CHAPTER 28

Management of Heart Failure Patients with Reduced Ejection Fraction

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Epidemiology

The worldwide prevalence and incidence rates of heart failure (HF) are approaching epidemic proportions, as evidenced by the relentless increase in the number of HF hospitalizations, the growing number of HF-attributable deaths, and the spiraling costs associated with the care of HF patients. Worldwide, HF affects almost 23 million people. In the United States, HF affects approximately 4.7 million persons (1.5% to 2% of the total population), with approximately 550,000 incident cases of HF diagnosed annually. Estimates of the prevalence of symptomatic HF in the general European population is similar to that in the United States, and ranges from 0.4% to 2%.[1] The prevalence of HF follows an exponential pattern, rising with age, and affects 6% to 10% of people older than 65 years (**Fig. 28-1**). Data from the Framingham Heart Study suggest that the overall incidence of HF has declined among women but not among men.[2] However, although the relative incidence of HF is lower in women than in men, women constitute at least 50% of cases of HF because of their longer life expectancy. In North America and Europe, the lifetime risk of developing HF is approximately one in five for a 40-year-old. The overall prevalence of HF is thought to be increasing, in part because our current therapies of cardiac disorders, such as myocardial infarction, valvular heart disease, and arrhythmias, are allowing patients to survive longer. Very little is known with respect to the prevalence or risk of developing HF in emerging nations because of the lack of population-based studies in these countries.[3] Although HF was once thought to arise primarily in the setting of a depressed left ventricular ejection fraction (LVEF), epidemiologic studies have shown that approximately 50% of patients who develop HF have a normal or preserved EF (EF > 40% to 50%). Accordingly, HF patients are now broadly categorized into one of two groups: (1) HF with a reduced (depressed) EF, commonly referred to as systolic failure; or (2) HF with a preserved EF, commonly referred to as diastolic failure. The epidemiology of HF with a normal EF is discussed in Chap. 30.

Based on population-attributable risks, hypertension has the greatest impact on the development of HF, accounting for 39% of HF events in men and 59% in women. Despite its much lower prevalence in the population (3% to 10%), myocardial infarction also has a high attributable risk in men (34%) and women (13%). Valvular heart disease only accounted for 7% to 8% of HF (**Table 28-1**). Dyslipidemia characterized by a high total high-density lipoprotein (HDL) cholesterol ratio, but not the total cholesterol alone, was also a risk factor for the development of HF.

Studies from the Framingham Study have suggested that obesity is a potential risk factor for the development of HF in men and women (**Fig. 28-2**).[4] However, although obesity is a risk factor for the development of HF, obese patients with HF seem to have a more favorable clinical prognosis. The association between obesity, a traditional cardiovascular risk factor, and improved clinical outcomes in HF patients (i.e., reverse epidemiology) has been termed the *obesity paradox*.

Causative Factors

As shown in **Table 28-2**, any condition that leads to an alteration in LV structure or function can predispose a patient to developing HF. Although the cause of HF in patients with a preserved EF differs from that of patient with depressed EF (see Chap. 30), there is considerable overlap between the causes of these two conditions. In industrialized countries, coronary artery disease (CAD) has become the predominant cause in men and women, and is responsible for 60% to 75% of cases of HF. Hypertension contributes to the development of HF in 75% of patients, including most patients with CAD. Both CAD and hypertension interact to augment the risk of HF. Rheumatic heart disease remains a major cause of HF in Africa and Asia, especially in the young. Hypertension is an important cause of HF in the African and African American population. Chagas disease is still a major cause of HF in South America.[3] Not surprisingly, anemia is a frequent concomitant factor in HF in many developing nations. As developing nations undergo socioeconomic development, the epidemiology of HF is becoming similar to that of Western Europe and North America, with CAD emerging as the single most common cause of HF. Although the contribution of diabetes mellitus to HF is not well understood, diabetes accelerates atherosclerosis and is often associated with hypertension.

In 20% to 30% of the cases of HF with a depressed EF, the exact causative basis is not known. These patients are referred to as having nonischemic, dilated, or idiopathic cardiomyopathy if the cause is unknown (see Chap. 68). Prior viral infection (see Chap. 70) or toxin exposure (e.g., alcohol [see Chap. 73] or use of chemotherapeutic agents [see Chap. 90]) may also lead to a dilated cardiomyopathy. Although excessive alcohol consumption can promote cardiomyopathy, alcohol consumption per se is not associated with increased risk for HF, and may protect against the development of HF when consumed in moderation.[5] It is also becoming increasingly clear that a large number of the cases of dilated cardiomyopathy are secondary to specific genetic defects, most notably those in the

TABLE 28-1 Risk Factors for Cardiac Failure: Framingham Offspring and Cohort Study*

	Age- and Risk Factor–Adjusted Hazard Ratio		*Prevalence (%)*		*Population-Attributable Risk (%)*	
PARAMETER	**MEN**	**WOMEN**	**MEN**	**WOMEN**	**MEN**	**WOMEN**
High blood pressure (≥140/90 mm Hg)	2.1	3.4	60	62	39	59
Myocardial infarction	6.3	6.0	10	3	34	13
Angina	1.4	1.7	11	9	5	5
Diabetes	1.8	3.7	8	5	6	12
Left ventricular hypertrophy	2.2	2.9	4	3	4	5
Valvular heart disease	2.5	2.1	5	8	7	8

*Subjects aged 40-89; 18-year follow-up.
From Levy D, Larson MG, Vasan RS, et al: The progression from hypertension to congestive heart failure. JAMA 275:1557, 1996.

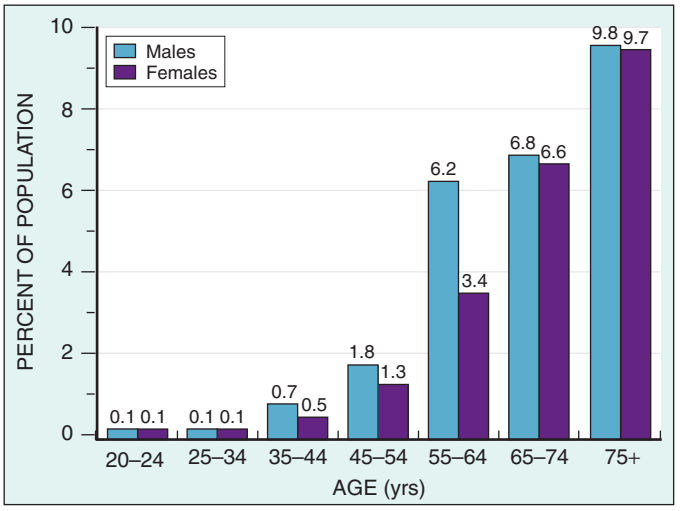

FIGURE 28-1 Prevalence rates of heart failure by gender and age in the United States, 1988-1994—the Third National Health and Nutrition Examination Survey (NHANES III). In men (blue), the prevalence increased from 18 cases/1000 in those aged 45 to 54 years to 98 cases/1000 in those aged 75 years and older. In women (purple), the prevalence increased from 13 cases/1000 in those aged 45 to 54 years to 97 cases/1000 in those aged 75 years and older. *(Data from American Heart Association: Heart Disease and Stroke Statistics—2003 Update. Dallas, American Heart Association, 2002.)*

TABLE 28-2 Causes of Chronic Heart Failure

- Myocardial disease
- Coronary artery disease
  - Myocardial infarction*
  - Myocardial ischemia*
- Chronic pressure overload
  - Hypertension*
  - Obstructive valvular disease*
- Chronic volume overload
  - Regurgitant valvular disease
  - Intracardiac (left-to-right) shunting
  - Extracardiac shunting
- Nonischemic dilated cardiomyopathy
  - Familial or genetic disorders
  - Infiltrative disorders*
  - Toxic or drug-induced damage
  - Metabolic disorder*
  - Viral or other infectious agents
- Disorders of rate and rhythm
  - Chronic bradyarrhythmias
  - Chronic tachyarrhythmias
- Pulmonary heart disease
  - Cor pulmonale
  - Pulmonary vascular disorders
- High-output states
- Metabolic disorders
  - Thyrotoxicosis
  - Nutritional disorders (beriberi)
- Excessive blood flow requirements
  - Systemic arteriovenous shunting
  - Chronic anemia

*Indicates conditions that can also lead to HF with a preserved EF.

cytoskeleton (see Chaps. 8 and 68). Most forms of familial dilated cardiomyopathy are inherited in an autosomal dominant fashion. Mutations of genes encoding cytoskeletal proteins (desmin, cardiac myosin, vinculin) and nuclear membrane proteins (lamin) have been identified thus far. Dilated cardiomyopathy is also associated with Duchenne, Becker, and limb girdle muscular dystrophies. Conditions that lead to a high cardiac output (e.g., arteriovenous fistula, anemia) are seldom responsible for the development of HF in a normal heart. However, in the presence of underlying structural heart disease, these conditions often lead to overt congestive failure.

