoid aldosterone antagonists in patients with renal dysfunction. It is important to emphasize here that serum creatinine may overestimate renal function in the elderly and in patients with decreased muscle mass, in whom creatinine clearance should serve as a guide for the appropriateness of aldosterone antagonist therapy. The risk for hyperkalemia is dose dependent, and the morbidity and mortality reductions with aldosterone antagonists in clinical trials occurred at low doses (i.e., spironolactone 25 mg/day and eplerenone 50 mg/day). Therefore, the doses of aldosterone antagonists should be limited to those associated with beneficial effects so as to decrease the risk for hyperkalemia.

Only 10% of RALES participants were taking β-blockers at baseline because the benefits of β-blockers in heart failure were not appreciated fully at the time the trial began.[16] β-Blockers inhibit plasma renin release and may provide additional suppression of the renin–angiotensin–aldosterone system when used with ACE inhib-

TABLE 16-8 Recommended Strategies for Reducing the Risk for Hyperkalemia with Aldosterone Antagonists

- Avoid starting aldosterone antagonists in patients with any of the following:
  - Serum creatinine concentration >2.0 in women or >2.5 mg/dL in men or a creatinine clearance <30 mL/min
  - Recent worsening of renal function
  - Serum potassium concentration ≥5.0 mEq/L
  - History of severe hyperkalemia
- Start with low doses (12.5 mg/day for spironolactone and 25 mg/day for eplerenone), especially in the elderly and in those with diabetes or a creatinine clearance <50 mL/min
- Decrease or discontinue potassium supplements when starting an aldosterone antagonist
- Avoid concomitant use of NSAIDs or COX-2 inhibitors
- Avoid concomitant use of high-dose ACE inhibitors or ARBs
- Avoid triple therapy with an ACE inhibitor, ARB, and aldosterone antagonist
- Monitor serum potassium concentrations and renal function within 3 days and 1 week after the initiation or dose titration of an aldosterone antagonist or any other medication that could affect potassium homeostasis; thereafter, potassium concentrations and renal function should be monitored monthly for the first 3 months, and then every 3 months
- If potassium exceeds 5.5 mg/dL at any point during therapy, discontinue any potassium supplementation or, in the absence of potassium supplements, reduce or stop aldosterone antagonist therapy
- Counsel patients to
  - Limit intake of high-potassium-containing foods and salt substitutes
  - Avoid the use of over-the-counter nonsteroidal antiinflammatory drugs
  - Temporarily discontinue aldosterone antagonist therapy if diarrhea develops or diuretic therapy is interrupted

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COX, cyclooxygenase; NSAIDs, nonsteroidal antiinflammatory drugs.

Adapted from Hunt SA, Abraham WT, Chin MH et al. Circulation 2005;112:e154–235.

itors. Thus, there has been some speculation about whether spironolactone will provide further benefit in patients receiving both ACE inhibitors and β-blockers. However, data from EPHESUS provide some clarity to this issue, as the majority of EPHESUS participants were on β-blockers at baseline and the trial still demonstrated significant reductions in mortality with the addition of eplerenone.[17]

Current guidelines state that it is reasonable to add an aldosterone antagonist to standard therapy in select patients provided that potassium and renal function can be carefully monitored.[1] Based on data from RALES and EPHESUS, low-dose aldosterone antagonists may be appropriate for two groups of patients: those with moderately severe to severe heart failure who are receiving standard therapy and those with left ventricular dysfunction early after MI.[1] For patients who fall outside the populations studied in these clinical trials, there are no clear guidelines on aldosterone antagonist use. Trials to address the efficacy of aldosterone antagonism in patients with mild to moderate heart failure symptoms or in patients with preserved left ventricular systolic function are ongoing. Although there are currently no data on the use of aldosterone antagonists in patients with class I, class II, or stable class III heart failure, it might be reasonable to consider their use in these patients who require potassium supplementation. The premise for use in this setting would be that it might be possible to reduce or eliminate potassium supplementation while potentially providing additional benefit with respect to altering the disease course.

9 Digoxin In 1785, William Withering was the first to report extensively on the use of foxglove (*Digitalis purpurea*) for the treatment of dropsy (i.e., edema). Although digitalis glycosides have been in clinical use for more than 200 years, not until the 1920s were they clearly demonstrated to have a positive inotropic effect on the heart. Furthermore, it was not until the late 1980s that clinical trials were conducted to critically evaluate the role of digoxin in the therapy of chronic heart failure. The results of the Digitalis Investigational Group (DIG) trial helped clarify the role of digoxin in this setting.[85] The view of digoxin has also shifted over the past decade. Although it was historically considered useful in heart failure because of its positive inotropic effects, it now seems clear that its real benefits in heart failure are related to its neurohormonal modulating effects.

The efficacy of digoxin in patients with heart failure and supraventricular tachyarrhythmias such as atrial fibrillation is well established and widely accepted. Its role in heart failure patients with normal sinus rhythm has been considerably more controversial. Until the 1980s, most data supporting efficacy of digoxin in these patients came from anecdotal evidence and seriously flawed or uncontrolled studies. Since then, a number of clinical trials have shown that digoxin improves LVEF, quality of life, exercise tolerance, and heart failure symptoms.[86,87] However, these studies involved small numbers of patients followed for short time periods with many of the patients being withdrawn from preexisting digoxin treatment upon entering the trial. Although these trials demonstrated hemodynamic and symptomatic improvement in heart failure patients receiving digoxin, an unresolved issue was the unknown effect of digoxin on mortality. This was of particular concern given the increased mortality seen with other positive inotropic drugs, and finally led to organization and performance of the DIG trial to determine the effects of digoxin on survival in patients with heart failure in sinus rhythm.[85]

The DIG trial was a double-blind, randomized, placebo-controlled trial with the primary end point of all-cause mortality.[85] Patients (n = 6,800) with heart failure symptoms and an ejection fraction of 45% or less were eligible and were followed for a mean of 37 months. Most patients received background therapy with diuretics and ACE inhibitors. The mean serum digoxin concentration achieved was 0.8 ng/mL after 12 months of therapy. No significant difference in all-cause mortality was found between patients receiving digoxin and placebo (34.8% and 35.1%, respectively). A trend toward lower mortality as a consequence of worsening heart failure was observed in the digoxin group, although this was offset by a trend toward an increased mortality from other cardiovascular causes (presumably arrhythmias) in patients receiving digoxin. Hospitalizations for worsening heart failure were reduced 28% by digoxin compared to placebo ($P < 0.001$), whereas hospitalizations for other cardiovascular causes were increased in the digoxin group. In all, 64.3% of digoxin-treated patients were hospitalized compared to 67.1% of patients receiving placebo ($P = 0.006$). Therefore, DIG is the first trial to show that a positive inotropic agent does not increase mortality and actually decreases morbidity in patients with heart failure.

Although digoxin does not improve survival in heart failure patients, multiple post-hoc analyses of data from studies evaluating the effect of digoxin withdrawal have helped clarify the role of digoxin use for patients in sinus rhythm.[86] Collectively, these studies suggested the drug produces important symptomatic benefits and that digoxin withdrawal increased the risk of treatment failure and deterioration of exercise capacity and ejection fraction. Furthermore, the risk of symptomatic exacerbation of heart failure after digoxin discontinuation was highest in patients with the most severe symptoms.[86] Based on this evidence, digoxin can be beneficial in patients with symptomatic or stage C heart failure and reduced LVEF in addition to standard therapy to reduce heart failure hospitalizations. Furthermore, digoxin should not be used in patients with a normal LVEF, sinus rhythm, and no history of heart failure symptoms, because the risk is not balanced by any known benefit.[1]

Two retrospective analyses of the combined PROVED/RADIANCE database[88] and the DIG Trial database[89] offer additional insights into the clinical benefit of low serum digoxin concentrations. While all patients in the Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin (PROVED) and Randomized Assessment of Digoxin on Inhibitors of the Angiotensin

Converting Enzyme (RADIANCE) trials who continued to take digoxin did significantly better than those who were withdrawn, those who had plasma digoxin concentrations between 0.5 and 0.9 ng/mL were just as likely to be free of worsening heart failure as those with higher plasma concentrations. Retrospective analysis of the DIG trial database suggests that a serum digoxin concentration of 0.5 to 0.8 ng/mL may be associated with a reduction in mortality, whereas higher concentrations may increase mortality.[89] In another post-hoc analysis of the DIG trial, digoxin therapy was associated with an increased risk of death in women, but not in men.[90] This finding was refuted in another analysis of the same data which demonstrated that a beneficial effect of digoxin was evident at serum concentrations from 0.5 to 0.9 ng/mL, whereas serum concentrations greater than or equal to 1.2 ng/mL were harmful.[91] More recently, the most comprehensive reanalysis of the DIG trial database found that serum concentrations of 0.5 to 0.9 ng/mL were associated with lower mortality, all-cause hospitalizations, and heart failure hospitalizations, whereas serum concentrations greater than or equal to 1 ng/mL were associated with lower heart failure hospitalizations with no effect on mortality. Serum concentrations of 0.5 to 0.9 ng/mL had no interaction with LVEF greater than 45% or gender.[92] Of the 7,788 patients randomized in the DIG trial, 988 patients had a LVEF greater than 45%; digoxin had no effect on mortality or hospitalization in these patients.[93]

These results suggest that most of the benefit from digoxin is achieved at low plasma concentrations and little additional effect is achieved with higher doses. Thus, for most patients, the target digoxin plasma concentration should be 0.5 to 1.0 ng/mL. This more conservative target would also be expected to decrease the risk of adverse effects from digoxin toxicity; in fact, more recent assessment of the rate of digoxin toxicity suggests a significant decline in the overall incidence.[94] In most patients with normal renal function, this plasma concentration range can be achieved with a daily dose of 0.125 mg. Patients with decreased renal function, the elderly, and those who are receiving interacting drugs (e.g., amiodarone) should receive 0.125 mg every other day. In patients with atrial fibrillation and a rapid ventricular response, the historic practice of increasing digoxin doses (and concentrations) until rate control is achieved is no longer recommended. Digoxin alone is often ineffective to control ventricular response in patients with atrial fibrillation and increasing the dose only increases the risk of toxicity. Digoxin combined with a β-blocker or amiodarone is superior to either agent alone for controlling ventricular response in patients with atrial fibrillation and heart failure.[95] Consequently, target digoxin plasma concentrations are the same regardless of whether the patient is in sinus rhythm or atrial fibrillation. Several equations and nomograms have been proposed to estimate digoxin maintenance doses based on estimated renal function for a particular patient and population pharmacokinetic parameters. These methods are extensively reviewed elsewhere.[96] Recently, investigators developed a digoxin dosing nomogram that targets a lower digoxin plasma concentration.[97] In the absence of supraventricular tachyarrhythmias, a loading dose is not indicated because digoxin is a mild inotropic agent that will produce gradual effects over several hours, even after loading.

Digoxin's place in the pharmacotherapy of chronic heart failure can be summarized for two patient groups. In patients with heart failure and supraventricular tachyarrhythmias such as atrial fibrillation, it should be considered early in therapy to help control ventricular response rate. For patients in normal sinus rhythm, although digoxin does not improve survival, its effects on symptom reduction and clinical outcomes are evident in patients with mild to severe heart failure. Consequently, it should be used in conjunction with other standard heart failure therapies, including diuretics, ACE inhibitors, and β-blockers, in patients with symptomatic heart failure to reduce hospitalizations.

⑩ Nitrates and Hydralazine Nitrates and hydralazine were combined originally in the treatment of heart failure because of their complementary hemodynamic actions. Nitrates, by serving as nitric oxide donors, activate guanylate cyclase to increase cyclic guanosine monophosphate in vascular smooth muscle. This results in venodilation and reductions in preload. Hydralazine is a direct-acting vasodilator that acts predominantly on arterial smooth muscle to reduce SVR and increase stroke volume and cardiac output (see Fig. 16–1). Hydralazine also has antioxidant properties and appears to prevent nitrate tolerance.[98] Evidence also suggests that the combination of hydralazine and nitrates may exert beneficial effects beyond their hemodynamic actions by interfering with the biochemical processes associated with heart failure progression.[1,99]

The efficacy of the combination of hydralazine and isosorbide dinitrate (ISDN) was evaluated in three large, randomized heart failure trials. The first trial predated the use of ACE inhibitors and β-blockers in heart failure and found that the combination of hydralazine 75 mg and ISDN 40 mg, each given four times daily, reduced mortality in patients receiving diuretics and digoxin compared to placebo.[100] However, a subsequent trial comparing the combination with an ACE inhibitor demonstrated greater mortality reduction with the ACE inhibitor.[101] Post-hoc analysis of these trials suggested that the combination of hydralazine and ISDN was particularly effective in African Americans, and led to examining the efficacy of adding the combination to standard therapy in this racial group.

The African American Heart Failure Trial (A-HeFT) randomized 1,050 self-identified African Americans with class III or IV heart failure to hydralazine plus ISDN or placebo, each in addition to standard therapy, usually including an ACE inhibitor (or ARB), β-blocker, and diuretic, with or without digoxin and spironolactone.[99] The trial used a fixed dose combination product, BiDil®, that contains hydralazine 37.5 mg and ISDN 20 mg. Therapy was initiated as a single tablet given three times daily, then titrated to two tablets (hydralazine 75 mg/ISDN 40 mg) three times daily if tolerated. The trial was terminated early after a mean followup of 10 months because of a significant (43%) reduction in all-cause mortality in patients receiving hydralazine/ISDN compared to placebo. The primary composite end point of mortality, hospitalizations for heart failure, and quality of life was also significantly improved with the combination product. Based on these results, BiDil® was approved by the FDA to treat heart failure exclusively in African Americans.

The mechanism for the beneficial effects of hydralazine/ISDN is believed to relate to an increase in nitric oxide bioavailability secondary to nitric oxide donation from ISDN and a hydralazine-mediated reduction in oxidative stress.[98] Nitric oxide attenuates myocardial remodeling and may play a protective role in heart failure.[102] It is suggested that African Americans have less nitric oxide than do non-African Americans, and thus, may derive particular benefit from therapy that enhances nitric oxide bioavailability. Whether the benefits of adding hydralazine/ISDN to standard therapy extend to non-African Americans remains to be determined.

Guidelines from the Heart Failure Society of America recommend the addition of hydralazine and ISDN as part of standard therapy, including ACE inhibitors, in African Americans with moderately severe to severe heart failure.[33] The addition of hydralazine and ISDN is also reasonable in patients of other ethnicities who continue to have symptoms despite optimized therapy with an ACE inhibitor (or ARB) and β-blocker.[1] For patients who are unable to tolerate an ACE inhibitor because of cough or angioedema, an ARB is recommended as the first-line alternative.[1] Hydralazine and ISDN is appropriate as first-line therapy in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or possibly hypotension.

There are several potential obstacles to successful therapy with hydralazine and ISDN in heart failure. First is the need for frequent

dosing, with the fixed-dose combination dosed three times daily and the individual drugs dosed four times daily in clinical trials. Second, adverse effects are common with hydralazine/ISDN, with headache, dizziness, and gastrointestinal distress occurring more frequently with hydralazine/ISDN than with placebo in clinical trials.[99,100] A third potential obstacle is the increased cost of the fixed-dose combination product compared to the individual drugs purchased separately, which may preclude the use of the combination product in some patients. Treatment with the two separate drugs rather than the combination product may compromise adherence to therapy. Thus, if therapy with hydralazine and ISDN is deemed appropriate, patients may need continual reinforcement to maintain good medication adherence, especially if the individual drugs are used. It is important to recognize that none of the above trials incorporated a nitrate-free interval in the dosing regimen.

Treatment of Concomitant Disorders

Heart failure is often accompanied by other disorders whose natural history or therapy may affect morbidity and mortality. In selected patients, optimal management of these concomitant disorders may have a profound impact on heart failure symptoms and outcomes.

Hypertension Although ischemic heart disease has replaced hypertension as the most common cause of heart failure, still nearly two-thirds of heart failure patients have current hypertension or a previous history of hypertension.[1] Hypertension can contribute directly to the development of heart failure and also contributes indirectly by increasing the risk of coronary artery disease. Pharmacotherapy of hypertension in patients with heart failure should initially involve agents that can treat both disorders such as ACE inhibitors, β-blockers, and diuretics. If control of hypertension is not achieved after optimizing treatment with these agents, the addition of an ARB, aldosterone antagonist, isosorbide dinitrate/hydralazine, or a second-generation calcium channel blocker such as amlodipine (or possibly felodipine) should be considered. Medications that should be avoided include the calcium channel blockers with negative inotropic effects (e.g., verapamil, diltiazem, and most dihydropyridines) and direct-acting vasodilators (e.g., minoxidil) that cause sodium retention.