Prognosis

Although several reports have suggested that the mortality for HF patients is improving, the overall mortality rate remains higher than for many cancers, including those involving the bladder, breast, uterus, and prostate. In the Framingham Study, the median survival was 1.7 years for men and 3.2 years for women, with only 25% of men and 38% of women surviving 5 years. European studies have confirmed a similarly poor long-term prognosis (**Fig. 28-3**).[1] More recent data from the Framingham Study have examined long-term trends in the survival of patients with HF and shown improved survival in men and women, with an overall decline in mortality of approximately 12%/decade from 1950 to 1999.[2] Moreover, reports from Scotland, Sweden, and the United Kingdom have also suggested that survival rates may be improving following hospital discharge.[1,6] Of note, the mortality of HF in epidemiologic studies is substantially higher than that reported in clinical HF trials involving drug and/or device therapies, in which the mortality figures are often deceptively low because the patients enrolled in these trials are younger and more stable and tend to be followed more closely clinically.

The role of gender and HF prognosis remains a controversial issue with respect to HF outcomes. Nonetheless, the aggregate data suggest that women with HF have a better overall prognosis than men.[2] However, women appear to have a greater degree of functional incapacity for the same degree of LV dysfunction and also have a higher prevalence of HF with a normal EF (see Chap. 30). Controversy has also arisen regarding the impact of race on outcome, with higher mortality rates being reported in blacks in some but not all studies. In the United States, HF affects approximately 3% of blacks, whereas in the general population the prevalence is about 2%.[7] Blacks with HF present at an earlier age and have more advanced LV dysfunction and

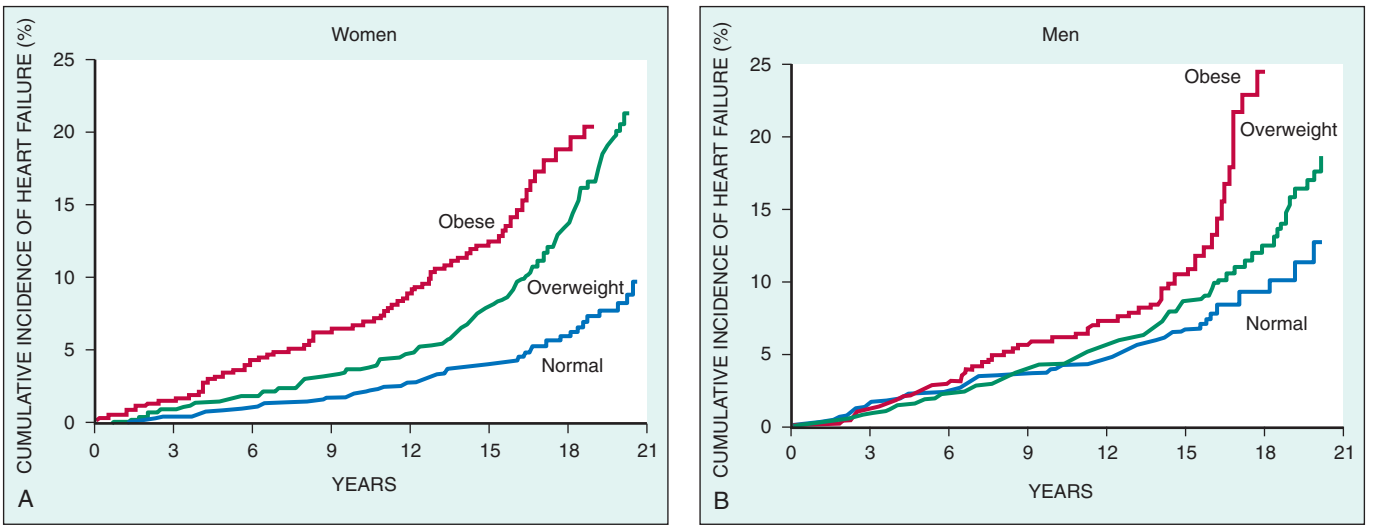

FIGURE 28-2 Cumulative incidence of heart failure in women **(A)** and men **(B)** according to body mass index (BMI) at the baseline examination. The BMI was 18.5 to 24.9 in normal subjects, 25.0 to 29.9 in overweight subjects, and 30.0 or more in obese subjects. *(Modified from Kenchaiah S, Evans JC, Levy D, et al: Obesity and the risk of heart failure. N Engl J Med 347:305, 2002.)*

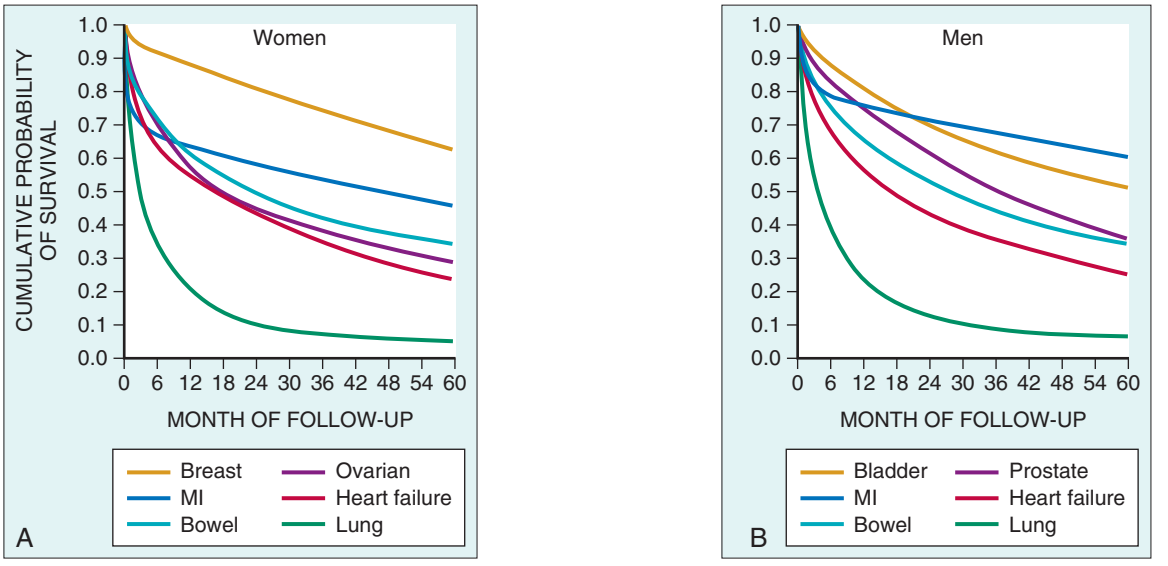

FIGURE 28-3 Survival in HF patients compared with cancer patients. Shown is 5-year survival following a first admission to any Scottish hospital in 1991 for HF, MI, and the four most common sites of cancer specific to women **(A)** and men **(B)**. *(Modified from Stewart S, MacIntyre K, Hole DJ, et al: More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 3:315, 2001.)*

a worse New York Heart Association (NYHA) class at the time of diagnosis. Although the reasons for these differences are not known, differences in HF etiology might explain some of these observations. In the registry for the Studies on Left Ventricular Dysfunction (SOLVD), 73% of whites had coronary heart disease as a cause for their HF compared to only 36% of black participants. On the other hand, 32% of blacks in the SOLVD registry had HF that was attributed to hypertension, with only 4% of whites having hypertension as a primary cause. When compared in the SOLVD registry, cardiovascular and total mortality were no different in the black and white cohorts, although the black cohort was younger and had a higher proportion of females than the white group.[8] There may also be additional socioeconomic factors that may influence outcomes in black patients, such as geographic location and access to health care. Age is one of the stronger and most consistent predictors of adverse outcome in HF (see later, "Special Populations").[2]

Many other factors have been associated with increased mortality in HF patients (**Table 28-3**). Most factors listed as outcome predictors have survived at least univariate analysis, with many standing out independently when multifactorial analysis techniques were used. Nonetheless, it is extraordinarily difficult to determine which prognostic variable is most important to predict individual patient outcome in either clinical trials or, more importantly, during the daily management of an individual patient. To this end, a multivariate model for predicting the HF prognosis has been developed and validated. The Seattle Heart Failure Model was derived by retrospectively investigating predictors of survival among HF patients in clinical trials.[9] The Seattle Heart Failure Model provides an accurate estimate of 1-, 2-, and 3-year survival with the use of easily obtained clinical, pharmacologic, device, and laboratory characteristics, and is accessible free of charge to all health care providers as an interactive Internet-based program (http://depts.washington.edu/shfm).

TABLE 28-3 Prognostic Variables in Heart Failure Patients

- Demographics
  - Gender
  - Race
  - Age
- Heart failure cause
  - CAD
  - IDCM
  - Valvular heart disease
  - Myocarditis
  - Hypertrophy
  - Alcohol
  - Anthracyclines
  - Amyloidosis
  - Hemachromatosis
  - Genetic factors
- Comorbidities
  - Diabetes
  - Systemic hypertension
  - Pulmonary hypertension
  - Sleep apnea
  - Obesity, cachexia (body mass)
  - Renal insufficiency
  - Hepatic abnormalities
  - COPD
- Clinical assessment
  - NYHA class (symptoms)
  - Syncope
  - Angina pectoris
  - Systolic versus diastolic dysfunction
- Hemodynamics
  - LVEF
  - RVEF
  - PAP
  - PCWP
  - CI
  - PAP-PCWP
  - Exercise hemodynamics
- Exercise testing
  - Metabolic assessment
  - BP response
  - Heart rate response
  - 6-min walk
  - Peak Vo_2
  - Anaerobic threshold
  - VE/Vco_2
  - Oxygen uptake slope
- Metabolic factors
  - Serum sodium level
  - Thyroid dysfunction
  - Anemia
  - Acidosis, alkalosis
- Chest x-ray
  - Congestion
  - Cardiothoracic ratio
- Electrocardiogram (ECG)
  - Rhythm (atrial fibrillation or arrhythmias)
  - Voltage
  - QRS width
  - QT interval
  - Signal-averaged ECG (T wave alternans)
  - HR variability
- Biomarkers
  - NE, PRA, AVP, aldosterone
  - ANP, BNP, endothelin-1
  - TNF, IL-1, IL-6, IL-10, CRP, ESR
  - Cardiac troponins, hematocrit
- Endomyocardial biopsy
  - Inflammatory states
  - Degree of fibrosis
  - Degree of cellular disarray
  - Infiltrative processes

ANP = atrial natriuretic peptide; AVP = arginine vasopressin; BNP = brain natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; CI = cardiac index; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IDCM = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NE = norepinephrine; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAP-PCWP = gradient across lung; PCWP = pulmonary capillary wedge pressure; PRA = plasma renin activity; RVEF = right ventricular ejection fraction; TNF = tumor necrosis factor, IL = interleukin.

Modified from Young JB: The prognosis of heart failure. *In* Mann DL (ed): Heart Failure: A Companion to Braunwald's Heart Disease. Philadelphia, Elsevier, 2004, pp 489-506.

Biomarkers and Prognosis

The observation that the renin angiotensin-aldosterone, adrenergic, and inflammatory systems are activated in HF (see Chap. 25) has prompted the examination of the relationships between a variety of biochemical measurements and clinical outcomes (see Table 28-3 and Chap. 26). Strong inverse correlations have been reported between survival and plasma levels of norepinephrine, renin, arginine vasopressin, aldosterone, atrial and brain natriuretic peptides (BNPs), and endothelin-1, and inflammatory markers such as tumor necrosis factor (TNF) and TNF receptors, C-reactive protein, and erythrocyte sedimentation rate. Markers of oxidative stress, such as oxidized low-density lipoprotein and serum uric acid, have also been associated with worsening clinical status and impaired survival in patients with chronic HF. Cardiac troponin T and I levels, sensitive markers of myocyte damage, may be elevated in patients with nonischemic and predict adverse cardiac outcomes. The association between low hemoglobin and hematocrit values and adverse HF outcomes has also long been recognized, but has garnered considerable attention after studies illustrated the independent prognostic value of anemia in patients with HF with reduced or normal EF.[10]

Published estimates of the prevalence of anemia in HF patients vary widely, ranging from 4% to 50% depending on the population studied and definition of anemia that is used.[10] In general, the prevalence of anemia is significantly greater in patients with more advanced disease. Furthermore, the severity of anemia may contribute to the increasing severity of HF. Multiple reports from observational data bases and clinical trial populations have demonstrated a relationship between lower hemoglobin levels and impaired survival in patients. However, it is unclear whether anemia is a cause of decreased survival, or simply a marker of more advanced disease. The underlying cause for anemia is likely multifactorial, including reduced sensitivity to erythropoietin receptors, the presence of a hematopoiesis inhibitor, and/or a defective iron supply for erythropoiesis given as possible explanations. Potential treatments for anemia include the use of red blood cell transfusions and treatment with erythropoietin analogues to increase red blood cell production, and intravenous iron.

At present, the role for blood transfusions in patients with cardiovascular disease is controversial. Although a transfusion threshold for maintaining the hematocrit higher than 30% in patients with cardiovascular disease has generally been accepted, this clinical practice has been based more on expert opinion rather than on direct evidence that documents the efficacy for this form of therapy. Given the risks and costs of red blood cell transfusion, the evanescent benefits of blood transfusions in patients with a chronic anemia, and the unclear benefit in HF patients, the routine use of blood transfusion cannot be recommended for treating the anemia that occurs in stable HF patients. In a randomized double-blind study,[11] intravenous iron (ferric carboxymaltose) improved patient symptoms (odds ratio for improvement, 2.51; 95% confidence interval [CI], 1.75 to 3.61), NYHA functional class (primary endpoints), and quality of life (secondary endpoint) when compared with placebo in patients with NYHA functional Class II (LVEF < 40%) or III (LVEF < 45%) HF iron deficiency (**Fig. 28-4**). The total iron dose for repletion was calculated at baseline; patients were administered intravenous ferric carboxymaltose until iron repletion was achieved, and then every 4 weeks during the maintenance phase of the study (total of 24 weeks of therapy). Of note,

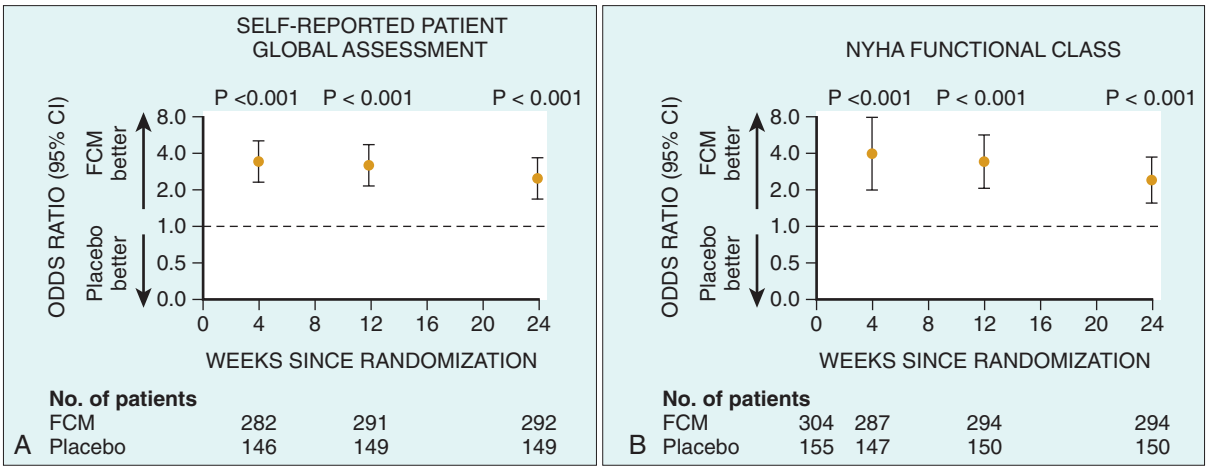

FIGURE 28-4 Effect of treatment with intravenous iron (ferric carboxymaltose) on patient symptoms and functional status. **A,** Effect of ferric carboxymaltose (FCM) on the self-reported Patient Global Assessment and NYHA functional status **(B)**. The data in **A** and **B** are presented as odds ratios for the FCM group compared with the placebo group, and being in an improved or worsened self-assessment category or improved or worsened NYHA functional class. Patients who were hospitalized at each time point were given an assessment of much worse, or NYHA Class IV. Patients who died before week 24 were categorized as dead (in **B**, corresponding to NYHA Class V). *(Modified from Anker SD, Comin CJ, Filippatos G, et al: Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 361:2436, 2009.)*

several small studies have suggested benefit from the use of erythropoietin analogues for the treatment of mild anemia in HF.[10] However, there is concern that thromboembolic events may be increased with this strategy. Treatment of anemic HF patients with the erythropoietin analogue darbepoetin alpha is undergoing further investigation in a large international study, Reduction of Events with Darbepoetin in Heart Failure (RED-HF; ClinicalTrials.gov identifier, NCT00358215).