Angina Coronary artery disease is the most common heart failure etiology. Consequently, appropriate management of coronary disease and its risk factors is an important strategy for the prevention and treatment of heart failure. Coronary revascularization should be strongly considered in patients with both heart failure and angina.[1] Pharmacotherapy of angina in patients with heart failure should use drugs that can successfully treat both disorders. Nitrates and β-blockers are effective antianginal agents and are the preferred agents for patients with both disorders as they may improve hemodynamics and clinical outcomes.[1] It should be noted that the antianginal effectiveness of these agents may be significantly limited if fluid retention is not controlled with diuretics. Similar to their use in hypertension, both amlodipine and felodipine appear to be safe to use in this setting. Optimization of other treatments for secondary prevention of coronary and other atherosclerotic vascular disease should also be considered.[37] Although their precise role in the treatment of heart failure awaits the results of additional studies, initial evidence suggests statins might decrease the risk of heart failure hospitalizations and death, regardless of heart failure etiology.[24]

Atrial Fibrillation Atrial fibrillation is the most frequently encountered arrhythmia and it is commonly found in patients with heart failure, affecting 10% to 30% of patients.[1] The high incidence of atrial fibrillation in the heart failure population is not surprising as each of these two disorders predisposes to the other and they share many risk factors, including coronary artery disease and hypertension. The presence of atrial fibrillation in patients with heart failure is associated with a worse long-term prognosis.[1] The combination of atrial fibrillation and heart failure may exert a number of detrimental effects, including increased risk of thromboembolism secondary to stasis of blood in the atria, a reduction in cardiac output because of loss of the atrial contribution to ventricular filling, and hemodynamic compromise from the rapid ventricular response. Moreover, heart failure exacerbations and atrial fibrillation are closely linked and it is often difficult to determine which disorder caused the other. For example, worsening heart failure results in volume overload which, in turn, causes atrial distension and increases the risk of atrial fibrillation. Similarly, atrial fibrillation with a rapid ventricular response can reduce cardiac output and lead to heart failure exacerbation. Thus, optimal management of both conditions is required with careful attention paid to control of ventricular response and anticoagulation for stroke prevention (see Chap. 19).[95]

Recent studies suggest that ACE inhibitors, ARBs, and β-blockers decrease the incidence of atrial fibrillation in patients with heart failure, providing further support for their use in these patients.[103,104] Digoxin is frequently used to slow ventricular response in patients with heart failure and atrial fibrillation. However, it is more effective at rest than with exercise and it does not affect the progression of heart failure. β-Blockers are more effective than digoxin and have the added benefits of improving morbidity and mortality. Combination therapy with digoxin and a β-blocker may be more effective for rate control than either agent used alone. Calcium channel blockers with negative inotropic effects, such as verapamil or diltiazem, should be avoided. Amiodarone is a reasonable alternative for rate control in those patients who are not responding to digoxin and/or β-blockers or who have contraindications to these agents.[95] Appropriate selection of antithrombotic therapy that considers the presence of risk factors for thromboembolism in an individual patient is also required.[95]

Because of the close association between atrial fibrillation, heart failure exacerbations, and hospitalizations, many clinicians prefer maintenance of sinus rhythm with antiarrhythmic drugs to the rate-control approach in the treatment of patients with both disorders. However, it must be noted that the benefits of restoring and maintaining sinus rhythm remain unclear in this population and is not without risk. Although the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study showed no difference in outcomes between the rhythm control and rate control approaches, less than 10% of the patients in this study had significant left ventricular dysfunction.[105] Several ongoing clinical trials should help clarify the best approach to these difficult-to-manage patients. In general, amiodarone is the preferred agent if the rhythm control approach is taken. Although it has many noncardiac toxicities, amiodarone does not have cardiodepressant or significant proarrhythmic effects and appears to be safe in heart failure. Dofetilide also appears to be safe and effective in this population. Class I antiarrhythmics should be avoided.[95]

Diabetes Diabetes is highly prevalent in the heart failure population, with current estimates indicating it is present in approximately one-third of heart failure patients.[30,106] As an important risk factor for coronary artery disease, diabetes directly contributes to the development of heart failure. Importantly though, diabetes is a risk factor for heart failure independent of coronary artery disease or hypertension, is associated with hastened heart failure progression, and is a significant predictor of mortality in patients with heart failure.[106]

Pharmacotherapy of diabetes in heart failure patients is complicated by concerns about adverse effects associated with metformin and the thiazolidinedione (TZD) drugs (rosiglitazone and pioglitazone). The beneficial effects of these agents on glucose control and

cardiovascular risk factors lead to their widespread use in patients with heart failure in spite of the warnings in the product labeling against their use.[106] The metformin product labeling states that it is contraindicated for use in patients with heart failure requiring pharmacologic treatment because of the purported risk of lactic acidosis. However, data from retrospective analyses involving more than 3,000 patients suggest that metformin is safe (no reports of lactic acidosis) in patients with heart failure.[107] In addition, these reports show that metformin treatment is associated with decreased mortality and hospitalizations compared to conventional antihyperglycemic therapy.[107] Consequently, some clinicians suggest that the contraindication to metformin use in heart failure should be reexamined. However, the lack of prospective data about the safety and efficacy of metformin in patients with heart failure indicates that if the drug is used, it should be used cautiously with careful monitoring of volume status and renal function. Although the mechanism(s) are presently unclear, the TZDs are associated with weight gain, peripheral edema, and heart failure. The TZD package insert indicates these agents should not be used in patients with class III or IV heart failure because they may cause intravascular volume expansion and heart failure exacerbation. Most clinical trials with these drugs excluded patients with moderate to severe heart failure, thus the evidence supporting this precaution comes mainly from retrospective analyses and case reports. Because of the potential risk, a recent consensus statement indicates TZDs should not be used in patients with NYHA class III or class IV heart failure.[30] TZDs should be used cautiously in patients with class I or II symptoms, with close observation needed to detect weight gain, edema formation, or heart failure exacerbation.[30]

Drug Class Information

7 Diuretics[44] Loop diuretics, as described earlier, represent the typical diuretic therapy for patients with heart failure because of their potency and, as such, are the only diuretics discussed here. There are currently three loop diuretics available that are used routinely: furosemide, bumetanide, and torsemide. They share many similarities in their pharmacodynamics, with their differences being largely pharmacokinetic in nature. Table 16–5 shows the relevant information on the loop diuretics. Following oral administration, the peak effect with all the agents occurs in 30 to 90 minutes, with duration of 2 to 3 hours (slightly longer for torsemide). Following intravenous administration, the diuretic effect begins within minutes. All three drugs are highly (>95%) bound to serum albumin and enter the nephron by active secretion in the proximal tubule. The magnitude of effect is determined by the peak concentration achieved in the nephron, and there is a threshold concentration that must be achieved before any diuresis is seen.

The biggest difference between the agents is bioavailability. Bioavailability of bumetanide and torsemide is essentially complete (80% to 100%), whereas furosemide bioavailability exhibits marked intra- and interpatient variability. Furosemide bioavailability ranges from 10% to 100%, with an average of 50%. Thus, if bioequivalent intravenous and oral doses are desired, oral furosemide doses should be approximately double that of the intravenous dose, whereas intravenous and oral doses are the same for torsemide and bumetanide. Coadministration of furosemide and bumetanide with food can decrease bioavailability significantly, whereas food has no effect on bioavailability of torsemide. The intraabdominal congestion that can occur in heart failure also may slow the rate (and thus decrease the peak concentration) of furosemide, which can reduce the diuretic's efficacy. Thus furosemide is most problematic with respect to rate and extent of absorption and the factors that influence it, whereas torsemide has the least-variable bioavailability.

Recent data suggest that these differences in bioavailability and variability may have clinical implications. For example, several studies suggest that torsemide is absorbed reliably and is associated with better outcomes than the more variably absorbed furosemide.[108,109] Torsemide is preferred in patients with persistent fluid retention despite high doses of other loop diuretics. And while the costs of torsemide exceed those of furosemide, pharmacoeconomic analyses suggest that the costs of care are similar or less with torsemide.[109] These data require confirmation in controlled, double-blinded clinical trials but provide preliminary evidence that the more reliably absorbed loop diuretics may be superior to furosemide.

The loop diuretics exhibit a ceiling effect in heart failure, meaning that once the ceiling dose is reached, no additional response is achieved by increasing the dose. Thus, when this dose is reached, additional diuresis is achieved by giving the drug more often (twice daily or occasionally three times daily) or by giving combination diuretic therapy. Table 16–5 lists the ceiling doses. Multiple daily dosing achieves a more sustained diuresis throughout the day. When dosed two or three times daily, the first dose is usually given first thing in the morning and the final dose in late afternoon/early evening.

Diuretics cause a variety of metabolic abnormalities, with severity related to the potency of the diuretic. Chapter 15 has a detailed discussion on the adverse effects of diuretic therapy. Hypokalemia is the most common metabolic disturbance with thiazide and loop diuretics, which in heart failure patients may be exacerbated by hyperaldosteronism. Hypokalemia increases the risk for ventricular arrhythmias in heart failure and is especially worrisome in patients receiving digoxin. Hypokalemia is often accompanied by hypomagnesemia. Because adequate magnesium is necessary for entry of potassium into the cell, cosupplementation with both magnesium and potassium may be necessary to correct the hypokalemia. Concomitant ACE inhibitor (or ARB) and/or aldosterone antagonist therapy may help to minimize diuretic-induced hypokalemia because these drugs tend to increase serum potassium concentration through their inhibitory effect on aldosterone secretion. Nonetheless, the serum potassium concentration should be monitored closely in heart failure patients and supplemented appropriately when needed. In addition to metabolic abnormalities, a recent post-hoc analysis of the DIG trial suggested that chronic diuretic use was associated with increased risk of mortality and hospitalization.[110] These findings must be interpreted with caution because this trial was not designed to evaluate outcomes associated with diuretic therapy. However, they do serve to remind clinicians of the importance of appropriate patient selection and monitoring when using diuretic therapy.

5 Angiotensin-Converting Enzyme Inhibitors A number of ACE inhibitors are available currently in the United States; Table 16–9 summarizes those commonly used in the treatment of patients with heart failure. Although ACE inhibitors vary in their chemical structure (e.g., sulfhydryl- vs. non–sulfhydryl-containing agents) and tissue affinity, the major differences in the ACE inhibitors are not in these pharmacologic properties but in their pharmacokinetic properties.[13] Although it appears that mortality reduction with ACE inhibitors is probably a drug class effect, not all ACE inhibitors that are FDA approved for treatment of heart failure have been evaluated for their effects on mortality in heart failure. Thus it seems most prudent to use those agents that have been documented to reduce morbidity and mortality because the dose required for this effect has been documented.[1] Table 16–9 also summarizes the target doses for survival benefit.

To minimize the risk of hypotension and renal insufficiency, ACE inhibitor therapy should be started with low doses followed by gradual titration to the target doses as tolerated.[1] Asymptomatic hypotension should not be considered a contraindication to initiation of an ACE inhibitor although initiation or dose increases in patients with systolic blood pressures less than 90 to 100 mm Hg should be done cautiously. Renal function and serum potassium

TABLE 16-9 Angiotensin-Converting Enzyme Inhibitors Routinely Used for the Treatment of Heart Failure

Generic Name	Brand Name	Initial Dose	Target Dosing–Survival Benefit[a]	Prodrug	Elimination[b]
Captopril	Capoten	6.25 mg tid	50 mg tid	No	Renal
Enalapril	Vasotec	2.5–5 mg bid	10 mg bid	Yes	Renal
Lisinopril	Zestril, Prinivil	2.5–5 mg daily	20–40 mg daily[c]	No	Renal
Quinapril	Accupril	10 mg bid	20–40 mg bid[d]	Yes	Renal
Ramipril	Altace	1.25–2.5 mg bid	5 mg bid	Yes	Renal
Fosinopril	Monopril	5-10 mg daily	40 mg daily[d]	Yes	Renal/hepatic
Trandolapril	Mavik	0.5–1 mg daily	4 mg daily	Yes	Renal/hepatic
Perindopril	Aceon	2 mg daily	8–16 mg daily[d]	Yes	Renal/hepatic

[a]Target doses associated with survival benefits in clinical trials.
[b]Primary route of elimination.
[c]Note that in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial (Circulation 1999;100:2312–2318), no significant difference in mortality was found between low dose (~5 mg/day) and high dose (~35 mg/day) lisinopril therapy.
[d]Effects on mortality have not been evaluated.

should be evaluated within 1 to 2 weeks after therapy is started with subsequent periodic assessments, especially after dose increases. Careful attention to appropriate doses of diuretics is important as fluid overload may blunt the beneficial effects of ACE inhibitors and overdiuresis increases the risk of hypotension and renal insufficiency. After titration of the drug to the target dose, most patients tolerate chronic therapy with few complications. Although symptoms may improve within a few days of initiating therapy, it may take weeks to months before the full benefits are apparent. Even if symptoms do not improve, long-term ACE inhibitor therapy should be continued to reduce the risk of mortality and hospitalization.

Because ACE inhibitors were the first agents to show improvements in heart failure survival and were frequently used as background therapy in clinical trials of other medications, they are often used as the initial therapy in patients with left ventricular systolic function. Traditionally, after titration of the ACE inhibitor dose, the addition of β-blockers was considered. The expected ACE inhibitor-mediated decrease in blood pressure made some clinicians reluctant to initiate β-blocker therapy. Because of the impressive benefits of β-blockers, initiation of β-blocker therapy should not be delayed in patients who fail to reach target ACE inhibitor doses.[1] Because activation of the SNS occurs before that of the RAAS and is an important stimulus for RAAS activation, there is debate over whether ACE inhibitors or β-blockers should be used as initial therapy. The results of the previously discussed CIBIS III trial did not provide compelling evidence to support initiation of β-blockers prior to ACE inhibitors.[68] Consequently, in most patients, ACE inhibitors should be the initial therapy, but it is important to remember that the greatest benefit is seen when both an ACE inhibitor and β-blocker are used.

Because of the high prevalence of coronary artery disease in patients with heart failure, aspirin is frequently coadministered with ACE inhibitors. Several retrospective cohort analyses suggest that aspirin may attenuate the hemodynamic and mortality benefits of ACE inhibitors.[111] The postulated mechanism of this interaction involves opposing effects on synthesis of vasodilatory prostaglandins. The ACE inhibitor–mediated increase in bradykinin increases the synthesis of vasodilatory prostaglandins that have favorable hemodynamic benefits in heart failure. Because of aspirin's effect on prostaglandin synthesis, this potentially beneficial action of ACE inhibitors may be negated. However, in contrast with studies that showed an ACE inhibitor-aspirin interaction, other investigators have found no interaction, even in patients without coronary artery disease or with impaired renal function.[111,112] Because there is no prospective evidence confirming an interaction between these agents, it is currently recommended that the decision to use each of these medications be made based on whether an individual patient has indications for each drug. Use of aspirin doses of 160 mg per day or less should be considered.

Adverse Effects. The primary adverse effects of ACE inhibitor therapy are secondary to their major pharmacologic effects of suppressing angiotensin II and increasing bradykinin. The reductions in angiotensin II are associated with hypotension and functional renal insufficiency which are the most common adverse effects observed with ACE inhibitors. Hypotension may be asymptomatic or manifested as dizziness, lightheadedness, presyncope, or syncope. It occurs most commonly early in therapy or after an increase in dose, although it may occur at any time during treatment. Risk factors for hypotension include hyponatremia (serum sodium <130 mEq/L), hypovolemia, and overdiuresis.[1] The occurrence of hypotension may be minimized by initiating therapy with lower ACE inhibitor doses and/or temporarily withholding or reducing the dose of diuretic, and liberalizing salt and fluid intake.[1] An often overlooked solution to hypotension is to space the administration times of vasoactive medications (e.g., diuretics and β-blockers) throughout the day so that these medications are not all administered at or near the same time. Many patients who experience symptomatic hypotension early in therapy are still good candidates for long-term treatment if risk factors for low blood pressure are addressed.

Functional renal insufficiency is manifested as increases in serum creatinine and blood urea nitrogen. As cardiac output and renal blood flow decline, renal perfusion is maintained by the vasoconstrictor effect of angiotensin II on the efferent arteriole. Patients most dependent on this system for maintenance of renal perfusion (and therefore most likely to develop functional renal insufficiency with ACE inhibitors) are those with severe heart failure, hypotension, hyponatremia, volume depletion, bilateral renal artery stenosis, and concomitant use of NSAIDs.[113] Sodium depletion, usually secondary to diuretic therapy, is the most important factor in the development of functional renal insufficiency with ACE inhibitor therapy. Renal insufficiency therefore can be minimized in many cases by reduction in diuretic dosage or liberalization of sodium intake. Increases in serum creatinine of 10% to 20% from baseline are commonly observed after initiation of ACE inhibitor therapy. In some patients, the serum creatinine will return to baseline levels without a reduction in ACE inhibitor dose.[113] Increases in serum creatinine of >0.5 mg/dL if the baseline creatinine is <2.0 mg/dL or >1.0 mg/dL if the creatinine is >2.0 mg/dL, should prompt clinicians to reconsider ACE therapy and evaluate potential causes for the abrupt decline in renal function.[113] Because renal dysfunction with ACE inhibitors is secondary to alterations in renal hemodynamics, it is almost always reversible upon discontinuation of the drug.[113]

Careful dose titration can minimize the risks of hypotension and transient worsening of renal function. Thus usual initial doses should be about one-fourth the final target dose with slow upward dose titration over several days based on blood pressure and serum

creatinine. In certain patients, especially those hospitalized patients who seem to be at high risk for hypotension or worsening of renal function, it also may be advisable to initiate therapy with a short-acting agent such as captopril. This will help minimize the duration of adverse effects should they occur. Once stabilized on ACE inhibitor therapy with captopril, the patient can then be switched to a longer-half-life drug.