Renal Insufficiency

Renal insufficiency is associated with poorer outcomes in patients with HF; however, it is uncertain whether renal impairment is a simply a marker for worsening HF or whether renal impairment might be causally linked to worsening HF. Although more common in patients hospitalized for HF, at least some degree of renal impairment is still present in about 50% of stable HF outpatients. Patients with renal hypoperfusion or intrinsic renal disease show an impaired response to diuretics and angiotensin-converting enzyme inhibitors (ACEIs) and are at increased risk of adverse effects during treatment with digitalis. In a recent meta-analysis, most HF patients had some degree of renal impairment. These patients represented a high-risk group with an approximately 50% increased relative mortality risk when compared with patients who had normal renal function.[12] Similar findings were observed in the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy, in which impaired renal function was a stronger predictor of mortality than impaired LV function and NYHA class in patients with advanced HF (**Fig. 28-5**).[13] Thus, renal insufficiency is emerging as a strong independent predictor of adverse outcomes in HF patients.

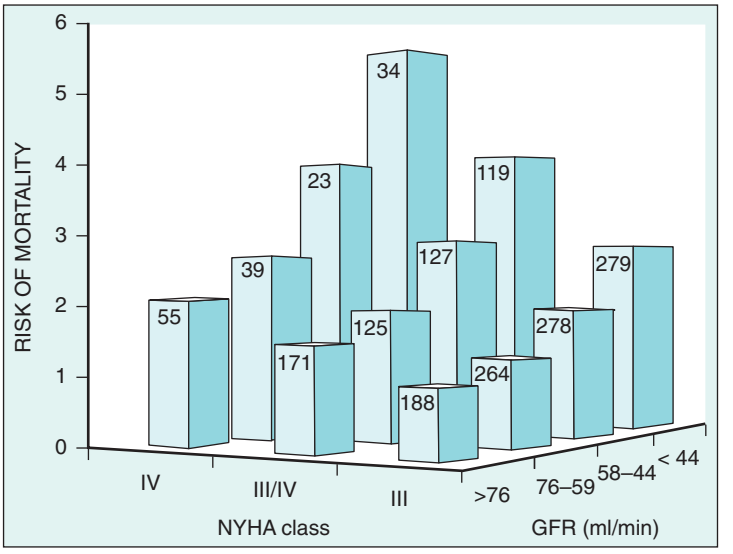

FIGURE 28-5 Effect of renal function on outcomes in HF patients. This three-dimensional bar graph shows the risk of mortality (vertical axis) in relation to decreasing NYHA class (horizontal axis) and decreasing quartiles of glomerular filtration rate (GFR; diagonal axis). *(From Hillege HL, Girbes AR, de Kam PJ, et al: Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 102:203, 2000.)*

Approach to the Patient

Stages of Heart Failure

HF should be viewed as a continuum that comprises four interrelated stages (**Fig. 28-6**).[14] Stage A includes patients who are at high risk for developing HF, but without structural heart disease or symptoms of HF (e.g., patients with diabetes or hypertension). Stage B includes patients who have structural heart disease but without symptoms of HF (e.g., patients with a previous myocardial infarction [MI] and asymptomatic LV dysfunction). Stage C includes patients who have structural heart disease who have developed symptoms of HF (e.g., patients with a previous MI with shortness of breath and fatigue). Stage D includes patients with refractory HF requiring special interventions (e.g., patients with refractory HF who are awaiting cardiac transplantation). A simplified algorithm for approaching patients with HF is illustrated in **Figure 28-7**. The diagnosis and clinical assessment of patients with HF with a reduced EF is discussed in detail in Chap. 26, and the diagnosis and management of patients with HF with a normal or preserved EF is discussed in detail in Chap. 30.

PATIENTS AT HIGH RISK FOR DEVELOPING HEART FAILURE (STAGE A). For patients at high risk of developing HF, every effort should be made to prevent HF using standard practice guidelines to treat preventable conditions that are known to lead to HF, including hypertension (see Chap. 45), hyperlipidemia (see Chap. 49) and diabetes (see Chap. 64). In this regard, ACEIs are particularly useful for preventing HF in patients who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors.

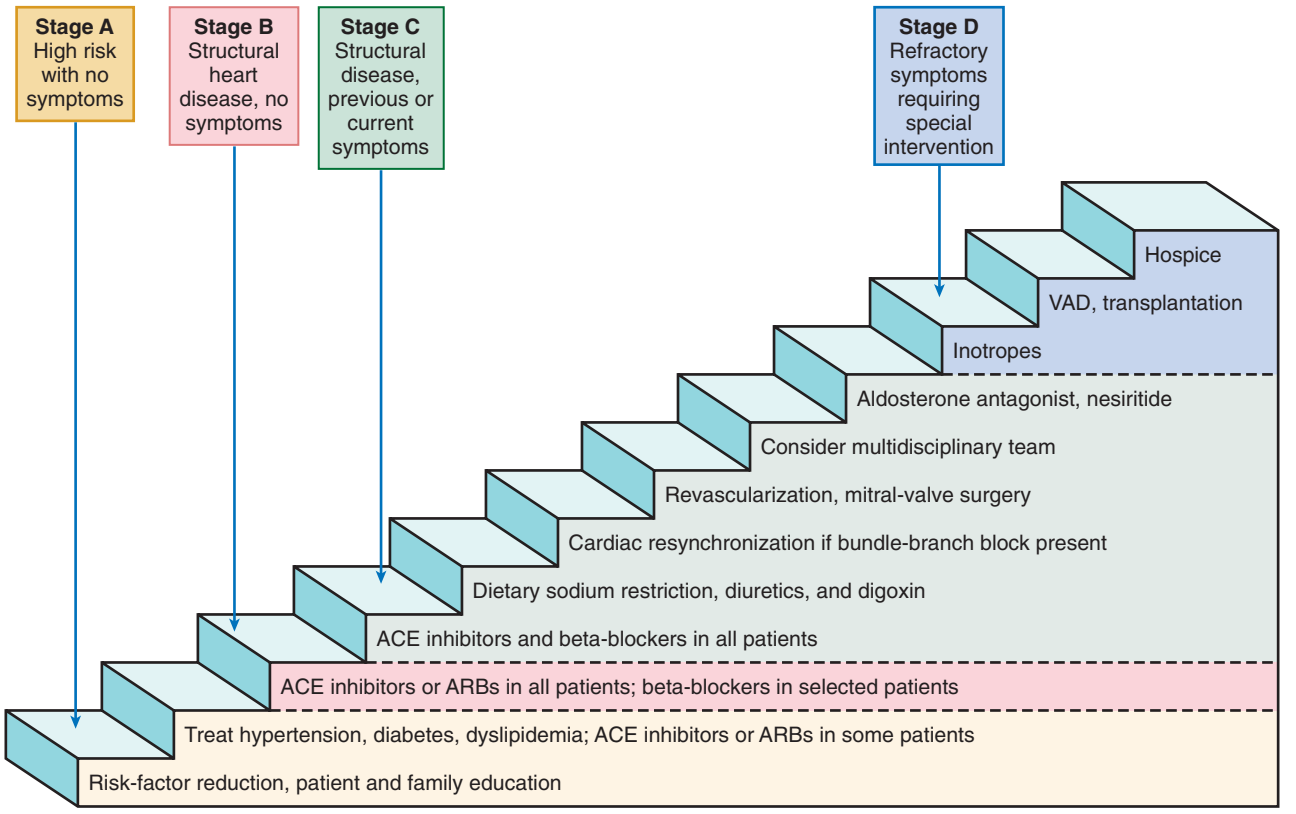

FIGURE 28-6 Stages of heart failure and treatment options for systolic heart failure. Patients with stage A HF are at high risk for HF but do not have structural heart disease or symptoms of HF. This group includes patients with hypertension, diabetes, coronary artery disease, previous exposure to cardiotoxic drugs, or a family history of cardiomyopathy. Patients with stage B HF have structural heart disease but no symptoms of HF. This group includes patients with left ventricular hypertrophy, previous myocardial infarction, left ventricular systolic dysfunction, or valvular heart disease, all of whom would be considered to have New York Heart Association (NYHA) Class I symptoms. Patients with stage C heart failure have known structural heart disease and current or previous symptoms of HF. Their symptoms may be classified as NYHA Class I, II, III, or IV. Patients with stage D HF have refractory symptoms of HF at rest despite maximal medical therapy, are hospitalized, and require specialized interventions or hospice care. All these patients would be considered to have NYHA Class IV symptoms. VAD = ventricular assist device. *(From Jessup M, Brozena S: Heart failure. N Engl J Med 348:2007, 2003.)*

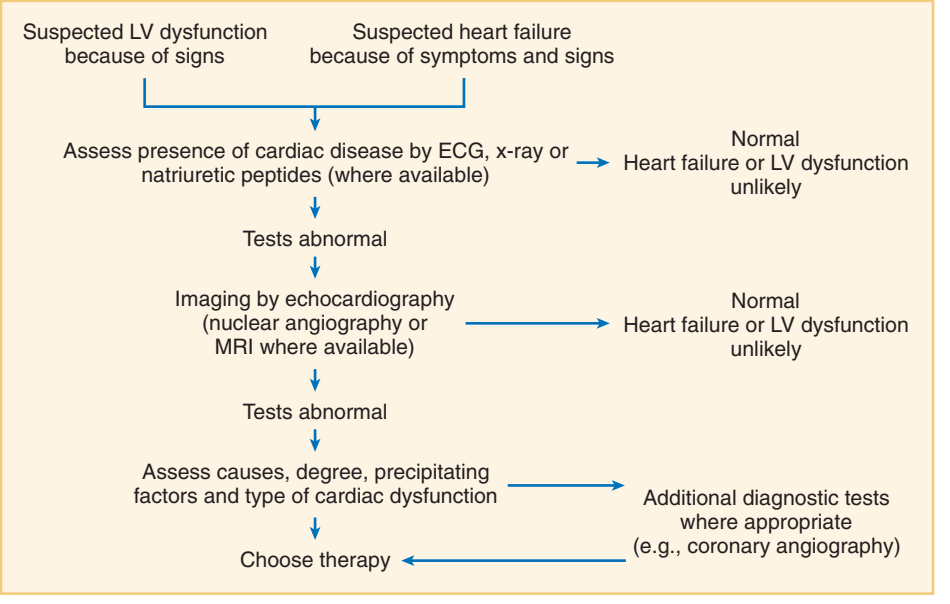

FIGURE 28-7 Relationships among cardiac dysfunction, symptomatic HF, and asymptomatic HF following appropriate treatment. *(From Swedberg K, Cleland J, Dargie H, et al: Guidelines for the diagnosis and treatment of chronic heart failure: Executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 26:1115, 2005.)*

TABLE 28-4 Diagnostic Criteria for Heart Failure in Population-Based Studies

Framingham Criteria

MAJOR CRITERIA	MINOR CRITERIA	MAJOR OR MINOR CRITERIA
Paroxysmal nocturnal dyspnea or orthopnea	Ankle edema	Weight loss > 4.5 kg in 5 days in response to treatment
Neck-vein distention	Night cough	
Rales	Dyspnea on exertion	
Cardiomegaly	Hepatomegaly	
Acute pulmonary edema	Pleural effusion	
S_3 gallop	Vital capacity decreased by one third from maximal capacity	
Increased venous pressure, >16 cm H_2O	Tachycardia (rate > 120 beats /min)	
Hepatojugular reflux		

NHANES Criteria

CATEGORY	CRITERIA	POINTS
History	Dyspnea	
	• Does patient have shortness of breath when hurrying on flat ground or a slight elevation?	1
	• Does patient have shortness of breath when walking on flat ground?	1
	• Does patient stop for breath when walking at an ordinary pace?	2
	• Does patient stop for breath after 100 yards when on flat ground?	2
Physical examination	Heart rate	
	• 91-110 beats/min	1
	• >110 beats/min	2
	Jugular venous pressure > 6 cm H_2O alone	1
	Plus hepatomegaly or edema	2
	Rales—basilar crackles	1
	Crackles—more than basilar crackles	2
Chest radiography	Upper zone flow redistribution	1
	Interstitial pulmonary edema	2
	Interstitial edema plus pleural fluid	3
	Alveolar fluid plus pleural fluid	3

The diagnosis of HF using the Framingham criteria requires the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria. Minor criteria are acceptable only if they cannot be attributed to another medical condition (e.g. pulmonary hypertension, chronic lung disease, cirrhosis, ascites, nephrotic syndrome).

NHANES criteria—diagnosis of HF if score ≥ 3 points.

Modified from Ho KK, Pinsky JL, Kannel WB et al: The epidemiology of heart failure: The Framingham Study. J Am Coll Cardiol 22:6A, 1993; and Schocken DD, Arrieta MI, Leaverton PE, et al: Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 20:301, 1992.

POPULATION SCREENING. At present, there is limited information available to support the screening of broad populations to detect undiagnosed HF and/or asymptomatic LV dysfunction. A study has suggested that elevated levels of BNP (see Chap. 26) can be used as a cost-effective strategy for screening asymptomatic people older than 60 years with an EF lower than 40%.[15] However, screening general populations with BNP is not recommended at this time. Patients who are at very high risk of a developing cardiomyopathy (e.g., those with a strong family history of cardiomyopathy or those receiving cardiotoxic interventions; see Chap. 90) are appropriate targets for more aggressive screening, such as two-dimensional echocardiography, to assess LV function. However, the routine periodic assessment of LV function in other patients is not currently recommended. Several sophisticated clinical scoring systems have been developed to screen for HF in population based studies, including the Framingham Criteria, which screens for HF on the basis of clinical criteria, and the National Health and Nutrition Survey (NHANES), which uses self-reporting of symptoms to identify HF patients (**Table 28-4**). As discussed in Chap. 26, additional laboratory testing is usually necessary to make the diagnosis of HF definitively when these methodologies are used.

Management of Patients with Symptomatic and Asymptomatic Heart Failure

Transient Left Ventricular Dysfunction

As noted in Chap. 25, the clinical syndrome of HF with reduced EF begins after an initial index event produces a decline in ejection performance of the heart. However, it is important to recognize that LV dysfunction may develop transiently in various different clinical settings, which may not lead invariably to the development of the clinical syndrome of HF. **Figure 28-8** illustrates the important relationship between LV dysfunction (transient and sustained) and the clinical syndrome of HF (asymptomatic and symptomatic). LV dysfunction with pulmonary edema may develop acutely in patients with previously normal LV structure and function. This occurs most commonly postoperatively following cardiac surgery, in the setting of severe brain injury, or after a systemic infection. The general pathophysiologic mechanism involved is some form of "stunning" of functional myocardium (see Chap. 52) or activation of proinflammatory cytokines that are capable of suppressing LV function (see Chap. 25). Emotional stress can also precipitate severe reversible LV dysfunction that is accompanied by chest pain, pulmonary edema, and cardiogenic shock in patients without coronary disease (takotsubo syndrome). In this setting, LV dysfunction is thought to occur secondary to the deleterious effects of catecholamines following heightened sympathetic stimulation.[16] It is also important to note that exercise-induced LV dysfunction, usually caused by myocardial ischemia, may lead to symptoms by causing a rise in LV filling pressure and a fall in cardiac output in the absence of discernable LV dysfunction at rest. If LV dysfunction persists following the initial cardiac injury, patients may remain asymptomatic for a period of months to years; however, the weight of epidemiologic and clinical evidence suggests that at some point these patients will undergo the transition to overt symptomatic HF.

Defining the Appropriate Strategy

The main goals of treatment are to reduce symptoms, prolong survival, improve the quality of life, and prevent disease progression.

TABLE 28-5 Pharmacologic and Device Therapy in Patients with Chronic Heart Failure

INDICATION	ACEI	ARB	DIURETIC	BETA BLOCKER	ALDOSTERONE ANTAGONISTS	CARDIAC GLYCOSIDES	CRT	ICD
Asymptomatic LV dysfunction (NYHA I)	Indicated	If ACEI-intolerant	Not indicated	Post-MI indicated*	Recent MI	With atrial fibrillation	Not indicated	Not indicated
Symptomatic HF (NYHA II)	Indicated	Indicated with or without ACEI	Indicated with fluid retention	Indicated	Recent MI	1. With atrial fibrillation 2. When improved from more severe HF in sinus rhythm	Not indicated	Indicated
Worsening HF (NYHA III, IV)	Indicated	Indicated with or without ACEI	Indicated, combination of diuretics	Indicated (under specialist's care)	Indicated	Indicated	Indicated if QRS > 0.12 msec†	Indicated
End-stage HF (NYHA IV)	Indicated	Indicated with or without ACEI	Indicated, combination of diuretics	Indicated (under specialist's care)	Indicated	Indicated	Indicated if QRS > 0.12 msec†	Not indicated

*Represents expert opinion.
†Patients must be in sinus rhythm.
Modified from 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 26:1115, 2005.