Retention of potassium with ACE inhibitor therapy can occur and is caused by the reduced feedback of angiotensin II to stimulate aldosterone release. Hyperkalemia is most likely to occur in patients with renal insufficiency and in those taking concomitant potassium supplements, potassium-containing salt substitutes, or potassium-sparing diuretic therapy (including an aldosterone antagonist), especially if they have diabetes.[113] The more widespread use of aldosterone antagonists (e.g., spironolactone) in patients with heart failure may increase the risk of hyperkalemia.[82]

ACE inhibitors are also associated with other important adverse effects. A dry, hacking cough occurs with a similar frequency (5% to 15% of patients) with all the agents and is related to bradykinin accumulation. The cough is usually nonproductive, occurs within the first few months of therapy, resolves within 1 to 2 weeks of drug discontinuation, and reappears with rechallenge. Because cough occurs in up to 40% of patients with heart failure, independent of ACE inhibitor use, it is important to rule out other potential causes of cough, such as pulmonary congestion. Because cough is a bradykinin-mediated effect, replacement of ACE inhibitor therapy with an ARB would be reasonable in those patients who cannot tolerate the cough. Angioedema is a rare, but potentially life-threatening complication that is also believed to be related to bradykinin accumulation. It may occur more frequently in African Americans than in other populations.[1] Use of ACE inhibitors is contraindicated in patients with a history of angioedema. ARBs may be an alternative therapy in patients with ACE inhibitor-induced angioedema, although caution is advised as rare cross-reactivity is reported.[1,77,79] ACE inhibitors are contraindicated during the second and third trimesters of pregnancy because of the increased risk of fetal renal failure, intrauterine growth retardation, and other congenital defects. A recent analysis using a Medicaid database of nearly 30,000 patients suggests that first trimester use of ACE inhibitors should also be avoided as the risk of major congenital defects was increased 2.7-fold in infants exposed to these agents during the first trimester.[114]

5 Angiotensin II Receptor Blockers Although ACE inhibitors remain the agents of first choice to treat stage C heart failure with reduced LVEF, ARBs approved for the treatment of heart failure are now the recommended alternatives in patients who are unable to tolerate an ACE inhibitor.[1] Although seven ARBs are currently on the market, only two, candesartan and valsartan, are approved for the treatment of heart failure. The use of these two agents is supported by clinical trial data that document a target dose associated with improved survival and other important outcomes in patients with decreased LVEF.[47,74,75] Thus, candesartan or valsartan are the preferred agents in patients with heart failure, whether used alone or in combination with ACE inhibitors. ARBs are also alternative to ACE inhibitors in patients with stages A or B heart failure.[1]

The clinical use of ARBs is also similar to that of ACE inhibitors. Therapy should be initiated at low doses (candesartan 4 to 8 mg once daily; valsartan 20 to 40 mg twice daily) and then titrated to target doses (candesartan 32 mg once daily; valsartan 160 mg twice daily).[1] Blood pressure, renal function, and serum potassium should be evaluated within 1 to 2 weeks after initiation of therapy and after increases in dose and these end points used to guide subsequent dose changes. It is not necessary to reach target ARB doses before adding a β-blocker.

Adverse Effects. The ARBs have a low incidence of adverse effects. Because they do not affect bradykinin, they are not associated with cough and have a lower risk of angioedema than ACE inhibitors. However, because of reports of recurrences of ACE inhibitor-related angioedema after ARB administration, ARBs should be used cautiously in any patient with a history of angioedema.[77,79] The major adverse effects are related to suppression of the RAAS. The incidence and risk factors for developing hypotension, decreases in renal function, and hyperkalemia with the ARBs is similar to that of ACE inhibitors.[12] Thus, ARBs are not alternatives in patients who develop these complications from ACE inhibitors. Careful monitoring is required when an ARB is used with another inhibitor of the RAAS (e.g., ACE inhibitor or aldosterone antagonist) as this combination increases the risk of these adverse effects. Similar to the ACE inhibitors, the ARBs are contraindicated in the second and third trimesters of pregnancy and should be avoided in the first trimester because of increased risk of fetal/neonatal morbidity and mortality. Neither candesartan nor valsartan are metabolized by the cytochrome P450 (CYP) system, so no pharmacokinetic drug–drug interactions with these agents are expected.

6 β-Blockers Metoprolol CR/XL, carvedilol, and bisoprolol are the only β-blockers shown to reduce mortality in large heart failure trials. Metoprolol and bisoprolol selectively block the β_1-receptor, whereas carvedilol blocks the β_1, β_2, and α_1-receptors and also possesses antioxidant effects. Although there is no clear evidence that these pharmacologic differences result in differences in efficacy among agents, they may aid in selection of a specific agent. For example, carvedilol is expected to have greater antihypertensive effects than the other agents because of its α-receptor blocking properties and may be preferred in patients with poorly controlled blood pressure. Conversely, metoprolol or bisoprolol may be preferred in patients with low blood pressure or dizziness and in patients with significant airway disease.

Bisoprolol is eliminated approximately 50% by renal elimination, whereas metoprolol and carvedilol are essentially completely metabolized and undergo extensive hepatic first-pass metabolism. Both metoprolol and carvedilol are also substrates for the CYP2D6, which is known to be polymorphic. The 7% of the white population and 1% to 2% of the Asian American and African American populations who are CYP2D6-poor metabolizers would be expected to have higher plasma concentrations than anticipated at the usual doses of carvedilol and metoprolol. However, given that β-blockers have a wide therapeutic index, it is unclear whether the poor metabolizer phenotype would result in more pronounced hemodynamic effects.

There is fairly strong evidence that benefits of β-blockers in heart failure are not a class effect. Specifically, in a study powered for mortality reduction, there was no difference in survival between the nonselective β-blocker bucindolol and placebo.[115] Although there has been considerable debate over why bucindolol failed to provide a survival benefit, it may be related to the drug's ancillary properties or differences among β-blocker trials in the characteristics of study participants. These data emphasize the importance of confining β-blocker use to one of the agents with proven survival benefits, especially given the diversity among β-blockers in their receptor sensitivities and ancillary properties.

There has been much debate over whether one β-blocker is superior to another. Specifically, it has been hypothesized that nonselective blockade with carvedilol might produce greater benefits than β_1-selective blockade. This hypothesis is based on observations that the β_1-receptor is downregulated, and the β_2- and α_1-receptors account for a larger proportion of total cardiac adrenergic receptors in the failing heart. Only one trial with a mortality end point has provided a head-to-head comparison of carvedilol and a β_1-selective blocker. The Carvedilol or Metoprolol European Trial

(COMET) compared carvedilol 25 mg twice daily and immediate-release metoprolol 50 mg twice daily and found a significant 17% lower mortality rate in patients treated with carvedilol.[116] However, concerns regarding the formulation and dose of metoprolol used in COMET limit the conclusions that can be drawn from these findings. Specifically, the study used the immediate-release formulation of metoprolol (metoprolol tartrate) not the sustained-release formation (metoprolol succinate) shown to reduce mortality compared to placebo.[59] The efficacy of the immediate-release formulation in reducing mortality in heart failure has not been proven. Metoprolol CR/XL provides more consistent plasma concentrations over a 24-hour period and appears to provide more favorable effects on heart rate variability, autonomic balance, and blood pressure, suggesting that this formulation might be superior to immediate-release metoprolol.[117] The target dose of metoprolol also differed between COMET and MERIT-HF. The target dose in COMET was 100 mg/day (50 mg twice daily), whereas the target dose of metoprolol in MERIT-HF was 200 mg/day. Many question whether the degree of β-blockade achieved in COMET with immediate-release metoprolol 50 mg twice daily is comparable to that achieved with metoprolol CR/XL 200 mg/day in MERIT-HF or carvedilol 25 mg twice daily in COMET. Thus, the debate over β-blocker superiority continues, and although some clinicians would argue superiority of carvedilol, it seems clear that what is most important is that one of the three β-blockers proven to reduce mortality is used.

Adverse Effects. Possible adverse effects with β-blocker use in heart failure include bradycardia or heart block, hypotension, fatigue, impaired glycemic control in diabetic patients, bronchospasm in patients with asthma, and worsening heart failure. Clinicians should monitor vital signs and carefully assess for signs and symptoms of worsening heart failure during β-blocker initiation and up-titration. Hypotension is more common with carvedilol because of its α_1-receptor–blocking properties. Bradycardia and hypotension generally are asymptomatic and require no intervention; however, β-blocker dose reduction is warranted in symptomatic patients. Fatigue usually resolves after several weeks of therapy, but sometimes requires dose reduction. In diabetic patients, β-blockers may worsen glucose tolerance and can mask the tachycardia and tremor (but not sweating) that accompany hypoglycemia. In addition, nonselective agents such as carvedilol may prolong insulin-induced hypoglycemia and slow recovery from a hypoglycemic episode. Despite this, there is evidence that carvedilol produces better glycemic control in diabetic patients compared to immediate-release metoprolol and may improve insulin sensitivity.[118] Diabetic patients should be warned of these potential adverse effects, and blood glucose should be monitored with initiation, adjustment, and discontinuation of β-blocker therapy. Adjustment of hypoglycemic therapy may be necessary with concomitant β-blocker use in diabetics.

Up-titration should be avoided if the patient experiences signs of worsening heart failure, including volume overload and poor perfusion. Fluid overload may be asymptomatic and manifest solely as an increase in body weight. Mild fluid overload may be managed by intensifying diuretic therapy. The treatment of moderate to severe congestion is discussed in the section on acute decompensated heart failure. Once the patient has been stabilized, dose titration may continue as tolerated until the target or highest tolerated dose is reached.

Absolute contraindications to β-blocker use include uncontrolled bronchospastic disease, symptomatic bradycardia, advanced heart block without a pacemaker, and acute decompensated heart failure. However, β-blockers may be tried with caution in patients with asymptomatic bradycardia or well-controlled asthma. Particular caution is warranted in patients with marked bradycardia (<55 beats/min) or hypotension (systolic blood pressure <80 mm Hg). Importantly, concerns of masking symptoms of hypoglycemia or worsening glycemic control should not preclude β-blockers use in patients with diabetes. Indeed, post-hoc analysis of heart failure trials shows that β-blockers are well tolerated and significantly reduce morbidity and mortality in patients with diabetes and heart failure.[119] β-Blockers should be used cautiously in patients with diabetes and recurrent hypoglycemia.

Digoxin Digoxin exerts its positive inotropic effect by binding to sodium- and potassium-activated adenosine triphosphatase (Na-K-ATPase or sodium pump). Inhibition of Na-K-ATPase decreases outward transport of sodium and leads to increased intracellular sodium concentrations. Higher intracellular sodium concentrations favor calcium entry and reduce calcium extrusion from the cell through effects on the sodium–calcium exchanger. The result is increased storage of intracellular calcium in the sarcoplasmic reticulum, and with each action potential, a greater release of calcium to activate contractile elements. Digoxin also has beneficial neurohormonal actions. These effects occur at low plasma concentrations, where little inotropic effect is seen, and are independent of inotropic activity. Unlike other positive inotropes that increase intracellular cyclic adenosine monophosphate (cAMP), digoxin attenuates the excessive SNS activation present in heart failure patients. Although the precise mechanism is unknown, a digoxin-mediated reduction in central sympathetic outflow and improvement in impaired baroreceptor function appear to play an important role. Because mortality and progression of heart failure are linked to the extent of SNS activation, these sympathoinhibitory effects may be an important component of the clinical response to the drug. Chronic heart failure is also marked by autonomic dysfunction, most notably suppression of the parasympathetic (vagal) system. Digoxin increases parasympathetic activity in heart failure patients and leads to a decrease in heart rate, thus enhancing diastolic filling. The vagal effects also result in slowed conduction and prolongation of atrioventricular node refractoriness, thus slowing the ventricular response in patients with atrial fibrillation. Because atrial fibrillation is a common complication of heart failure, the combined positive inotropic, neurohormonal, and negative chronotropic effects of digoxin can be particularly beneficial for such patients. The overall response to digoxin is usually an increase in cardiac index and a decrease in PAOP with relatively little change in arterial blood pressure.[86,87,96]

Pharmacokinetics. Numerous studies of digoxin pharmacokinetics have been published; Table 16–10 summarizes them. Digoxin

TABLE 16-10 Clinical Pharmacokinetics of Digoxin

Oral bioavailability	
Tablets	0.5–0.9 (0.65)[a]
Elixir	0.75–0.85 (0.80)
Capsules	0.9–1.0 (0.95)
Onset of action	
Oral	1.5–6 h
Intravenous	15–30 min
Peak effect	
Oral	4–6 h
Intravenous	1.5–4 h
Terminal half-life	
Normal renal function	36 h
Anuric patients	5 days
Volume of distribution at steady state	7.3 L/kg
Fraction unbound in plasma	0.75–0.80
Fraction excreted unchanged in urine	0.65–0.70

[a] Range and mean value in parentheses.

Data from Schentag JJ, Bang AJ, Kozinski-Tober JL. Digoxin. In: Burton ME, Shaw LM, Schentag JJ, Evans WE, eds. Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring, 4th ed. Baltimore: Lippincott Williams & Wilkins, 2006:410–439.

TABLE 16-11 Digoxin Drug Interactions

Drugs	Mechanism/Effect	Suggested Clinical Management
Amiodarone	Inhibits P-glycoprotein resulting in decrease in renal and nonrenal clearance; can increase SDC by 70%–100%	Monitor SDC and adverse effects; anticipate the need to reduce the dose by 50%
Antacids	Concurrent administration may decrease digoxin bioavailability by 20%–35%	Space doses at least 2 h apart or avoid concurrent use if possible
Cholestyramine, colestipol	Bind digoxin in gut and decrease bioavailability 20%–35%; may also decrease enterohepatic recycling	Space doses at least 2 h apart or avoid concurrent colestipol use if possible
Diuretics	Thiazides or loop diuretics may cause hypokalemia and hypomagnesemia, thereby increasing the risk of digitalis toxicity	Monitor and replace electrolytes if necessary
Erythromycin, clarithromycin, tetracycline	Alter gut bacterial flora; bioavailability and SDC increase 40%–100% in approximately 10% of patients who extensively metabolize digoxin in the gut; may also be caused by inhibition of P-glycoprotein by macrolides	Monitor SDC and anticipate the need to reduce the dose; avoid concurrent use if possible
Ketoconazole, itraconazole	Decrease in renal and nonrenal clearance by inhibition of P-glycoprotein; SDC may increase by 50%–100%	Monitor SDC and anticipate the need to reduce the dose by 50%
Kaolin-pectin	Large dose (30–60 mL) may decrease digoxin bioavailability by approximately 60%	Space doses at least 2 h apart or avoid concurrent use if possible
Metoclopramide	Increase in gut mobility may decrease bioavailability of slow dissolving tablets; unknown significance	Effect is minimized by administration of digoxin capsules
Neomycin, sulfasalazine	Decrease in bioavailability by 20%–25% sulfasalazine	Space doses at least 2 h apart or avoid concurrent use if possible
Propafenone	Decrease in renal clearance; SDC may increase 30%–40%	Monitor SDC and anticipate the need to reduce the dose
Quinidine	Inhibits P-glycoprotein resulting in decrease in renal and nonrenal clearance; also displacement of digoxin from tissue-binding sites with decrease in the volume of distribution; SDC generally increases about twofold	Monitor SDC and adverse effects; anticipate the need to reduce dose by 50%
Spironolactone	Decrease in renal and nonrenal clearance; also interference with some digoxin assays thus increasing apparent SDC	Monitor SDC and anticipate the need to reduce dose; check assay for interference
Verapamil	Inhibits P-glycoprotein resulting in decrease in renal and nonrenal clearance, SDC may increase 70%–100%	Monitor SDC and anticipate the need to reduce the dose by 50%; consider using another calcium channel blocker

SDC, serum digoxin concentration.

has a large volume of distribution and is extensively bound to various tissues, most notably to Na-K-ATPase in skeletal and cardiac muscles. Because it does not distribute appreciably to body fat, loading doses of digoxin (when necessary) should be calculated based on estimates of lean body weight. There is a long "distribution phase" after administration of oral or intravenous digoxin, resulting in a lag time before maximum pharmacologic response is observed (Table 16–10). Transiently elevated serum digoxin concentrations during the distribution phase are not associated with increased therapeutic or adverse effects, although they can mislead the clinician who is unaware of the timing of blood sampling relative to the previous digoxin dose. Consequently, blood samples for measurement of serum digoxin concentrations should be collected at least 6 hours, and preferably 12 hours or more, after the last dose.