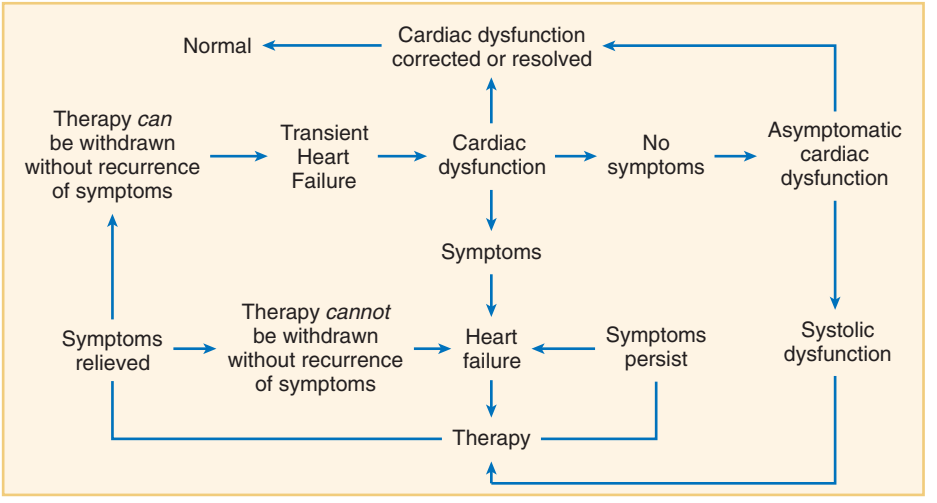

FIGURE 28-8 Algorithm for the diagnosis of heart failure or LV dysfunction. *(From Swedberg K, Cleland J, Dargie H, et al: Guidelines for the diagnosis and treatment of chronic heart failure: Executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 26:1115, 2005.)*

As discussed later, the current pharmacologic, device, and surgical therapeutic armamentarium for the management of patients with a reduced EF permits health care providers to achieve each of these goals in the great majority of patients. As shown in **Table 28-5**, once patients have developed structural heart disease (stages B to D), the choice of therapy for patients with HF with a reduced EF depends on their NYHA functional classification (see Chap. 26 and Table 26-3). Although this classification system is notoriously subjective, and has large interobserver variability, it has withstood the test of time and continues to be widely applied to patients with HF. For patients who have developed LV systolic dysfunction, but who remain asymptomatic (Class I), the goal should be to slow disease progression by blocking neurohormonal systems that lead to cardiac remodeling (see Chap. 25). For patients who have developed symptoms (Classes II to IV), the primary goal should be to alleviate fluid retention, lessen disability, and reduce the risk of further disease progression and death. As will be discussed subsequently, these goals generally require a strategy that combines diuretics (to control salt and water retention) with neurohormonal interventions (to minimize cardiac remodeling).

General Measures

Identification and correction of the condition(s) responsible for the cardiac structural and/or functional abnormalities are critical (see Table 28-2), insofar as some conditions that provoke LV structural and functional abnormalities are potentially treatable and/or reversible. Furthermore, clinicians should aim to screen for and treat aggressively comorbidities such as hypertension and diabetes, which are thought to underlie the structural heart disease. In addition to searching for reversible causes and comorbidities that contribute to the development of HF, it is equally important to identify factors that provoke worsening HF in stable patients (**Table 28-6**). Among the most common causes of acute decompensation in a previously stable patient are dietary indiscretion and inappropriate reduction of HF therapy, either from patient self-discontinuation of medication or from physician withdrawal of effective pharmacotherapy (e.g., because of concern over azotemia). HF patients should be advised to stop smoking and to limit daily alcohol consumption to two standard drinks in men or one standard drink in women. Patients suspected of having an alcohol-induced cardiomyopathy should be advised to abstain from alcohol consumption indefinitely. Excessive temperature extremes and heavy physical exertion should be avoided. Certain drugs are known to make HF worse and should also be avoided. For example, nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2 (COX-2) inhibitors, are not recommended in patients with chronic HF because the risk of renal failure and fluid retention is markedly increased in the setting of reduced renal function and/or ACEI use. Patients should be advised to weigh themselves on a regular basis to monitor weight gain and alert a health care provider or adjust their diuretic dose in the case of a sudden unexpected weight gain of more than 3 to 4 pounds over a 3-day period. Although there is no documented evidence of the effects of immunization in HF patients, they are at high risk of developing pneumococcal pneumonia and influenza. Accordingly, clinicians should consider recommending influenza and pneumococcal vaccines to their HF patient to prevent respiratory infections.

It is equally important to educate the patient and family about HF, the importance of proper diet, and the importance of compliance with the medical regimen. Supervision of outpatient care by a specially trained nurse or physician assistant and/or specialized HF clinics have all been found to be helpful, particularly in patients with advanced disease (see later, "Disease Management").

ACTIVITY. Although heavy physical labor is not recommended in HF, routine modest exercise has been shown to be beneficial in select patients with NYHA Classes I to III HF. The HF-ACTION trial[17] a controlled trial investigating outcomes of exercise training) was a large, multicenter, randomized controlled study whose primary endpoint was a composite of all-cause mortality and all-cause hospitalization. Secondary end points included all-cause mortality, all-cause hospitalization, and the composite of cardiovascular mortality or cardiovascular hospitalization. HF-ACTION failed to show a significant improvement in all-cause mortality or all-cause hospitalization (hazard ratio [HR], 0.93; 95% CI, 0.84 to 1.02; $P = 0.13$) in patients who received a 12-week (three times/week) exercise training program followed by a 25- to 30-minute, home-based, self-monitored exercise workout on a treadmill or stationary bicycle 5 days/week (**Fig. 28-9A**) . Moreover, there was no difference in all-cause mortality (HR, 0.96; 95% CI, 0.79 to 1.17; $P = 0.70$; see Fig. 28-9B). However, there was a trend toward decreased cardiovascular mortality or HF hospitalizations (HR, 0.87; 95% CI, 0.74 to 0.99; $P = 0.06$) and quality of life was significantly improved in the exercise group. For euvolemic patients, regular isotonic exercise such as walking or riding a stationary bicycle with an ergometer may be useful as an adjunctive therapy to improve clinical status after patients have undergone exercise testing to determine suitability for exercise training (i.e., patient does not develop significant ischemia or arrhythmias). Exercise training is not recommended, however, for HF patients with a reduced EF who have had a major cardiovascular event or procedure within the last 6 weeks, patients with cardiac devices that limit the ability to achieve target heart rates, and patients with significant arrhythmia or ischemia during baseline cardiopulmonary exercise testing.

TABLE 28-6 Potential Precipitating Factors of Acute Decompensation in Patients with Chronic Heart Failure

Dietary indiscretion
Inappropriate reduction in HF medications
Myocardial ischemia, infarction
Arrhythmias (tachycardia, bradycardia)
Infection
Anemia
Initiation of medications that worsen the symptoms of HF
Calcium antagonists (verapamil, diltiazem)
Beta blockers
Nonsteroidal anti-inflammatory drugs
Thiazolidinediones
Antiarrhythmic agents (all Class I agents, sotalol [Class III])
Anti-TNF antibodies
Alcohol consumption
Pregnancy
Worsening hypertension
Acute valvular insufficiency

From Mann DL: Heart failure and cor pulmonale. *In* Kasper DL, Braunwald E, Fauci AS, Hauser SL, et al (eds): Harrison's Principles of Internal Medicine. 17th ed. New York, McGraw-Hill, 2007, p 1448.

DIET. Dietary restriction of sodium (2 to 3 g daily) is recommended for all patients with the clinical syndrome of HF and preserved or depressed EF. Further restriction (<2 g daily) may be considered in moderate to severe HF. Fluid restriction is generally unnecessary unless the patient is hyponatremic (<130 mEq/liter), which may develop because of activation of the renin angiotensin system, excessive secretion of arginine vasopressin (AVP), or loss of salt in excess of water from prior diuretic use. Fluid restriction (<2 liters/day) should be considered in hyponatremic patients (<130 mEq/liter) or for those patients whose fluid retention is difficult to control despite high doses of diuretics and sodium restriction. Caloric supplementation is recommended for patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia); however, anabolic steroids are not recommended for these patients because of potential problems with volume retention. The measurement of nitrogen balance, caloric intake, and prealbumin level may be useful in determining appropriate nutritional supplementation. The use of dietary supplements (nutraceuticals) should be avoided in the management of symptomatic HF because of the lack of proven benefit and the potential for significant interactions with effective HF therapeutics (see Chap. 33).