In patients with normal renal function, 60% to 80% of a dose of digoxin is eliminated unchanged in urine via glomerular filtration and tubular secretion. The terminal half-life of digoxin is approximately 1.5 days in subjects with normal renal function but approximately 5 days in anuric patients (see Table 16–10). Recent evidence indicates that the drug efflux transporter P-glycoprotein plays an important role in the bioavailability, renal and nonrenal clearance, and drug interactions with digoxin. Table 16–11 summarizes clinically important pharmacokinetic/pharmacodynamic drug interactions. An extensive review of the pharmacokinetics and pharmacodynamics of digoxin is available.[96]

Adverse Effects. Although digoxin can produce a variety of cardiac and noncardiac adverse effects, it is usually well tolerated by most patients (Table 16–12).[86,87] Noncardiac adverse effects frequently involve the CNS or gastrointestinal systems but also may be nonspecific (e.g., fatigue or weakness). Cardiac manifestations include numerous different arrhythmias that are believed to be caused by multiple electrophysiologic effects (Table 16–12). Cardiac arrhythmias may be the first evidence of toxicity in a patient (before any noncardiac symptoms occur). Rhythm disturbances are of particular concern because patients with chronic heart failure are already at increased risk for sudden cardiac death, presumably as a consequence of ventricular arrhythmias. Patients who are at increased risk of toxicity include those with impaired renal function, decreased lean body mass, the elderly, and those taking interacting drugs. Hypokalemia, hypomagnesemia, and hypercalcemia will predispose patients to cardiac manifestations of digoxin toxicity. Thus, concomitant therapy with diuretics may lead to electrolyte abnormalities and increase the likelihood of cardiac arrhythmias. Similarly, hypothyroidism, myocardial ischemia, and acidosis will also increase the risk of cardiac adverse effects. Although digoxin toxicity is commonly associated with plasma concentrations greater than 2 ng/mL, clinicians should remember that digoxin toxicity is based on the presence of symptoms rather than a specific plasma concentration.[96] Usual treatment of digoxin toxicity

TABLE 16-12 Signs and Symptoms of Digoxin Toxicity

Noncardiac (mostly CNS) adverse effects
Anorexia, nausea, vomiting, abdominal pain
Visual disturbances
Halos, photophobia, problems with color perception (i.e., red-green or yellow-green vision), scotomata
Fatigue, weakness, dizziness, headache, neuralgia, confusion, delirium, psychosis
Cardiac adverse effects[a,b]
Ventricular arrhythmias
Premature ventricular depolarizations, bigeminy, trigeminy, ventricular tachycardia, ventricular fibrillation
Atrioventricular (AV) block
First degree, second degree (Mobitz type I), third degree
AV junctional escape rhythms, junctional tachycardia
Atrial arrhythmias with slowed AV conduction or AV block
Particularly paroxysmal atrial tachycardia with AV block
Sinus bradycardia

[a] Some adverse effects may be difficult to distinguish from the signs/symptoms of heart failure.
[b] Digoxin toxicity has been associated with almost every known rhythm abnormality (only the more common manifestations are listed).
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includes drug withdrawal or dose reduction and treatment of cardiac arrhythmias and electrolyte abnormalities. In patients with life-threatening digoxin toxicity, purified digoxin-specific Fab antibody fragments should be administered. Serum digoxin concentrations will not be reliable until the antidote has been eliminated from the body.[87]

TREATMENT

Acute Decompensated Heart Failure

As discussed previously, the number of patients with heart failure is substantial and continues to increase. Although mortality from heart failure has improved, the growing number of patients with the disorder and the progressive nature of the syndrome have led to substantial increases in hospitalizations for heart failure.[4] Recent data indicate approximately 1 million patients are hospitalized annually for heart failure, resulting in significant morbidity, mortality, and consumption of large quantities of healthcare resources.[4] Inpatient admission for heart failure exacerbations is associated with an increased risk of subsequent hospitalization and decreased survival.[120] The economic impact of heart failure is considerable with cost driven primarily by hospitalization and inpatient care.[4]

A number of descriptive terms have been used to characterize patients with worsening heart failure requiring hospitalization. Patients with persistent symptoms or *refractory* heart failure requiring specialized interventions despite optimal standard therapy such as ACE inhibitors and β-blockers are classified as stage D in the ACC/AHA classification scheme. These patients typically fall into the category of NYHA class III or IV heart failure, with symptoms upon minimal exertion or at rest.[1] The terms *decompensated heart failure* or *exacerbation of heart failure* refer to those patients with new or worsening signs or symptoms, which are usually caused by volume overload and/or hypoperfusion and lead to additional medical care, such as emergency room visits and hospitalizations. The term *acute* heart failure may be misleading as it more often refers to the patient with a sudden onset of signs or symptoms of heart failure in the setting of previously normal cardiac function. This section of the chapter focuses on the management of patients with acute decompensated heart failure. Clinical syndromes within decompensated heart failure include systemic volume overload, low output, and acute pulmonary edema. It is important to recognize that such patients may present with impaired or preserved left ventricular function and a variety of etiologies may be responsible for the primary disease process. The clinical course of heart failure manifests as periods of relative stability with an increasing frequency in episodes of decompensation as the underlying disease progresses.[121]

Despite the considerable morbidity and mortality associated with decompensated heart failure, the first randomized placebo-controlled trials in this patient population were published in 2002.[122,123] In addition, it was not until recently that guidelines were generated focusing specifically on managing decompensated heart failure. Currently, the ACC/AHA guidelines focus a portion of their recommendations for chronic heart failure on the decompensated patient, but the HFSA and the European Society of Cardiology have published separate guidelines for evaluating and treating decompensated heart failure.[1,34,124] Because available drug therapies differ between Europe and the United States, the HFSA guidelines are the focus of the remainder of this chapter.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

Patients requiring intensive therapy for decompensated heart failure may have a variety of underlying etiologies and clinical presentations. Patients with worsening chronic heart failure associated with reduced or preserved left ventricular function comprise approximately 70% of heart failure hospital admissions. These patients can become refractory to available oral therapy and decompensate following a relatively mild insult (e.g., dietary indiscretion), medical noncompliance, or a noncardiac concurrent illness (e.g., infection). A new cardiac event, such as recurrent MI, atrial fibrillation, myocarditis, or acute valvular insufficiency also can cause a stable patient to decompensate. Secondly, de novo heart failure may occur following a large myocardial infarction or sudden increase in blood pressure in the setting of left ventricular dysfunction and represents approximately 25% of admissions. A third group of patients with severe left ventricular systolic dysfunction associated with progressive worsening of cardiac output and refractoriness to therapy represents approximately 5% of heart failure admissions.[125] Additional insight into the clinical characteristics of decompensated heart failure patients unexpectedly indicates that a high percentage of patients present with hypertension and preserved systolic function.[126]

Several studies provide a better understanding of the prognostic factors associated with decompensated heart failure. Data from the Acute Decompensated Heart Failure Registry (ADHERE), a registry of hospitalized patients with a primary diagnosis of decompensated heart failure, found blood urea nitrogen greater than or equal to 43 mg/dL to be the best individual predictor of in-hospital mortality, followed by systolic blood pressure less than 115 mm Hg and then by serum creatinine greater than or equal to 2.75 mg/dL. Using these three parameters, patients were identified as low, intermediate, high, and very high risk with an in-hospital mortality of 2%, 6%, 13%, and 20%, respectively.[127] Additional studies confirm an increase in in-hospital mortality in patients with low systolic blood pressure and worsening renal function on admission.[128,129] Hyponatremia, elevations in troponin I, ischemic etiology, and poor functional capacity are additional negative prognostic factors.[125]

GENERAL APPROACH TO TREATMENT

The overall goals of therapy in the patient with decompensated heart failure are to relieve congestive symptoms or optimize volume status, as well as treat symptoms of low cardiac output, so that the patient can be discharged in a compensated state on oral drug therapy. Although diuretic, vasodilator, and positive inotrope therapy can be very effective at achieving these goals, their efficacy must be balanced against the potential for serious toxicity. Thus, another important goal is to minimize the risks of pharmacologic therapy. Maintenance of vital organ perfusion to preserve renal function and prevention of additional myocardial injury, diuretic-induced electrolyte depletion, hypotension from vasodilators, and myocardial ischemia and arrhythmias from positive inotropes are all important goals.

In addition, all patients should be evaluated for potential etiologies and precipitating factors, including atrial fibrillation and other arrhythmias, worsening hypertension, myocardial ischemia or infarction, anemia, hypothyroidism or hyperthyroidism, and other causes. Medications, including noncardiac medications, which may worsen cardiac function, should also be considered as precipitating or contributing factors. Patients who may benefit from revascularization should also be identified. Prior to discharge, optimization of chronic oral therapy and patient education are critical to preventing future hospitalizations. When available and appropriate, patients should be referred to a heart failure disease management program.[124] A careful history and physical examination are key components in the diagnosis of decompensated heart failure. The history should focus on the potential etiologies of heart failure, the presence of any precipitating factors, onset, duration, and severity of symptoms, and a careful medication history. Current guidelines recommend making the diagnosis of decompensated heart failure based primarily on signs and symptoms.[124] With congestion representing

the more common presentation of heart failure, orthopnea is the main symptom of fluid overload that best correlates with elevated pulmonary pressures.[129] Important elements of the physical examination include assessment of vital signs and weight, cardiac auscultation for heart sounds and murmurs, pulmonary exam for the presence of rales, and evaluation for the presence of peripheral edema. The jugular venous pressure is the most reliable indicator of the patient's volume status and should be carefully evaluated on admission and closely followed during hospitalization as an indicator of the efficacy of diuretic therapy.[129] An S_3 gallop also represents ventricular filling and has high diagnostic specificity for heart failure decompensation. Other physical findings, such as pulmonary crackles and lower-extremity edema, have low specificity and sensitivity for the diagnosis of decompensated heart failure.[124] The development of a bedside assay for plasma BNP has focused considerable attention on the use of BNP as an aid in the diagnosis of suspected heart failure. Plasma BNP is positively correlated with the degree of left ventricular dysfunction and heart failure and this assay is now frequently used in acute care settings to assist in the differential diagnosis of dyspnea (heart failure vs. asthma, chronic obstructive pulmonary disease, or infection). A low BNP concentration has a 96% predictive value for excluding heart failure as an etiology when evaluating patients presenting with dyspnea. In addition, an elevated prehospital discharge BNP concentration is associated with an increased risk of worse long-term outcome. It is important to note that any disease process that increases right heart pressures will elevate BNP, including pulmonary emboli, chronic obstructive lung disease, and primary pulmonary hypertension. Also, BNP levels may be mildly increased with increasing age, female gender, and renal dysfunction, whereas concentrations may be lower with obesity.[129] Additional research will better characterize the role of BNP measurement in the diagnosis and treatment of heart failure. When the diagnosis of decompensated heart failure is uncertain, current guidelines recommend obtaining a BNP concentration in conjunction with assessing signs and symptoms.

Hospitalization *should occur* or *should be considered* depending on each patient's presenting symptoms and physical examination. Table 16–13 describes the clinical presentation of patients in whom hospitalization should occur or should be considered. Most patients do not require admission to an intensive care unit and are admitted to a monitored unit or general medical floor. Admission to an intensive care unit may be required if the patient experiences hemodynamic instability requiring frequent monitoring of vital signs, invasive hemodynamic monitoring, or rapid titration of intravenous medications with concurrent monitoring to assure safe and effective outcomes.

The first step in the management of decompensated heart failure is to ascertain that optimal treatment with oral medications has been achieved. If fluid retention is evident on physical examination, aggressive diuresis should be accomplished. Although increasing the dose of oral diuretic may be effective in some cases, the use of intravenous diuretics frequently is necessary. Every effort should be made to optimally treat the patient with an ACE inhibitor. β-Blocker therapy should generally be continued during the hospital admission unless recent dose initiation or up-titration was responsible for the decompensated state. In such cases, β-blocker therapy may need to be temporarily held or dose reduced. Appropriateness of initiating this therapy prior to hospital discharge will be discussed later in this chapter. Discontinuation of ACE inhibitor or β-blocker therapy occasionally may be necessary in the setting of cardiogenic shock or symptomatic hypotension. Certain therapies may also need to be temporarily held in the setting of renal dysfunction, especially in the setting of oliguria or hyperkalemia (e.g., ACE inhibitor, ARB, and/or aldosterone antagonist) or elevated serum digoxin concentrations. Most patients should be receiving digoxin

TABLE 16-13 Recommendations for Hospitalizing Patients Presenting with Acute Decompensated Heart Failure

Recommendation	Clinical Circumstances
Hospitalization recommended	Evidence of severely decompensated heart failure, including • Hypotension • Worsening renal function • Altered mentation Dyspnea at rest • Typically reflected by resting tachypnea • Less commonly reflected by oxygen saturation <90% Hemodynamically significant arrhythmia • Including new onset of rapid atrial fibrillation Acute coronary syndromes
Hospitalization should be considered	Worsened congestion • Even without dyspnea • Typically reflected by a weight gain of ≥5 kg Signs and symptoms of pulmonary or systemic congestion • Even in the absence of weight gain Major electrolyte disturbance Associated comorbid conditions • Pneumonia • Pulmonary embolus • Diabetic ketoacidosis • Symptoms suggestive of transient ischemic accident or stroke Repeated implantable cardioverter-defibrillator firings Previously undiagnosed heart failure with signs and symptoms of systemic or pulmonary congestion

Adapted from Adams KF, Lindenfield J, Arnold JMO, et al. HFSA 2006 comprehensive heart failure practice guidelines. J Card Fail 2006;12:e1–e122.

at a low dose prescribed to achieve a trough serum concentration of 0.5 to 1.0 ng/mL.[1]

There are two general approaches to maximize therapy in the decompensated heart failure patient. One is to use simple clinical parameters (signs and symptoms, blood pressure, renal function) and the second is to use invasive hemodynamic monitoring in addition to these clinical parameters. In all decompensated heart failure patients, close monitoring is essential for assuring optimal response to therapy while avoiding adverse effects. Daily monitoring should include weight, strict fluid intake and output, and heart failure signs and symptoms to assess clinical efficacy of drug therapy. Foley catheter placement is not recommended unless close monitoring of urine output is needed. As safety end points, monitoring for electrolyte depletion, symptomatic hypotension, and renal dysfunction should be assessed frequently. Although many of the above parameters may be monitored daily, some will need to be monitored more frequently as dictated by the patient's clinical status. Vital signs should be assessed multiple times throughout the day at a frequency that is appropriate for a given patients' level of stability. Orthostatic blood pressure should be assessed at least once daily.[124] Table 16–14 summarizes the recommendations for monitoring.

PRINCIPLES OF THERAPY BASED ON CLINICAL PRESENTATION

Appropriate medical management of the patient presenting with decompensated heart failure is aided by determination of whether the patient has signs and symptoms of fluid overload ("wet" heart failure) or low cardiac output ("dry" heart failure).[129,130] As previously discussed, most patients present with *fluid overload* (or the "wet" profile). Symptoms consistent with pulmonary congestion include orthopnea and dyspnea with minimal exertion and those of systemic congestion include gastrointestinal discomfort, ascites, and peripheral edema. Patients with no or minimal fluid overload (or the "dry" category of decompensated heart failure) may have symptoms that

TABLE 16-14 Monitoring Recommendations for Patients Hospitalized with Acute Decompensated Heart Failure

Value	Frequency	Specifics
Weight	At least daily	Determine after voiding in the morning Account for possible increased food intake as a result of improved appetite
Fluid intake/output	At least daily	Strict documentation necessary
Vital signs	More than daily	Including orthostatic blood pressure
Signs	At least daily	Edema, acites, pulmonary rales, hepatomegaly, increased jugular venous pressure, hepatojugular reflux, liver tenderness
Symptoms	At least daily	Orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, dyspnea, fatigue
Electrolytes	At least daily	Potassium, magnesium, sodium
Renal function	At least daily	blood urea nitrogen, serum creatinine

Adapted from Adams KF, Lindenfield J, Arnold JMO, et al. HFSA 2006 comprehensive heart failure practice guidelines. J Card Fail 2006;12:e1–e122.

are more difficult to distinguish. This is a syndrome of *low cardiac output* and is characterized principally by extreme fatigue and tiredness as well as other symptoms not commonly attributed to cardiac causes such as poor appetite, nausea, and early satiety. It is important to recognize that gastrointestinal symptoms may be associated with congestion rather than low cardiac output to the gastrointestinal tract. Moreover, these patients frequently exhibit worsening renal function and a decline in serum sodium level. Many patients will present with signs and symptoms of both types of advanced heart failure. In these patients, low-output symptoms may not be obvious until congestion is optimally treated. Figure 16–8 outlines a suggested treatment approach based on whether the patient has signs and symptoms of fluid overload and/or low cardiac output.

■ PRINCIPLES OF THERAPY BASED ON HEMODYNAMIC SUBSETS

Patients with decompensated heart failure may have critically reduced cardiac output, usually with low arterial blood pressure and systemic hypoperfusion resulting in organ system dysfunction (i.e., cardiogenic shock). They also may have pulmonary edema with hypoxemia, respiratory acidosis, and markedly increased work of breathing. With cardiopulmonary support, response to interventions should be assessed promptly to allow for timely adjustments in treatment. Because cardiopulmonary support must be instituted and adjusted rapidly, immediate assessment of the results of an intervention limits risks and makes adjustments in therapy more prompt. ECG monitoring, continuous pulse oximetry, urine flow monitoring, and automated blood pressure recording are now the minimal noninvasive standard of care for critically ill patients with cardiopulmonary decompensation. Peripheral or femoral arterial catheters may be used for continuous and accurate assessment of arterial pressure.

Hemodynamic Monitoring

The role of invasive hemodynamic monitoring for improving outcomes in patients with decompensated heart failure remains controversial. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial assessed the role of invasive hemodynamic monitoring in the management of patients hospitalized for heart failure. The use of a pulmonary artery catheter had no impact on survival after hospital discharge.[131] It is important to note that patients with a clear indication for pulmonary artery catheter were excluded from this trial. Thus, the routine use of invasive monitoring is not recommended. However, invasive hemodynamic monitoring often provides essential information necessary to achieve optimal drug therapy in patients with a confusing or complicated clinical picture and during dose titration of rapidly acting medications. And thus, such monitoring should be considered in patients who are refractory to initial therapy, whose volume status is unclear, or who has clinically significant hypotension such as a systolic blood pressure less than 80 mm Hg, or worsening renal function despite therapy. Such monitoring is required to document adequate hemodynamic response to inotropic therapy prior to committing to chronic outpatient inotropic therapy.[124] Finally, assessment of hemodynamic parameters is required to document adequate reversal of pulmonary hypertension prior to cardiac transplantation.[129]

Invasive hemodynamic monitoring is usually performed with a flow-directed pulmonary artery or Swan-Ganz catheter placed percutaneously through a central vein and advanced through the right side of the heart and into the pulmonary artery. Inflation of a balloon proximal to the end port allows the catheter to "wedge," yielding the PAOP, which estimates the pulmonary venous (left atrial) pressure and, in the absence of intracardiac shunt, mitral valve disease or pulmonary disease, the left ventricular diastolic pressure. Additionally, cardiac output may be measured and systemic vascular resistance (SVR) calculated. Table 16–15 lists the normal values for hemodynamic parameters.

In addition to the clinical presentation, invasive hemodynamic monitoring helps in the selection of appropriate medical therapy as well as in the classification of patients into specific subsets. These *hemodynamic subsets* were first proposed for patients with left ventricular dysfunction following an acute MI but also are applicable to patients with acute or severe heart failure from other causes (Fig. 16–9).[132] This hemodynamic classification has four subsets and is based on a cardiac index above or below 2.2 L/min/m^2 and a PAOP above or below 18 mm Hg. Figure 16–10 is a treatment algorithm based on hemodynamic subsets. In addition to using the above profiles or categories to stratify patients with decompensated heart failure, these four hemodynamic profiles are predictive for outcome with patients in the wet-warm profile having a twofold greater risk of death and those in the wet-cold profile having a 2.5-fold increased risk of death at 1 year compared to dry-warm patients.[129]

Subset I Patients in hemodynamic subset I have a cardiac index and PAOP within generally acceptable ranges and have the lowest mortality of any subset. These patients do not need immediate specific interventions other than maximizing oral therapy and monitoring. It should be emphasized that patients with significant left ventricular dysfunction may still present in subset I because normal compensatory mechanisms and/or appropriate drug therapy may at least partially correct an otherwise abnormal hemodynamic profile.

Subset II As shown in Fig. 16–9, patients in subset II have an adequate cardiac index but a PAOP greater than 18 mm Hg. These patients are likely to have pulmonary congestion (i.e., "wet" heart failure) secondary to increased hydrostatic pressure in the pulmonary capillaries but no evidence of peripheral hypoperfusion. The primary goal of therapy in these patients is to reduce pulmonary congestion by lowering PAOP which is associated with improved outcomes. Accordingly, the therapeutic goal in this setting is to reduce filling pressures without reducing cardiac output, increasing heart rate, or further activating neurohormones. And thus, it is critically important that PAOP not be decreased excessively so as to cause a significant decrease in cardiac index. Although the normal range of PAOP is 5 to 12 mm Hg for individuals without cardiac dysfunction, higher pressures of 15 to 18 mm Hg frequently are necessary for heart failure patients to optimize cardiac index while avoiding pulmonary congestion. Generally, the PAOP can be low-

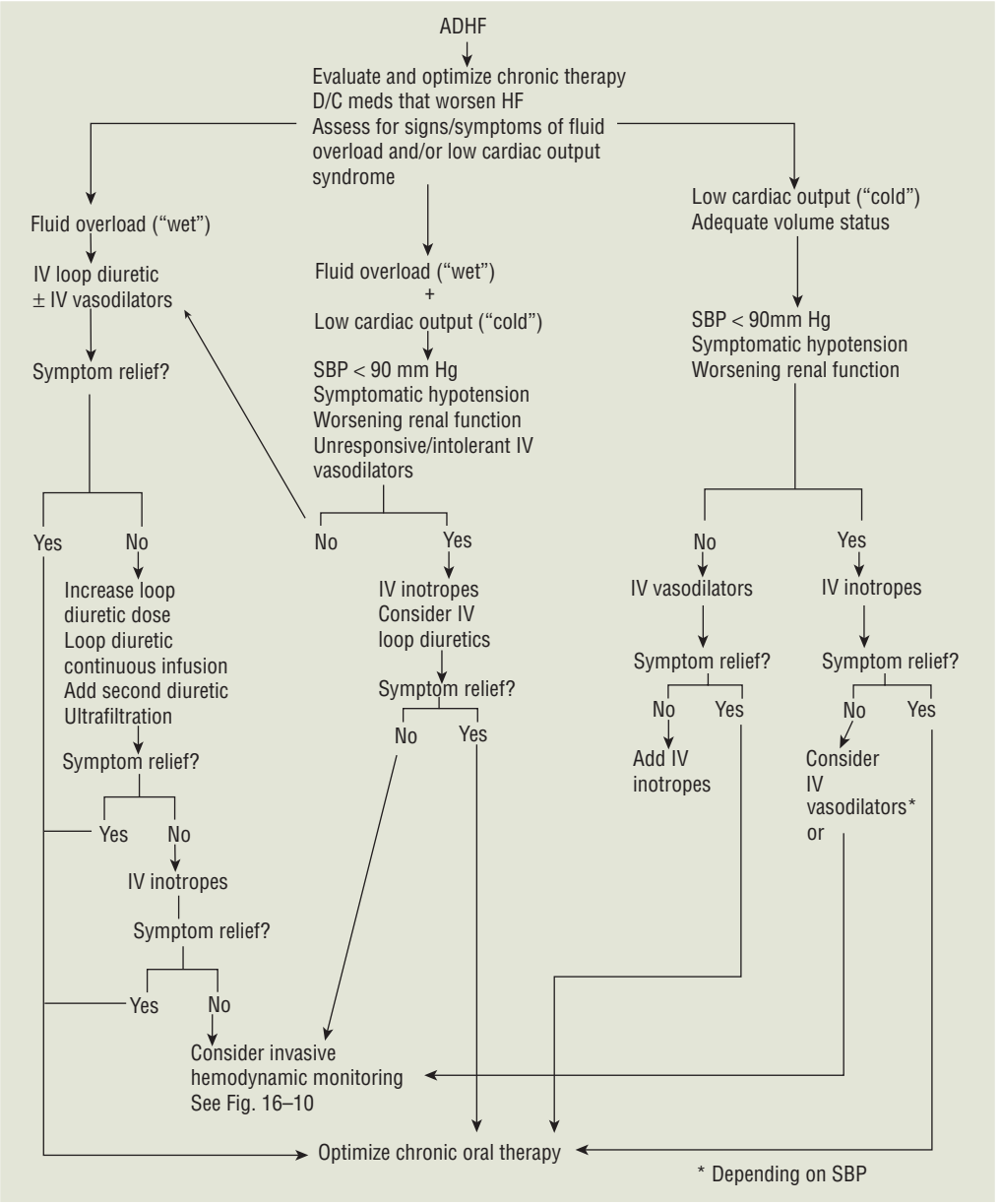

FIGURE 16-8. General treatment algorithm for acute decompensated heart failure (ADHF) based on clinical presentation. IV vasodilators that may be used include nitroglycerin, nesiritide, or nitroprusside. Metolazone or spironolactone may be added if the patient fails to respond to loop diuretics and a second diuretic is required. IV inotropes that may be used include dobutamine or milrinone. (D/C, discontinue; HF, heart failure; SBP, systolic blood pressure.) *(Reprinted and adapted from J Cardiac Fail, Vol. 12, Pages e1–e122, Copyright 2006, with permission from Elsevier.)*

TABLE 16-15 Hemodynamic Monitoring: Normal Values

Central venous (right atrial) pressure, mean	<5 mm Hg
Right ventricular pressure	25/0 mm Hg
Pulmonary artery pressure	25/10 mm Hg
Pulmonary artery pressure, mean	<18 mm Hg
Pulmonary artery occlusion pressure, mean	<12 mm Hg
Systemic arterial pressure	120/80 mm Hg
Mean arterial pressure	90–110 mm Hg
Cardiac index	2.8–4.2 L/min/m^2
Stroke volume index	30–65 mL/b/m^2
Systemic vascular resistance	900–1,400 dyne.sec.cm^{-5}
Pulmonary vascular resistance	150–250 dyne.sec.cm^{-5}
Arterial oxygen content	20 mL/dL
Mixed venous oxygen content	15 mL/dL
Arteriovenous oxygen content difference	3–5 mL/dL

ered to the range of 15 to 18 mm Hg with relatively little decrease in cardiac index because the Frank-Starling curve is flatter at higher PAOP values, particularly in patients with heart failure. Intravenous administration of agents that reduce preload (i.e., loop diuretics, nitroglycerin, or nesiritide) is the most appropriate acute therapy to achieve the therapeutic goal for patients in subset II. These agents will produce a very rapid decrease in preload, although signs and symptoms of pulmonary congestion may take longer to resolve.

Current guidelines recommend loop diuretics as first-line therapy for management of heart failure patients admitted with fluid overload and that such agents should typically be administered intravenously. The rate of diuresis should achieve a desirable volume status without causing a rapid reduction in intravascular volume resulting in symptomatic hypotension or renal dysfunction. Electrolyte depletion should be monitored for closely, especially

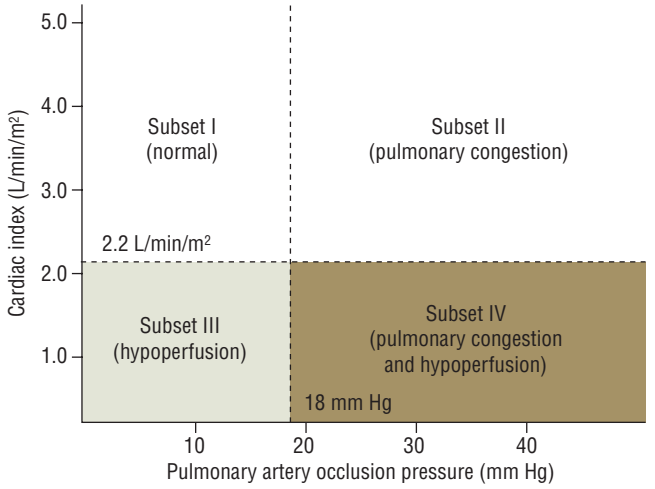

FIGURE 16-9. Hemodynamic subsets of heart failure based on cardiac index and pulmonary artery occlusion pressure. *(Adapted with permission from N Engl J Med 1976;295:1356–1362.)*

when a high dose or diuretic combination therapy is used. In addition to sodium restriction (less than 2 g daily), supplemental oxygen should be administered as needed for hypoxemia. In patients with moderate hyponatremia (less than 130 mEq/L), fluid restriction (less than 2 L daily) should be considered, and in patients with worsening or severe hyponatremia (less than 125 mEq/L), stricter fluid restriction may be necessary.[124]

Intravenous vasodilators may be considered in addition to diuretics for rapid symptom resolution and may be especially useful in patients with acute pulmonary edema or severe hypertension, as well as in patients who fail to respond to aggressive treatment with diuretics. It is essential to avoid use of vasodilators in patients with symptomatic hypotension, and frequent blood pressure monitoring is essential for the safe use of these agents. In addition, these agents should not be used in patients with low left-heart filling pressures. If symptomatic hypotension occurs with vasodilator therapy, the dose should be reduced or the agent discontinued. If patients fail to respond to the above therapies or experience worsening renal function, intravenous inotropic therapy should be considered.[124]

Subset III Patients in hemodynamic subset III have a cardiac index of less than 2.2 L/min/m^2 but without an abnormally elevated PAOP (see Fig. 16–9). These patients usually present without evidence of pulmonary congestion, but the low cardiac index results in signs and symptoms of peripheral hypoperfusion (i.e., decreased urine output, weakness, peripheral vasoconstriction, weak pulses). The mortality rate of subset III patients is reported to be four times higher than that of patients without hypoperfusion.[132] Although the treatment goal is to alleviate signs and symptoms of hypoperfusion by increasing cardiac index and perfusion to essential organs, therapy will differ among patients. If the PAOP is significantly below 15 mm Hg, initial therapy will be to administer intravenous fluids to provide a more optimal left ventricular filling pressure of 15 to 18 mm Hg and consequently improve cardiac index. When there is only mild left ventricular dysfunction, intravenous fluid administration may be all that is necessary to achieve a cardiac index above 2.2 L/min/m^2. However, many patients will have significant left ventricular dysfunction and a depressed Frank-Starling relationship despite adequate preload (i.e., PAOP of 15 to 18 mm Hg). In these patients, intravenously administered positive inotropic agents (e.g., dobutamine, milrinone) and/or arterial vasodilators (e.g., nitroprusside or nitroglycerin) are often necessary to achieve an adequate cardiac index. It is noteworthy that some positive inotropic medications also will have arterial vasodilating activity (see specific drug classes that follow).

Current guidelines recommend intravenous inotropes for symptom relief or end-organ dysfunction in patients with left ventricular dysfunction and low cardiac output syndrome. Such therapy may be especially useful in patients with low systolic blood pressure (less than 90 mm Hg) or symptomatic hypotension in the setting of adequate filling pressures. As previously discussed (see Subset II above), inotropic therapy may be considered in patients who do not tolerate or respond to intravenous vasodilators or patients with worsening renal function. As with vasodilators, inotrope administration requires frequent blood pressure monitoring as well as continuous monitoring for arrhythmias. If arrhythmias arise, dose reduction or discontinuation of inotropic therapy should occur. Also, these agents should be avoided in patients with low left-heart filling pressures. Given the potential risks associated with inotropic therapy, vasodilators should be considered prior to using inotropes.[124]

In general, inotropic therapy should not be used in the broad decompensated heart failure population. They are useful to increase cardiac output in the patients described above. These agents may be used to "bridge" patients with cardiogenic shock to heart transplantation or left ventricular assist device. Inotropes may also be used as palliative therapy to improve functional status and quality of life in patients who are not considered optimal candidates for these definitive therapies.[124]

Subset IV Patients with a cardiac index of less than 2.2 L/min/m^2 and a PAOP higher than 18 mm Hg are in hemodynamic subset IV. These patients have the worst prognosis of any subset and illustrate the typical hemodynamic profile for the patient hospitalized for severe heart failure.

Because of severe pump failure, these patients cannot maintain an adequate cardiac index despite the elevated left ventricular filling pressure and increased myocardial fiber stretch. These patients will present with signs and symptoms of both "wet" and low-output heart failure. The treatment goals are to alleviate these signs and symptoms by increasing cardiac index above 2.2 L/min/m^2 and reducing PAOP to 15 to 18 mm Hg while maintaining an adequate mean arterial pressure. Thus therapy will involve a combination of agents used for subset II and subset III patients to achieve these goals (i.e., combination of diuretic plus positive inotrope). These targets may be difficult to achieve and will necessitate careful monitoring and individualization of drug therapy. Nitroprusside is a particularly useful agent in this setting because of its mixed arterial–venous vasodilating effects. In the presence of significant hypotension, inotropic agents with vasopressor activity may be required initially to achieve an adequate perfusion pressure to essential organs and can then be combined, if necessary, with diuretics and/or vasodilators to obtain the desired hemodynamic effects and clinical response.

PHARMACOLOGIC THERAPY OF ACUTE DECOMPENSATED HEART FAILURE

Unfortunately, the treatment of decompensated heart failure has not improved substantially in the past decade in large part because of the lack of clinical trial data in this population. The pharmacotherapeutic agents used to treat patients with decompensated heart failure rarely, if ever, produce a single cardiovascular action. Even when intended for a single purpose (e.g., a positive inotrope), other drug effects (tachycardia, vasodilation, or vasoconstriction) may either add to the therapeutic effect or cause adverse events that negate or even outweigh the intended therapeutic benefit. It often can be difficult to anticipate how an individual patient will respond to a given intervention. For this reason, hemodynamic monitoring can be useful, and many drugs are considered first-line therapy due in part to their short half-lives and ease of titration. The description of expected drug actions outlined below should be viewed as a general guide to the clinician, who must continuously reassess the

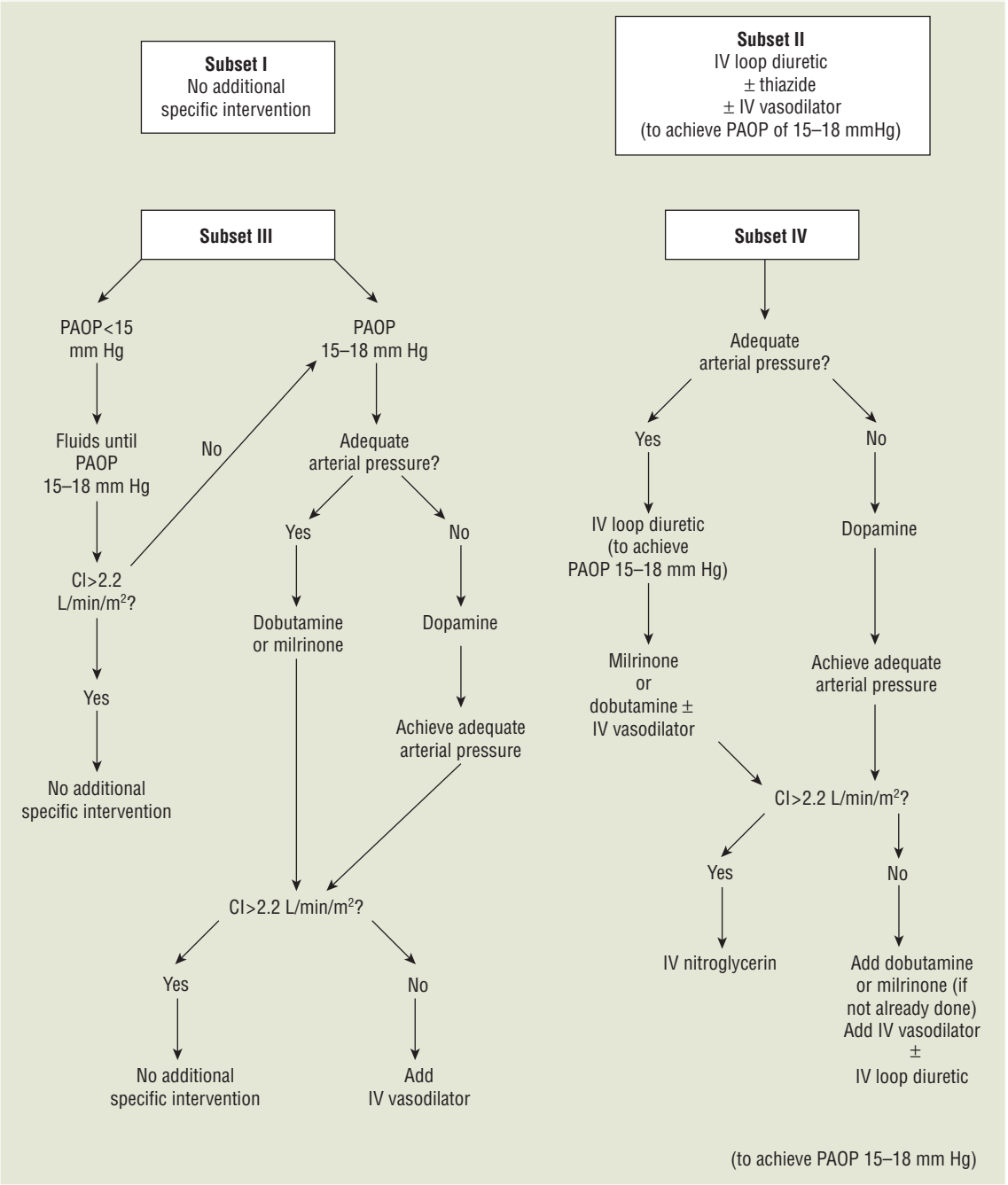

FIGURE 16-10. General treatment algorithm for patients with advanced/decompensated heart failure based on hemodynamic monitoring and hemodynamic subsets. IV vasodilators that may be used include nitroglycerin, nesiritide, or nitroprusside. See text for details. (CI, cardiac index; PAOP, pulmonary artery occlusive pressure.)

patient for desired outcomes. Table 16–16 contains a summary of the expected hemodynamic effects of the various drugs discussed below (see also Chap. 25).