Management of Fluid Status

Many clinical manifestations result from excessive salt and water retention that leads to an inappropriate volume expansion of the

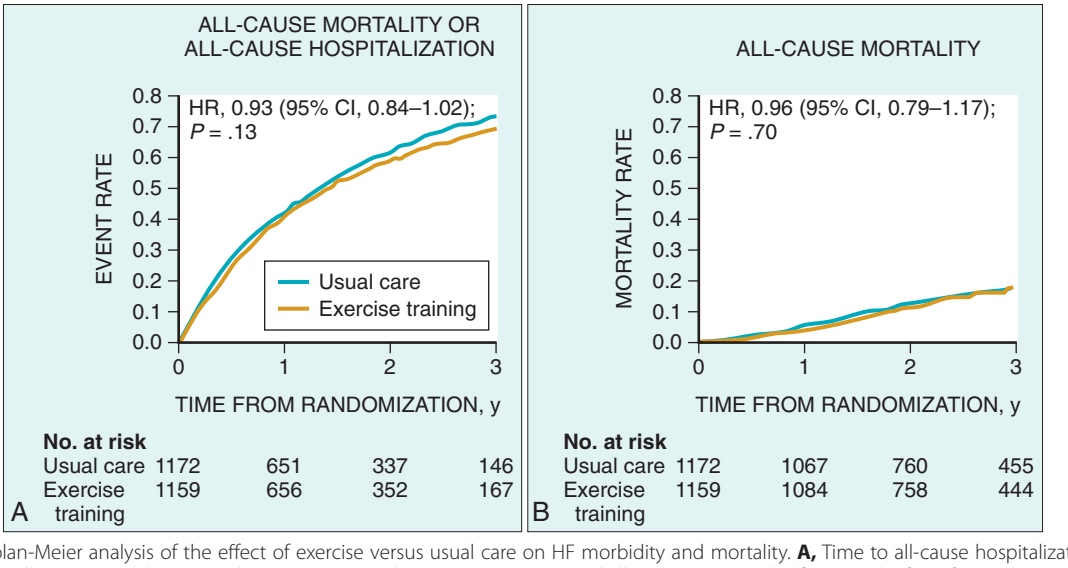

FIGURE 28-9 Kaplan-Meier analysis of the effect of exercise versus usual care on HF morbidity and mortality. **A,** Time to all-cause hospitalization and all-cause mortality and time to all-cause mortality **(B)** in the HF-ACTION trial. *(From O'Connor CM, Whellan DJ, Lee KL, et al: Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 301:1439, 2009.)*

TABLE 28-7 Diuretics for Treating Fluid Retention in Chronic Heart Failure

DRUG	INITIAL DAILY DOSAGE	MAXIMUM TOTAL DAILY DOSAGE	DURATION OF ACTION (HR)
Loop diuretics*			
Bumetanide	0.5-1.0 mg qd or bid	10 mg	4-6
Furosemide	20-40 mg qd or bid	600 mg	6-8
Torsemide	10-20 mg qd	200 mg	12-16
Ethacrynic acid	25-50 mg qd or bid	200 mg	6
Thiazide diuretics†			
Chlorothiazide	250-500 mg qd or bid	1000 mg	6-12
Chlorthalidone	12.5-25 mg qd	100 mg	24-72
Hydrochlorothiazide	25 mg qd or bid	200 mg	6-12
Indapamide	2.5 mg qd	5 mg	36
Metolazone	2.5-5 mg qd	20 mg	12-24
Potassium-sparing diuretics			
Amiloride	12.5-25 mg qd	20 mg	24
Triamterene	50-75 mg bid	200 mg	7-9
AVP antagonists			
Satavaptan	25 mg qd	50 mg qd	NS
Tolvaptan	15 mg qd	60 mg qd	NS
Lixivaptan	125 mg qd	250 mg bid	NS
Conivaptan (IV)	20-mg IV loading dose, followed by 20-mg continuous IV infusion/day	40-mg IV infusion/day	7-9
Sequential nephron blockade			
Metolazone	2.5 to 10 mg qd plus loop diuretic		
Hydrochlorothiazide	25 to 100 mg qd or bid plus loop diuretic		
Chlorothiazide (IV)	500 to 1000 mg qd plus loop diuretic		

NOTE: Unless indicated, all doses are for oral diuretics.
*Equivalent doses: 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide = 50 mg of ethacrynic acid.
†Do not use if estimated glomerular filtration is <30 mL/min or with cytochrome 3A4 inhibitors.
NS = not specified.
Modified from 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. Circulation 112:e154, 2005.

vascular and extravascular space. Although both digitalis and low doses of ACEIs enhance urinary sodium excretion, few volume-overloaded HF patients can maintain proper sodium balance without the use of diuretic drugs. Attempts to substitute ACEIs for diuretics have been shown to lead to pulmonary edema and peripheral congestion. In short-term clinical trials, diuretic therapy has led to a reduction in jugular venous pressure, pulmonary congestion, peripheral edema, and body weight, all of which were observed within days of initiation of therapy. In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in HF patients.[18] To date, there have been no long-term studies of diuretic therapy in HF; thus, their effects on morbidity and mortality are not clearly known. Although retrospective analyses of clinical trials have suggested that diuretic use is associated with worse clinical outcomes,[19] a meta-analysis[18] has suggested that treatment with diuretic therapy produces a significant reduction in mortality (odds ratio [OR], 0.24; 95% CI, 0.07 to 0.83; $P = 0.02$) and worsening HF (OR, 0.07; 95% CI, 0.01 to 0.52; $P = 0.01$). However, given the retrospective nature of this review, this analysis cannot be used as formal evidence to recommend the use diuretics to reduce HF mortality.

A number of classification schemes have been proposed for diuretics on the basis of their mechanism of action, anatomic locus of action within the nephron, and the form of diuresis that they elicit (solute versus water diuresis). The most common classification for diuretics uses an admixture of chemical (e.g., thiazide diuretic), site of action (e.g., loop diuretic), or clinical outcomes (e.g., potassium-sparing diuretic). The loop diuretics increase sodium excretion by up to 20% to 25% of the filtered load of sodium, enhance free water clearance, and maintain their efficacy unless renal function is severely impaired. In contrast, the thiazide diuretics increase the fractional excretion of sodium to only 5% to 10% of the filtered load, tend to decrease free water clearance, and lose their effectiveness in patients with impaired renal function (creatinine clearance less than 40 mL/min). Consequently, the loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF. Diuretics that induce a water diuresis (aquaretics) include demeclocycline, lithium, and vasopressin V_2 receptor antagonists, each of which inhibits the action of AVP on the collecting duct through different mechanisms, thereby increasing free water clearance. Drugs that cause solute diuresis are subdivided into two types—osmotic diuretics, which are nonresorbable solutes that osmotically retain water and other solutes in the tubular lumen, and drugs that selectively inhibit ion transport pathways across tubular epithelia, which constitute the majority of potent, clinically useful diuretics. The classes of diuretics and individual class members are listed in **Table 28-7** and their renal sites of action are depicted in **Figure 28-10**.

LOOP DIURETICS. The agents classified as loop diuretics, including furosemide, bumetanide, and torsemide, act by reversibly inhibiting the Na^+-K^+-$2Cl^-$ symporter (cotransporter) on the apical membrane of epithelial cells in the thick ascending loop of Henle (see Fig. 28-10). Because furosemide, bumetanide, and torsemide are bound extensively to plasma proteins, delivery of these drugs to the tubule by filtration is limited. However, these drugs are secreted efficiently by the organic acid transport system in the proximal tubule and thereby gain access to their binding sites on the Na^+-K^+-$2Cl^-$ symporter in the luminal membrane of the ascending limb. Thus, the efficacy of loop diuretics is dependent on sufficient renal plasma blood flow and proximal tubular secretion to deliver these agents to their site of action. Probenecid shifts the plasma concentration-response curve for furosemide to the right by competitively inhibiting furosemide excretion by the organic acid transport system. The bioavailability of furosemide ranges from 40% to 70% of the oral dose. In contrast, the oral bioavailability of bumetanide and torsemide exceed 80%. Accordingly, these agents may be more effective for those with advanced HF or right-sided HF, albeit at considerably greater cost. Agents in a second functional class of loop diuretics (e.g., ethacrynic acid) exhibit a slower onset of action and have delayed and only partial reversibility. Ethacrynic acid may be safely used in sulfa-allergic HF patients.