Diuretics[44,133,134]

Intravenous loop diuretics, including furosemide, bumetanide, and torsemide, are used in the management of decompensated heart failure, with furosemide being the most widely studied and used agent in this setting. Bolus administration of diuretics decreases preload within 5 to 15 minutes by functional venodilation and later (>20 minutes) via sodium and water excretion, thereby improving pulmonary congestion. However, the acute reduction in venous return may severely compromise effective preload in patients with significant diastolic dysfunction or intravascular depletion. This results in a reflex increase in sympathetic activation, renin release, NE, and AVP elevations and the expected consequences of arteriolar and coronary constriction, tachycardia, and increased PAOP and myocardial oxygen consumption. Unlike arterial dilators and positive inotropic agents, diuretics do not cause an upward shift in the Frank-Starling curve or increase cardiac index significantly in most patients (see Table 16–16). Excessive preload reduction with diuretics can lead to a decline in cardiac output (see Fig. 16–3). Consequently, diuretics must be used judiciously to obtain the desired improvement in symptoms of congestion while avoiding a reduction in cardiac output, symptomatic hypotension, or worsening renal function. Although counterintuitive, renal function may also improve in the setting of diuresis.

Diuretic Resistance Occasionally, patients respond poorly to large doses of loop diuretics, and heart failure is the most common clinical setting in which diuretic resistance is observed. Data from

TABLE 16-16 Usual Hemodynamic Effects of Intravenous Agents Commonly Used for Treatment of Advanced or Decompensated Heart Failure[a]

Drug	Dose	HR	MAP	PAOP	CO	SVR
Dopamine	0.5–3 mcg/kg/min	0	0	0	0/+	–
Dopamine	3–10 mcg/kg/min	+	+	0	+	0
Dopamine	>10 mcg/kg/min	+	+	+	+	+
Dobutamine	2.5–20 mcg/kg/min	0/+	0	–	+	–
Milrinone	0.375–0.75 mcg/kg/min	0/+	0/–	–	+	–
Nitroprusside	0.25–3 mcg/kg/min	0/+	0/–	–	+	–
Nitroglycerin	5–200 mcg/min	0/+	0/–	–	0/+	0/–
Furosemide	20–80 mg, repeated as needed up to six times per day	0	0/–	–	0	0
Enalaprilat	1.25–2.5 mg q6-8h	0	0/–	–	+	+
Nesiritide	bolus: 2 mcg/kg; infusion 0.01 mcg/kg/min 0	0	0/–	–	+	–

+, increase; –, decrease; 0, no change; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; SVR, systemic vascular resistance.
[a]See text for a more detailed description of the interpatient variability in response.

retrospective analyses suggest that diuretics, especially aggressive diuretic administration, may be harmful. The use of diuretics is associated with a dose-dependent increase in mortality.[135] Recent evidence also suggests that high diuretic doses are associated with a decline in renal function in decompensated heart failure.[134,136] Thus, the need for increased exposure to diuretics in the setting of diuretic resistance is concerning.

The mechanisms responsible for diuretic resistance in heart failure patients appear to be both pharmacokinetic and pharmacodynamic. The bioavailability of furosemide is relatively normal in heart failure patients, but the rate of absorption is prolonged approximately twofold, and peak concentrations are about half of normal. Because loop diuretics have a sigmoidal-shaped urine concentration–response curve, prolonged absorption may result in concentrations that fail to reach the steep portion of this curve, resulting in diminished responsiveness. Despite normal pharmacokinetics following intravenous administration, diuretic resistance is also observed with this route, suggesting an important pharmacodynamic component to diuretic resistance. The decreased responsiveness in heart failure patients is explained in part by the high concentrations of sodium reaching the distal tubule as a result of the blockade of sodium reabsorption in the loop of Henle. As a consequence, the distal tubule hypertrophies, increasing its ability to reabsorb sodium. In addition, low cardiac output, reduced renal perfusion, and subsequent decreased delivery of drug to the kidney may also contribute to resistance.

Several maneuvers can be attempted to overcome diuretic resistance. Treatment of heart failure with other agents (e.g., positive inotropes or afterload reducers) may improve diuresis by increasing cardiac output and renal perfusion. Administration of low doses of dopamine with the hope of enhancing diuresis is also a common practice. However, data suggest that addition of dopamine to furosemide provides no additional diuresis.[124] Larger intravenous bolus doses of diuretics may achieve concentrations closer to the top of the concentration–response curve, or a continuous intravenous infusion may be used to maintain more constant concentrations in the steep portion of the concentration–response curve. Studies of continuous-infusion furosemide suggest a greater natriuretic effect and no difference in metabolic adverse effects when compared with the same total daily dose given by intravenous bolus.[124] Continuous infusions also may limit adverse hemodynamic events.

Another approach to improving diuresis is addition of a second diuretic with a different mechanism of action. Combining a loop diuretic with a distal tubule blocker such as metolazone or hydrochlorothiazide can produce a synergistic diuretic effect. The synergism is not a pharmacokinetic interaction but is related to the increased delivery of sodium to the distal convoluted tubule. Enhanced sodium delivery to (and reabsorption in) the distal tubule can then be blocked by the thiazide-type diuretic. Thus, when thiazide-type diuretics are added to a loop diuretic, they block more than their normal 5% to 8% of filtered sodium, and the combination results in synergistic natriuresis.

The loop diuretic–thiazide combination generally should be reserved for the inpatient setting, where the patient can be monitored closely, because it can induce a profound diuresis with severe electrolyte and volume depletion. When used in the outpatient setting, very low doses or only occasional doses of the thiazide-type diuretic should be used along with close followup (weight, vital signs, dizziness) to avoid serious adverse events.

Current guidelines support each of the above mentioned options for managing patients who do not initially respond to diuretic therapy. Further restricting sodium and fluid (e.g., less than 1 g and less than 1 L per day, respectively) beyond that which is routine may also prove useful in managing diuretic refractory patients. Such severe fluid restrictions also will be helpful in managing moderate to severe hyponatremia. Ultrafiltration is an additional therapeutic option in the diuretic refractory patient. This topic is discussed within Mechanical Circulatory Support below.

Positive Inotropic Agents[137,138]

Drugs that increase intracellular cAMP are the only positive inotropic agents currently approved for the treatment of acute heart failure. β-Agonists activate adenylate cyclase through stimulation of β-adrenergic receptors, with the enzyme then catalyzing the conversion of adenosine triphosphate to cAMP. Phosphodiesterase inhibitors raise cAMP concentrations by reducing its degradation. Consequently, both drug classes increase intracellular cAMP, which enhances phospholipase (and, subsequently, phosphorylase) activity, increasing the rate and extent of calcium influx during systole and enhancing contractility. Additionally, cAMP enhances reuptake of calcium by the sarcoplasmic reticulum during diastole, improving active relaxation. Table 16–17 summarizes the receptor activities of the β-agonists. Although rarely used in management of heart failure, the receptor effects of epinephrine, NE, and isoproterenol are provided for reference.

Digoxin has little, if any, place in the acute treatment of patients with decompensated heart failure who are hemodynamically unstable. The delay in peak inotropic effect, limited inotropic effect, long duration of action, and potential toxicity (arrhythmic, vasoconstrictive, neurologic) are disadvantages in the acute setting. However, in patients with acute decompensation who are taking digoxin as part of their chronic therapy, it is generally unnecessary to adjust the dose or discontinue its use unless changes in renal function increase the risk of toxicity.

Although a number of parenteral agents have been used for the treatment of patients with decompensated heart failure, dobutamine and milrinone have emerged as the two drugs most commonly

TABLE 16-17 Relative Effects of Adrenergic Drugs on Receptors

Drug	α_1	β_1	β_2	Dopamine$_1$
Norepinephrine	++++	++++	0	0
Epinephrine	++++	++++	++	0
Dopamine[a]	++++	++++	++	++
Isoproterenol	0	++++	++++	0
Dobutamine[b]	+	++++	++	0

[a]See text for a more detailed description of the dose-dependent hemodynamic effects.
[b]Combined effects of the commercially available racemic mixture (see text).

administered. These drugs differ in their mechanism of action and resulting pharmacologic effects and provide advantages and disadvantages in any given patient.

Dobutamine Dobutamine, a synthetic catecholamine, is a β_1- and β_2-receptor agonist with some α_1-agonist effects (see Table 16–17). Unlike dopamine, dobutamine does not cause release of NE from nerve terminals. The overall hemodynamic effects of dobutamine are the result of its effects on adrenergic receptors and reflex-mediated actions. Its β_2-receptor-mediated effects are greater than those of dopamine, and β_2-receptor-mediated vasodilation will tend to offset some of the α_1-receptor-mediated vasoconstriction. Thus the net vascular effect is usually vasodilation. The positive inotropy is primarily a β_1-receptor mediated effect. Cardiac β_1-receptor stimulation by dobutamine causes an increase in contractility but generally no significant change in heart rate and may provide an explanation for the apparently more modest chronotropic actions of dobutamine compared with dopamine.

The overall hemodynamic effects of dobutamine are those of a potent inotropic agent with vasodilating action. Initial doses of 2.5 to 5 mcg/kg per minute can be increased progressively to 20 mcg/kg/min based on clinical and hemodynamic responses. The onset of action is within minutes; however, peak effects may take 10 minutes to become evident. Dobutamine has a half-life of 2 minutes. Cardiac index is increased because of inotropic stimulation, arterial vasodilation, and a variable increase in heart rate. Because of the offsetting changes in arteriolar resistance and cardiac index, dobutamine usually will cause relatively little change in mean arterial pressure although these effects may be variable. This is compared with the more consistent increase observed with dopamine. Dobutamine's vasodilating action usually can decrease PAOP, making it particularly useful in the presence of low cardiac index and an elevated left ventricular filling pressure, or detrimental in the presence of a reduced filling pressure. Unfortunately, an increase in oxygen consumption with dobutamine has been demonstrated in patients with both ischemic and nonischemic cardiomyopathy. The major adverse effect of dobutamine is tachycardia. Although concern over attenuation of dobutamine's hemodynamic effects has been raised with prolonged administration, some effect is likely still retained. And thus, dobutamine dose should be tapered rather than abruptly discontinued.

In some patients, dobutamine (or milrinone) dose reduction or discontinuation results in acute decompensation and these patients may then require placement of an indwelling intravenous catheter for continuous therapy. This approach may be used to "bridge" patients awaiting cardiac transplantation, and may also be used to facilitate the discharge of patients who are not transplant candidates, but who cannot be weaned from inotrope therapy. In this latter group, the use of continuous outpatient dobutamine therapy is for palliative use only and should only be considered after multiple unsuccessful attempts to maximize oral therapy and discontinue inotrope therapy. Although effective for symptom palliation, it should be realized that the risk of mortality is likely increased. In contrast, the use of regularly scheduled intermittent dobutamine infusions at home or in an outpatient clinic is not recommended in the current guidelines.[124]

Milrinone Milrinone is a bipyridine derivative that inhibits phosphodiesterase III, an enzyme responsible for the breakdown of cAMP to adenosine monophosphate. Milrinone has supplanted the use of amrinone, the prototype drug for milrinone, because of the more frequent occurrence of thrombocytopenia with amrinone. Both positive inotropic and arterial and venous vasodilating effects contribute to the therapeutic response in heart failure patients; hence milrinone has been referred to as an *inodilator*. The relative balance of these pharmacologic effects may vary with dose and underlying cardiovascular pathology.

During intravenous administration, there is an increase in stroke volume (and, therefore, cardiac output) with little change in heart rate (see Table 16–16). Despite the increase in cardiac index, mean arterial pressure may remain constant as a result of a concomitant decrease in arteriolar resistance. In contrast, the vasodilating effects may predominate and lead to a decrease in blood pressure and a reflex tachycardia. Like dobutamine, milrinone lowers PAOP by venodilation and thus is particularly useful in patients with a low cardiac index and an elevated left ventricular filling pressure. Such a reduction in preload, however, can be hazardous for patients without excessive filling pressure (especially those with symptoms of "dry" heart failure), leading to a decrease in cardiac index. Such an effect would blunt the improvement in cardiac output that would otherwise be produced by the positive inotropic and arterial dilating actions. Milrinone should be used cautiously as a single agent in severely hypotensive heart failure patients because it will not increase, and may even decrease, arterial blood pressure. The results of controlled studies comparing dobutamine with milrinone indicate that these agents produce generally similar hemodynamic effects. A clinically insignificant but greater increase in heart rate with dobutamine is the most consistent difference in these studies.

Milrinone has a longer terminal elimination half-life than adrenergic agonists. The average milrinone half-life in healthy subjects is about 1 hour and approximately 3 hours in patients with heart failure. This long elimination half-life may be a disadvantage in this patient population because a loading dose may be necessary to obtain a prompt initial response, minute-to-minute titrations in dose cannot be made based on response, and adverse effects (arrhythmias or hypotension) will persist longer after drug discontinuation. The usual loading dose for milrinone is 50 mcg/kg administered over 10 minutes. However, if rapid hemodynamic changes are unnecessary, the loading dose should be eliminated because of the risk of hypotension. Thus, most patients are simply started on the maintenance infusion without a preceding bolus dose. The maintenance infusion for milrinone is 0.25 mcg/kg/min (up to 0.75 mcg/kg/min). Milrinone is excreted unchanged in urine, and thus, its infusion rate should be decreased by 50% to 70% in patients with significant renal impairment.

The most notable adverse events associated with milrinone are arrhythmia, hypotension, and thrombocytopenia. Although the incidence of thrombocytopenia associated with milrinone therapy is rare, patients should still have platelet counts determined before and during therapy.

The combination of dobutamine and milrinone is expected to produce additive effects on cardiac index and PAOP reduction, suggesting this regimen as an option in patients who have dose-limiting adverse effects with either class of drugs. It is unclear, however, if this combination provides a therapeutic advantage over the combination of a positive inotrope and a traditional pure vasodilator such as nitroprusside.

One study with milrinone points out the risk associated with routine administration of inotropic therapy to a broad population of patients admitted to the hospital with an acute exacerbation of heart failure. Although this approach is not supported by clinical trial data, many patients without signs or symptoms of hypoperfusion receive milrinone or other inotropic therapy with the belief that the hemodynamic effects may shorten hospitalization and improve clinical outcomes. Designed to evaluate this strategy, the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial was a randomized, double-blind trial comparing the effects of milrinone and placebo in patients hospitalized with an acute exacerbation of chronic heart failure who, in the investigator's opinion, did not require inotropic therapy.[122] The 949 patients received a 48-hour infusion of milrinone 0.5 mcg/kg/min with no loading dose or placebo. No difference

between milrinone and placebo was found in the primary end point of the number of days patients were hospitalized for cardiovascular causes within 60 days of randomization. However, adverse events were more common in the milrinone group. Sustained hypotension requiring intervention (10.7% vs. 3.2%; $P < 0.001$) and new onset of atrial fibrillation or flutter (4.6% vs. 1.5%; $P = 0.004$) occurred more frequently in patients receiving milrinone.

Recently, data from the ADHERE Registry (n = 15,230) was used to compare in-hospital mortality with intravenous nitroglycerin, nesiritide, milrinone, and dobutamine. After adjusting for baseline parameters that predict in-hospital mortality, both dobutamine- and milrinone-treated patients had a higher in-hospital mortality when compared to patients receiving either nitroglycerin or nesiritide ($P < 0.005$). There was no difference in in-hospital mortality between nitroglycerin- and nesiritide-treated patients ($P = 0.58$). In-hospital mortality was higher in patients receiving dobutamine compared to milrinone ($P = 0.027$).[139]

These results add to the growing concern about the use of inotropic drugs in patients with decompensated heart failure and strongly suggest that milrinone, and probably other inotropes, should not be routinely used for the treatment of acute heart failure exacerbations. Although the routine use of milrinone should be discouraged, clinicians should be aware that inotropic therapy may be needed in selected patients such as those with low cardiac output states with organ hypoperfusion or with cardiogenic shock. Generally, milrinone should be considered for patients who are receiving chronic β-blocker therapy because its positive inotropic effect does not involve stimulation of β-receptors. In contrast to dobutamine, milrinone's positive hemodynamic effects persist despite concomitant β-blocker therapy.

Dopamine Although dopamine generally should be avoided in the treatment of decompensated heart failure, the only clinical scenario where its pharmacologic actions may be preferable to dobutamine or milrinone is in the patient with marked systemic hypotension or cardiogenic shock in the face of elevated ventricular filling pressures, where dopamine in doses greater than 5 mcg/kg per minute may be necessary to raise central aortic pressure. However, there are no data to support this commonly employed practice.

Dopamine, the endogenous precursor of NE, exerts its effects by directly stimulating adrenergic receptors, as well as causing release of NE from adrenergic nerve terminals. Dopamine produces dose-dependent hemodynamic effects because of its relative affinity for α_1-, β_1-, β_2-, and D_1- (vascular dopaminergic) receptors (see Table 16–17). The following dose-dependent actions are intended as a general guide to the clinician.

Positive inotropic effects mediated primarily by β_1-receptors become more prominent with dopamine doses of 2 to 5 mcg/kg/min. Cardiac index is increased because of an increase in stroke volume and a variable increase in heart rate, which is partially dose dependent. There is usually little change in SVR, presumably because neither vasodilation (D_1- and β_2-receptor mediated) nor vasoconstriction (α_1-receptor mediated) predominates. At doses between 5 and 10 mcg/kg/min, chronotropic and α_1-receptor–mediated vasoconstricting effects become more prominent. Mean arterial pressure usually increases because of an increase in both cardiac index and SVR (see Table 16–16). The vasoconstricting effects of higher doses could indirectly limit the increase in cardiac index by increasing afterload and PAOP, thus complicating the management of patients with preexisting high afterload. In such patients, alternative agents (dobutamine, milrinone) or the addition of diuretics and/or vasodilators may be necessary.

Dopamine, particularly at higher doses, may alter several parameters that increase myocardial oxygen demand (increased heart rate, contractility, and systolic pressure) and potentially decrease myocardial blood flow (coronary vasoconstriction and increased wall tension), worsening ischemia in some patients with coronary disease. As with dobutamine and milrinone, arrhythmogenesis is also more common at higher doses.

Vasodilators[134,140]

Activation of the SNS, the RAAS, AVP, and other mediators all cause vasoconstriction and increased SVR. In patients with heart failure, stroke volume varies inversely with SVR such that an increase in peripheral resistance leads to a severe decline in stroke volume and cardiac output (see Fig. 16–1).

Vasodilators typically are described by their prominent site of action (arterial or venous). Arterial vasodilators act as impedance-reducing agents, reducing afterload and a reflexive increase in cardiac output. Venodilators act as preload reducers by increasing venous capacitance, reducing symptoms of pulmonary congestion in patients with high cardiac filling pressures. Mixed vasodilators act on both resistance and capacitance vessels, reducing congestive symptoms while increasing cardiac output. Nitroprusside, nitroglycerin, and nesiritide are the most commonly used intravenous vasodilating agents in decompensated heart failure.

Nitroprusside Sodium nitroprusside, a mixed arterial–venous vasodilator, acts on vascular smooth muscle, increasing synthesis of nitric oxide to produce its balanced vasodilating action. As such, it both increases cardiac index and decreases venous pressure. Nitroprusside's effects on these parameters are qualitatively similar to those produced by dobutamine and phosphodiesterase inhibitors, despite the fact that it has no direct inotropic activity (see Table 16–16). However, nitroprusside generally causes a greater decrease in PAOP, SVR, and blood pressure than these agents. Mean arterial pressure may remain fairly constant but often decreases depending on the relative increase in cardiac output and reduction in arteriolar tone. Hypotension is an important dose-limiting adverse effect of nitroprusside and other vasodilators. Consequently, this drug is used primarily in patients who have a significantly elevated SVR and often requires invasive hemodynamic monitoring.

Patients with normal left ventricular function will not have an increase in stroke volume when SVR falls because the normal ventricle is fairly insensitive to small changes in afterload. Consequently, these patients experience a significant decrease in blood pressure after administration of arterial vasodilators. This explains why nitroprusside is a potent antihypertensive agent in patients without heart failure but causes less hypotension and reflex tachycardia in patients with left ventricular dysfunction. Nonetheless, even a modest increase in heart rate could have adverse consequences in patients with underlying ischemic heart disease and/or resting tachycardia, and close monitoring is necessary during therapy.

Nitroprusside has been studied extensively and shown to be effective in the short-term management of patients with severe heart failure in a variety of settings (i.e., acute MI, valvular regurgitation, after coronary bypass surgery, decompensated chronic heart failure). Generally, nitroprusside will not worsen, and may improve, the balance between myocardial oxygen demand and supply. This is mainly a result of a decrease in oxygen demand caused by the lowering of left ventricular wall tension and a possible increase in subendocardial blood flow resulting from decreased left ventricular end-diastolic pressure. However, an excessive decrease in systemic arterial pressure can reduce coronary perfusion and worsen ischemia, leading to increased risk of coronary steal.

Nitroprusside has a rapid onset of action and a duration of action of less than 10 minutes, necessitating its administration by continuous intravenous infusion. This allows for precise dose titration based on measured clinical and hemodynamic parameters. It, like other vasodilators used in heart failure, should be initiated at a low dose (0.1 to 0.2 mcg/kg/min) to avoid excessive hypotension and then

increased by small increments (0.1 to 0.2 mcg/kg/min) every 5 to 10 minutes as needed and tolerated. Effective doses usually range from 0.5 to 3.0 mcg/kg/min. A rebound phenomenon has been reported after abrupt withdrawal of nitroprusside in patients with heart failure and is apparently caused by reflex neurohormonal activation during therapy. If renal perfusion pressure is compromised by the drug, salt and water retention can contribute to volume expansion and tachyphylaxis; this is seen typically only in patients with chronic hypertension, baseline azotemia, or when therapeutic augmentation of cardiac output during therapy is minimal. When stopping nitroprusside and switching to oral drugs, it is usually advisable to taper doses slowly. Nitroprusside can cause cyanide and thiocyanate toxicity, but these are very unlikely when doses less than 3 mcg/kg/min are administered for less than 3 days, except in patients with a serum creatinine level greater than 3 mg/dL.

Given the potent pulmonary vasodilatory effects of nitroprusside as well as its short half-life, this agent is frequently used to determine reversibility of pulmonary hypertension in patients being assessed for heart transplantation. This is the most common use of nitroprusside for the management of decompensated heart failure.

Nitroglycerin Intravenous nitroglycerin is often considered the preferred agent for preload reduction in patients with severe heart failure. Because of its short half-life, intravenous nitroglycerin is administered by continuous infusion. Its major hemodynamic actions are reductions in preload and PAOP via functional venodilation and mild arterial vasodilation that is particularly evident in patients with heart failure and elevated SVR or when given in doses approaching 200 mcg/min (see Table 16–16). Intravenous nitroglycerin is used primarily as a preload reducer for patients with pulmonary congestion. In higher doses, nitroglycerin displays potent coronary vasodilating properties and beneficial effects on myocardial oxygen demand and supply, making it the vasodilator of choice for patients with severe heart failure and ischemic heart disease.

Nitroglycerin should be initiated at a dose of 5 to 10 mcg/min (0.1 mcg/kg/min) and increased every 5 to 10 minutes as necessary and tolerated. Hypotension and an excessive decrease in PAOP are important dose-limiting side effects. Maintenance doses usually vary from 35 to 200 mcg/min (0.5 to 3.0 mcg/kg/min). Tolerance to the hemodynamic effects of nitroglycerin may develop over 12 to 72 hours of continuous administration, but some patients have a sustained response. Neither nitroglycerin nor nitroprusside should be used in the presence of elevated intracranial pressure because either may worsen cerebral edema in this setting.

Nesiritide Nesiritide is the first new drug approved for the treatment of decompensated heart failure since milrinone. Manufactured by recombinant techniques, it is identical to the endogenous human BNP secreted by the ventricular myocardium in response to volume overload. Exogenous administration of nesiritide mimics the vasodilatory and natriuretic actions of the endogenous peptide by stimulating the natriuretic peptide receptor A which leads to increased levels of cyclic guanosine monophosphate in target tissues. Nesiritide produces dose-dependent venous and arterial vasodilation, increases in cardiac output, natriuresis, and diuresis, and decreases cardiac filling pressures, SNS and RAAS activity. Unlike nitroglycerin or dobutamine, tolerance does not develop to nesiritide's pharmacologic actions. It does not affect cAMP or stimulate β-receptors, mechanisms that are thought to contribute to the myocardial toxicity associated with the positive inotropic drugs. Thus, nesiritide does not have the proarrhythmic effects associated with dobutamine. Nesiritide is eliminated by several pathways including the natriuretic peptide receptor C on target tissues, proteolytic cleavage by neutral endopeptidase, and renal filtration. Its elimination half-life of 18 minutes is considerably longer than that of other vasodilators or β-agonists.

The Vasodilation in the Management of Acute CHF (VMAC) trial was a randomized, double-blind trial that compared the effects of nesiritide, IV nitroglycerin, and placebo in patients with decompensated heart failure and dyspnea who were receiving standard background therapy.[123] Patients received pulmonary artery catheterization at the discretion of the investigators. The primary end points were the patient's self-assessment of dyspnea (all patients) and the change in PAOP at 3 hours after the start of the study drug infusion (only in patients with a pulmonary artery catheter) compared to placebo. Although nesiritide reduced dyspnea at 3 hours compared to placebo, no difference between nesiritide and nitroglycerin was found.

The precise role of nesiritide in the pharmacotherapy of decompensated heart failure remains controversial. Some of this controversy centers on the marginal lack of improvement in mortality or other clinical outcomes with nesiritide compared to nitroglycerin (or nitroprusside) balanced against nesiritide's significantly greater costs (~$450 for a 24-hour nesiritide infusion compared to $10 to $15 for nitroglycerin). In addition, two recent meta-analyses suggest an increased risk of worsening renal function, as well as an increase in mortality with nesiritide.[141,142] The authors of these studies concluded that these finding are hypothesis generating and should be further investigated. More recently, the safety of nesiritide in 303 patients with a low LVEF (<40%) who were undergoing coronary artery bypass surgery was evaluated in the multicenter, randomized, placebo-controlled Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) study.[143] Patients received intravenous nesiritide 0.01 mcg/kg/min or placebo in the perianesthesia period and the infusion continued for 24 to 96 hours at the investigator's discretion. Serum creatinine increased and glomerular filtration rate decreased after surgery compared with preoperative values in both treatment groups. However, the changes in creatinine and glomerular filtration rate were significantly greater in placebo-treated patients. In contrast, the mean hospital length of stay was significantly shorter and the 180-day mortality rate was significantly lower in the nesiritide group. To clarify these issues about the safety and efficacy of nesiritide, its manufacturer is conducting an additional prospective randomized controlled trial.

■ MECHANICAL CIRCULATORY SUPPORT[144]

Intraaortic Balloon Pump

The intraaortic balloon pump (IABP) is a frequently used form of mechanical circulatory assistance and typically is employed in patients with advanced heart failure who do not respond adequately to drug therapy, such as those with intractable myocardial ischemia or patients in cardiogenic shock. The IABP consists of a polyethylene balloon mounted on a catheter that is usually inserted percutaneously into the femoral artery and the balloon is then advanced into the descending thoracic aorta. During counterpulsation, the balloon is synchronized with the ECG so that it inflates during diastole and displaces aortic blood thus increasing aortic diastolic pressure and coronary perfusion. The balloon deflates just prior to the opening of the aortic valve during systole and causes a sudden decrease in aortic pressure, allowing the left ventricle to pump against reduced arterial impedance. IABP support results in increased cardiac index, coronary artery perfusion, and myocardial oxygen supply accompanied by decreased myocardial oxygen demand. Thus, it is particularly useful for short-term use in patients with decompensated heart failure in the setting of myocardial ischemia (evolving infarction, patients awaiting emergency coronary bypass surgery). It is also used in hemodynamically unstable patients who are unresponsive to inotropic therapy to stabilize them prior to insertion of a left ventricular assist device that will serve as a bridge to transplantation. Generally, intravenous vasodilators and

inotropic agents are used in conjunction with the IABP to maximize hemodynamic and clinical benefits.

Ventricular Assist Devices

A number of ventricular assist devices are available or under investigation. These pumps are surgically implanted and assist, or in some cases replace, the pumping functions of the right and/or left ventricles. A left ventricular assist device (LVAD) removes blood directly from the left ventricle or the left atrium and pumps it to the aorta. The right ventricular assist device works similar to the LVAD and may be used alone or in conjunction with the LVAD.

LVADs can be used in the short-term (days to a couple of weeks) for temporary stabilization of a patient awaiting an intervention to correct the underlying cardiac dysfunction. Alternatively, these devices can be used in the long-term (several months to a couple of years) as a bridge to heart transplantation. More recently, permanent device implantation has become an option for patients who are not heart transplantation candidates.

The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial randomized 129 patients with decompensated heart failure to LVAD or optimal medical therapy. LVAD patients experienced improved 2-year survival; however, only 23% of these patients were alive at 2 years, compared to only 8% in the medically managed group.[145] The REMATCH trial was responsible for the approval of the use of these devices as "destination" therapy, destination being the last therapeutic option for a given patient. It also raised awareness regarding some of the limitations of these devices. Complications with LVADs include bleeding, air embolism, and right ventricular failure, as well as those complications associated with a major surgical procedure, including infection. In addition, these pumps can cause hemolysis, thrombosis, renal and hepatic dysfunction, and arrhythmias. Finally, device malfunction may occur. Controversy exists regarding the cost of such procedures given the already significant economic impact of this disease state on the healthcare system. Although only a small number of patients were studied, recent research suggests that prolonged unloading of the left ventricle with an LVAD in combination with drug therapy to induce reverse remodeling can produce sustained recovery in left ventricle function and amelioration of symptoms.[146]

For complete heart replacement therapy, the total artificial heart systems continue to be investigated; however, embolic complications, as well as the large size of the currently available systems, are limiting their use. Inserted percutaneously, catheter-based LVADs are a more recent advancement. Although these small pumps may offer an advantage as they avoid the need for open-heart surgery, the technology is still in developmental stages.

Ultrafiltration

Renal dysfunction often occurs in the setting of decompensated heart failure, and thus, renal replacement therapy may be necessary. Ultrafiltration provides an additional modality for fluid removal by rapidly removing salt and water (up to 500 mL/h) in a predictable manner. It reduces PAOP and increases cardiac output and diuresis without adversely affecting blood pressure, heart rate, or renal function. Also, ultrafiltration is proposed to be safer than diuretics because removal of sodium and water is isotonic. Potential candidates for ultrafiltration include patients with diuretic resistance, renal impairment with diuretic administration, and renal impairment despite inotropic therapy. Complications of ultrafiltration include those associated with central venous access, such as infection, as well as those associated with rapid volume removal and intravascular depletion. Electrolyte depletion is not significant, but still requires close monitoring.

Small studies suggest that ultrafiltration is an effective method to remove fluid in heart failure patients and that early initiation prior to intravenous diuretics is effective and safe in reducing hospital length of stay and readmission in diuretic resistant patients. Recently, the Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial investigated the effects of early ultrafiltration alone compared to intravenous diuretics alone in 200 patients hospitalized for decompensated heart failure and evidence of fluid overload. The primary end point of weight loss after 48 hours was significantly greater in the ultrafiltration group (5.0 kg) than in the diuretic group (3.1 kg). There was no significant difference between the two treatment groups in the dyspnea score at 48 hours, another primary end point. Compared with the diuretic group, the net fluid loss was significantly greater in the ultrafiltration group (4.6 L vs. 3.3 L) after 48 hours. After 90 days, the incidence and duration of rehospitalization and the incidence of unscheduled office or emergency department visits were significantly lower in patients who were treated using ultrafiltration than in patients who were treated with intravenous diuretics.[147]

SURGICAL THERAPY

Orthotopic cardiac transplantation remains the best therapeutic option for patients with chronic, irreversible NYHA class IV heart failure, with a 10-year survival of approximately 50% in well-selected patients.[148] Unfortunately, the shortage of acceptable donor hearts has resulted in long waiting times for transplantation, with many patients succumbing to their disease prior to transplantation. Another large percentage of patients are rejected from consideration for transplantation because of age, concurrent illnesses, psychosocial factors, and other reasons. See Chap. 92 for additional details on cardiac transplantation. The shortage of donor hearts has prompted development of new surgical techniques, including ventricular aneurysm resection, mitral valve repair, and myocardial cell transplantation, which have resulted in variable degrees of symptomatic improvement. Further development of these and other techniques may offer additional options in patients who are not transplantation candidates.

PREPARATION FOR HOSPITAL DISCHARGE

For patients who are hospitalized with decompensated heart failure, all factors contributing to decompensation should be addressed. Patients should be near if not at optimal fluid status, transitioned from intravenous to oral diuretic therapy. Both the patient and family should receive appropriate education (see details below). Chronic drug therapy should be optimized and appropriate followup clinic appointments scheduled. Typically, patients should be seen in the clinic in 7 to 10 days following hospital discharge. For patients with recurrent hospital admissions, additional discharge criteria should be considered (Table 16–18).[124]

Patient education is essential in the discharge process and should be multidisciplinary involving input from dietitians, pharmacists, and other healthcare providers. Teaching should promote self-care by incorporating identification of specific positive and negative behaviors. By having a better understand of the key concepts of the disease and its management, patient self-care should improve and future hospitalizations may be avoided.[124]

Although all patients should benefit from education, those with more severe symptoms (NYHA class III or IV) require the most intensive counseling. During a hospitalization, only essential education is recommended, which should be supplemented within a couple of weeks after discharge in the clinic setting. Patients recently hospitalized for heart failure should be considered for referral to a disease-management program.

TABLE 16-18 Discharge Criteria for Patients with Heart Failure

Recommended for all heart failure patients	• Exacerbating factors addressed • At least near-optimal volume status achieved • Transition from intravenous to oral diuretic successfully completed • Patient and family education completed • At least near-optimal pharmacologic therapy achieved • Followup clinic visit scheduled, usually for 7–10 days after discharge
Should be considered for patients with advanced heart failure or recurrent admissions for heart failure	• Oral medication regimen stable for 24 hours • No intravenous vasodilator or inotropic agent for 24 hours • Ambulation before discharge to assess functional capacity after therapy • Plans for postdischarge management (scale present in home, visiting nurse or telephone followup generally no longer than 3 days after discharge) • Referral for disease management

Adapted from Adams KF, Lindenfield J, Arnold JMO, et al. HFSA 2006 comprehensive heart failure practice guidelines. J Card Fail 2006;12:e1–e122.

For patients with end-stage disease, quality of life and prognosis should be discussed with the patient and caregivers. The patient's clinical status should be optimally managed prior to discussing end-of-life care. If possible, this discussion should occur while the patient is still able to participate in the decision-making process. End-of-life care should be considered in patients with persistent symptoms at rest despite multiple attempts to optimize therapy as evidenced by frequent hospitalizations (three or more per year), ongoing limited quality of life, requiring intermittent or continuous intravenous therapy, or consideration of assist devices as destination therapy. In such cases, inactivation of an ICD should be discussed and patients may be considered for hospice services.[124] Integration of a palliative care approach may be necessary. As clinical status deteriorates and medical therapies become ineffective, healthcare providers should transition from focusing on mortality reduction to palliative care.[149]

PHARMACOECONOMIC CONSIDERATIONS

Heart failure imposes a tremendous economic burden on the healthcare system. In patients older than age 65 years, it is the most common reason for hospitalization, with hospital admission rates for this disorder continuing to increase. Heart failure is also associated with unacceptably high readmission rates during the 3 to 6 months after initial discharge. Current estimates of costs of heart failure treatment in the United States approach $30 billion with most of the costs associated with hospitalization.[1,4] The prevalence of heart failure and the costs associated with patient care are expected to increase as the population ages and as survival from ischemic heart disease is improved. Thus approaches to improve the quality and cost-effectiveness of care for these patients may have a significant impact on healthcare costs.

Studies to assess the cost-effectiveness of drug therapy for heart failure were recently reviewed.[150] Many studies provide direct cost estimates, demonstrating an economic value when employing standard heart failure therapies, specifically ACE inhibitors, β-blockers, and digoxin. Much of the economic benefit of these therapies is a result of a reduction in hospitalization. While the clinical and economic benefits of these therapies are well-recognized, standard heart failure therapies are often underprescribed. A recent study found that more optimal use of evidence-based therapies with a 10% increase in the use of ACE inhibitors, β-blockers, digoxin, and spironolactone would result in cost savings as a consequence of a reduction in hospitalization.[151] In addition, prescribing optimal doses that approach target doses shown in clinical trials to affect outcomes would have a similar impact. For example, patients receiving high doses versus low doses of ACE inhibitors experienced cost saving as a consequence of fewer heart failure hospitalizations.[152]

More recent pharmacoeconomic studies have focused on the impact of newer heart failure therapies or those used as alternatives to standard therapy. ARBs have been shown to be cost effective in patients not receiving ACE inhibitors.[153] Eplerenone is a cost-effective therapy in patients with post-MI heart failure.[154] Fixed-dose combination hydralazine and isosorbide dinitrate is cost-effective in black patients with severe heart failure.[155] Other cost-effective studies have focused on device therapy. Prophylactic ICD implantation in heart failure patients with systolic dysfunction is cost-effective.[156] Although cost-effectiveness of CRT has been suggested, it was found to be sensitive to changes in several key variables. Thus investigators cautioned that such therapy should not be considered in patients with any comorbid illnesses that may shorten life expectancy.[157] Finally, LVADs as a bridge to heart transplantation were found to be cost-ineffective unless costs associated with their implantation decrease or their clinical benefits increase.[158]

As the management of heart failure has become increasingly complex, the development of disease-management programs approaches that use multidisciplinary teams has been studied extensively. These programs use several broad approaches, including heart failure specialty clinics and/or home-based interventions. Most are multidisciplinary and may include physicians, advanced practice nurses, dieticians, and pharmacists. In general, the programs focus on optimization of drug and nondrug therapy, patient and family education and counseling, exercise and dietary advice, intense followup by telephone or home visits, and monitoring and management of signs and symptoms of decompensation. In general, multidisciplinary disease management programs reduce heart failure and all-cause hospitalizations, mortality, and costs.[159]

12 Pharmacists can play an important role in the multidisciplinary team management of heart failure.[160,161] Compared to conventional treatment, pharmacist interventions, that included medication evaluation and therapeutic recommendations, patient education, and followup telephone monitoring, reduced hospitalizations for heart failure. Adherence to guideline-recommended therapy was also improved by pharmacist intervention. A recent study found that pharmacist intervention improved medication adherence and reduced emergency department visits and hospitalizations in low-income patients with heart failure.[162] Thus, the role and cost benefits of pharmacist involvement in the multidisciplinary care of heart failure patients are now apparent and should include optimizing doses of heart failure drug therapy, screening for drugs that exacerbate heart failure, monitoring for adverse drug effects and drug interactions, educating patients, and patient followup.

CURRENT CONTROVERSIES

1. For patients with chronic heart failure who remain symptomatic despite standard therapy (ACE inhibitor, β-blocker, diuretic, digoxin), which additive therapy should be used is uncertain. Agents that can be considered are aldosterone antagonists, ARBs, or hydralazine/nitrates. Drug selection should be based on patient-specific criteria (e.g., renal function, ethnicity) that will influence the benefits and risks of each agent.
2. The African American Heart Failure Trial confirmed that the addition of a fixed-dose combination of isosorbide dinitrate and hydralazine to standard background therapy improved survival in African American patients with heart failure. Whether isosorbide/hydralazine is beneficial in non-African American patients is unknown.
3. The optimal pharmacotherapy for patients with acute decompensated heart failure who are refractory to diuretic therapy is controversial. Recent meta-analyses suggest that nesiritide use

is associated with worsening renal function and increased mortality. However, the safety of other vasodilators, such as nitroglycerin or nitroprusside, is not well established and the use of positive inotropes is associated with poor outcomes.

EVALUATION OF THERAPEUTIC OUTCOMES

CHRONIC HEART FAILURE

Although mortality is an important end point, it does not give a complete measure of the overall effects of the disease on patient outcomes because many patients are hospitalized repeatedly for heart failure exacerbations and continue to survive. Thus some of the more important therapeutic outcomes in heart failure management, such as prolonged survival or prevention or slowing of the progression of heart failure, cannot be quantified in an individual patient. However, after appropriate diagnostic evaluation to determine the etiology of heart failure, ongoing clinical assessment of patients typically focuses on three general areas: (a) evaluation of functional capacity, (b) evaluation of volume status, and (c) laboratory evaluation.

The evaluation of functional capacity should focus on the presence and severity of symptoms the patient experiences during activities of daily living and how their symptoms affect these activities. Questions directed toward the patient's ability to perform specific activities may be more informative than general questions about what symptoms the patient may be experiencing. For example, ask patients if they can participate in exercise, climb stairs, get dressed without stopping, check the mail, or clean the house. Another important component of assessment of functional capacity is to ask patients what activities they would like to do but are now unable to perform.

Assessment of volume status is a vital component of the ongoing care of patients with heart failure. This evaluation provides the clinician important information about the adequacy of diuretic therapy. Because the cardinal signs and symptoms of heart failure are caused by excess fluid retention, the efficacy of diuretic treatment is readily evaluated by the disappearance of these signs and symptoms. The physical examination is the primary method for the evaluation of fluid retention and specific attention should be focused on the patient's body weight, extent of jugular venous distension, presence of hepatojugular reflux, presence and severity of pulmonary congestion, and peripheral edema. Specifically, in a patient with pulmonary congestion, monitoring is indicated for resolution of rales and pulmonary edema and improvement or resolution of dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. For patients with systemic congestion, a decrease or disappearance of peripheral edema, jugular venous distension, and hepatojugular reflux is sought. Other therapeutic outcomes include an improvement in exercise tolerance and fatigue, decreased nocturia, and a decrease in heart rate. Clinicians also will want to monitor blood pressure and ensure that the patient does not develop symptomatic hypotension as a result of drug therapy. Body weight is a sensitive marker of fluid loss or retention, and patients should be counseled to weigh themselves daily, reporting changes to their healthcare provider so that adjustments can be made in diuretic doses. It should be noted, particularly with β-blocker therapy, that symptoms may worsen initially and that it may take weeks to months of treatment before patients notice improvement in symptoms. Also, patients and healthcare providers should be aware that heart failure progression may be slowed even though symptoms have not resolved.

Routine monitoring of serum electrolytes and renal function is required in patients with heart failure. Assessment of serum potassium is especially important because hypokalemia is a common adverse effect of diuretic therapy and is associated with an increased risk of arrhythmias and digoxin toxicity. Serum potassium monitoring is also required because of the risk of hyperkalemia associated with ACE inhibitors, ARBs, and aldosterone antagonists. A serum potassium ≥4.0 mEq/L should be maintained with some evidence suggesting it should be ≥4.5 mEq/L.[163] Assessment of renal function (blood urea nitrogen and serum creatinine) is also an important end point for monitoring diuretic and ACE inhibitor therapy. Common causes of worsening renal function in patients with heart failure include overdiuresis, adverse effects of ACE inhibitor or ARB therapy, and hypoperfusion.

ACUTE DECOMPENSATED HEART FAILURE

Assessment of adequacy of therapy in the acute decompensated heart failure patient can be separated into two general categories: initial improvement of physiologic parameters and safe discharge from the intensive care unit following conversion to a chronic oral therapeutic regimen. Both goals must be achieved because hemodynamic improvement has not correlated with prolonged symptom improvement or enhanced survival.

Initial stabilization requires achievement of adequate arterial oxygen saturation and content. Cardiac index and blood pressure must be sufficient to ensure adequate organ perfusion, as assessed by alert mental status, creatinine clearance sufficient to prevent metabolic azotemic complications, hepatic function adequate to maintain synthetic and excretory functions, a stable heart rate and rhythm (predominately sinus rhythm, rate-stabilized atrial fibrillation or flutter, or paced rhythm), absence of ongoing myocardial ischemia or infarction, skeletal muscle and skin blood flow sufficient to prevent ischemic injury, and normal arterial pH (7.34 to 7.47) with a normal serum lactate concentration. Although these goals are achieved most often with a cardiac index greater than 2.2 L/min/m^2, a mean arterial blood pressure greater than 60 mm Hg, and a PAOP of 15 mm Hg or greater, the absolute values are highly variable and depend on chronicity of illness, efficacy of chronic compensatory mechanisms, previous chronic therapy, and concurrent illness.

Discharge from the intensive care unit requires maintenance of the preceding parameters in the absence of ongoing intravenous infusion therapy, mechanical circulatory support, or positive-pressure ventilation. Some patients may achieve this goal with markedly lower blood pressure or higher filling pressure than suggested earlier; hence numerical goals cannot always be substituted for clinical status. Nonpharmacologic treatments aimed at the precipitants of a patient's heart failure exacerbation include permanent pacing, CRT with or without ICD, coronary angioplasty or valvuloplasty, pericardial drainage, cardiac surgery (coronary bypass, valve replacement or reconstruction, closure of intracardiac shunts), or even cardiac transplantation, to achieve initial stabilization, definitive therapy, or both.

ABBREVIATIONS

ACE: angiotensin-converting enzyme

ARB: angiotensin receptor blocker

AVP: arginine vasopressin

BNP: B-type natriuretic peptide

cAMP: cyclic adenosine monophosphate

COX-2: cyclooxygenase-2

CRT: cardiac resynchronization therapy

HFSA: Heart Failure Society of America

IABP: intraaortic balloon pump

ICD: implantable cardioverter-defibrillator

JVD: jugular venous distension

LVAD: left ventricular assist device

LVEF: left ventricular ejection fraction

MI: myocardial infarction

NE: norepinephrine

NSAID: nonsteroidal antiinflammatory drug

NYHA: New York Heart Association

PAOP: pulmonary artery occlusion pressure

RAAS: renin–angiotensin–aldosterone system

SNS: sympathetic nervous system

SVR: systemic vascular resistance

TNF-α: tumor necrosis factor-α

TZD: thiazolidinedione

REFERENCES

1. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. Circulation 2005;112:e154–e235.
2. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–259.
3. Gheorghiade M, Sopko G, De Luca L, et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation 2006;114:1202–1213.
4. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69–e171.
5. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397–1402.
6. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007–2018.
7. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: Prediction of survival in heart failure. Circulation 2006;113:1424–1433.
8. Colucci W, Braunwald E. Pathophysiology of heart failure. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia: Elsevier Saunders, 2005:509–538.
9. Richard P, Villard E, Charron P, Isnard R. The genetic bases of cardiomyopathies. J Am Coll Cardiol 2006;48:A79–A89.
10. Mann DL, Bristow MR. Mechanisms and models in heart failure: The biomechanical model and beyond. Circulation 2005;111:2837–2849.
11. Small KM, Wagoner LE, Levin AM, et al. Synergistic polymorphisms of $beta_1$- and $alpha_{2C}$-adrenergic receptors and the risk of congestive heart failure. N Engl J Med 2002;347:1135–1142.
12. Patterson JH. Angiotensin II receptor blockers in heart failure. Pharmacotherapy 2003;23:173–182.
13. Wong J, Patel RA, Kowey PR. The clinical use of angiotensin-converting enzyme inhibitors. Prog Cardiovasc Dis 2004;47:116–130.
14. Weber KT. The proinflammatory heart failure phenotype: A case of integrative physiology. Am J Med Sci 2005;330:219–226.
15. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689–1697.
16. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–717.
17. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–1321.
18. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart failure. CMAJ 2006;175:611–617.
19. Greenberg A, Verbalis JG. Vasopressin receptor antagonists. Kidney Int 2006;69:2124–2130.
20. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099–2112.
21. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST Outcome Trial. JAMA 2007;297:1319–1331.
22. Gheorghiade M, Konstam MA, Burnett JC, Jr, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: The EVEREST Clinical Status Trials. JAMA 2007;297:1332–1343.
23. Mann DL. Inflammatory mediators and the failing heart: Past, present, and the foreseeable future. Circ Res 2002;91:988–998.
24. Laufs U, Custodis F, Bohm M. HMG-CoA reductase inhibitors in chronic heart failure: Potential mechanisms of benefit and risk. Drugs 2006;66:145–154.
25. Tsuyuki RT, McKelvie RS, Arnold JM, et al. Acute precipitants of congestive heart failure exacerbations. Arch Intern Med 2001;161:2337–2342.
26. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. Circulation 2003;107:2920–2925.
27. Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: Results from the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. J Am Coll Cardiol 2006;47:1997–2004.
28. Go AS, Yang J, Ackerson LM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: The Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation 2006;113:2713–2723.
29. Bleumink GS, Feenstra J, Sturkenboom MC, Stricker BH. Nonsteroidal anti-inflammatory drugs and heart failure. Drugs 2003;63:525–534.
30. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: A consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003;108:2941–2948.
31. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–2471.
32. Givertz M, Colucci W, Braunwald E. Clinical aspects of heart failure: High-output failure, pulmonary edema. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia: Elsevier Saunders, 2005:539–568.
33. Adams K, Lindenfeld J, Arnold J, et al. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. J Card Fail 2006;12:10–38.
34. Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: The Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:384–416.
35. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: Executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–1140.
36. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 2003;289:2560–2572.
37. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: Endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113:2363–2372.
38. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781–788.
39. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
40. DiMarco JP. Implantable cardioverter-defibrillators. N Engl J Med 2003;349:1836–1847.
41. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–2150.