MECHANISMS OF ACTION. Loop diuretics are believed to improve symptoms of congestion by several mechanisms. First, loop diuretics reversibly bind to and reversibly inhibit the action of the Na^+,K^+-$2Cl^-$ cotransporter, thereby preventing salt transport in the thick ascending loop of Henle. Inhibition of this symporter also inhibits Ca^{2+} and Mg^{2+} resorption by abolishing the transepithelial potential difference that is the driving force for absorption of these cations. By inhibiting the concentration of solute within the medullary interstitium, these drugs also reduce the driving force for water resorption in the collecting duct, even in the presence of AVP (see Chaps. 25 and 27). The decreased resorption of water by the collecting duct results in the production of urine that is almost isotonic with plasma. The increase in delivery of Na^+ and water to the distal nephron segments also markedly enhances K^+ excretion, particularly in the presence of elevated aldosterone levels.

Loop diuretics also exhibit several characteristic effects on intracardiac pressure and systemic hemodynamics. Furosemide acts as a venodilator and reduces right atrial and pulmonary capillary wedge pressure within minutes when given intravenously (0.5 to 1.0 mg/kg). Similar data, although not as extensive, have accumulated for bumetanide and torsemide. This initial improvement in hemodynamics may be secondary to the release of vasodilatory prostaglandins, insofar as studies in animals and humans have demonstrated that the venodilatory actions of furosemide are inhibited by indomethacin. There have also been reports of an acute rise in systemic vascular resistance in response to loop diuretics, which has been attributed to the transient activation of the systemic or intravascular renin-angiotensin system (RAS). The potentially deleterious rise in LV afterload reinforces the importance of initiating vasodilator therapy with diuretics in patients with acute pulmonary edema and adequate blood pressure (see Chap. 27).

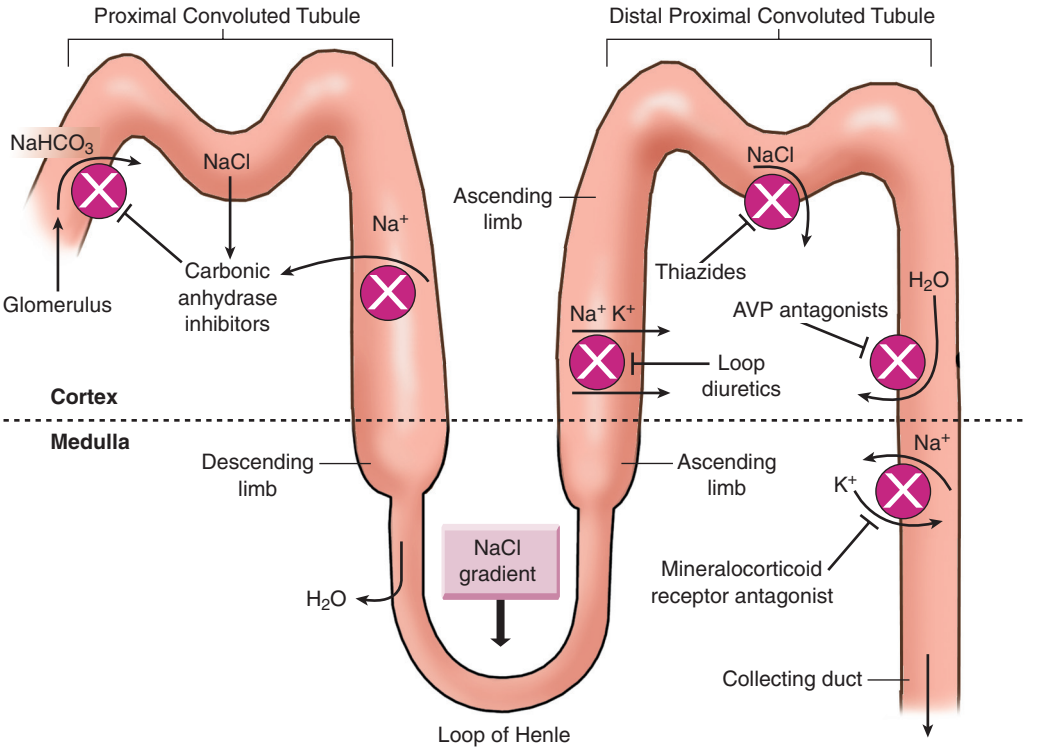

FIGURE 28-10 Sites of action of diuretics in the kidney. AVP = arginine vasopressin. *(From Bristow MR, Linas S, Port DJ: Drugs in the treatment of heart failure. In Zipes DP, Libby P, Bonow RO, Braunwald E [eds]: Braunwald's Heart Disease. 7th ed. Philadelphia, Elsevier, 2004, p 573.)*

THIAZIDE AND THIAZIDE-LIKE DIURETICS. The benzothiadiazides, also known as thiazide diuretics, were the initial class of drugs synthesized to block the Na^+-Cl^- transporter in the distal nephron. Subsequently, drugs that share similar pharmacologic properties became known as thiazide-like diuretics, even though they were technically not benzothiadiazine derivatives. Because thiazide and thiazide-like diuretics prevent maximal dilution of urine, they decrease the kidney's ability to increase free water clearance, and may therefore contribute to the development of hyponatremia. Thiazides increase Ca^{2+} resorption in the distal nephron (see Fig. 28-10) by several mechanisms, occasionally resulting in a small increase in serum Ca^{2+} levels. In contrast, Mg^{2+} resorption is diminished and hypomagnesemia may occur with prolonged use. Increased delivery of NaCl and fluid into the collecting duct directly enhances K^+ and H^+ secretion by this segment of the nephron, which may lead to clinically important hypokalemia.

MECHANISMS OF ACTION. The site of action of these drugs within the distal convoluted tubule has been identified as the Na^+-Cl^- symporter of the distal convoluted tubule. Although this cotransporter shares approximately 50% amino acid homology with the Na^+-K^+-$2Cl^-$ symporter of the ascending limb of the loop of Henle, it is insensitive to the effects of furosemide. This cotransporter (or related isoforms) is also present on cells within the vasculature and many cell types in other organs and tissues, and may contribute to some of the other actions of these agents, such as their usefulness as antihypertensive agents. Similar to the loop diuretics, the efficacy of thiazide diuretics is dependent, at least in part, on proximal tubular secretion to deliver these agents to their site of action. However, unlike the loop diuretics, the plasma protein binding varies considerably among the thiazide diuretics; accordingly, this parameter will determine the contribution that glomerular filtration makes to tubular delivery of a specific diuretic.

MINERALOCORTICOID RECEPTOR ANTAGONISTS. Mineralocorticoids such as aldosterone cause retention of salt and water and increase the excretion of K^+ and H^+ by binding to specific mineralocorticoid receptors. Early studies indicated that spirolactones block the effects of mineralocorticoids, which subsequently led to the development of specific antagonists for the mineralocorticoid receptor. Spironolactone and eplerenone are synthetic mineralocorticoid receptor antagonists that act on the distal nephron to inhibit Na^+-K^+ excretion at the site of aldosterone action (see Fig. 28-10). Spironolactone has antiandrogenic and progesterone-like effects, which may cause gynecomastia or impotence in men and menstrual irregularities in women. To overcome these side effects, eplerenone was developed by replacing the 17-alpha thioacetyl group of spironolactone with a carbomethoxy group. As a result of this modification, eplerenone has greater selectivity for the mineralocorticoid receptor than for steroid receptors, and has less sex hormone side effects than spironolactone. Eplerenone is further distinguished from spironolactone by its shorter half-life and the fact that it does not have any active metabolites. Although spironolactone and eplerenone are both weak diuretics, clinical trials have shown that both of these agents have profound effects on cardiovascular morbidity and mortality (**Fig. 28-11**) by virtue of their ability to antagonize the deleterious effects of aldosterone in the cardiovascular system (see Chap. 25). Hence, these agents are used in patients more for their ability to antagonize the renin angiotensin aldosterone system (see later) than for their diuretic properties.

MECHANISMS OF ACTION. Spironolactone (see Table 28-7) and its active metabolite, canrenone, competitively inhibit the binding of aldosterone to mineralocorticoid or type I receptors in many tissues, including

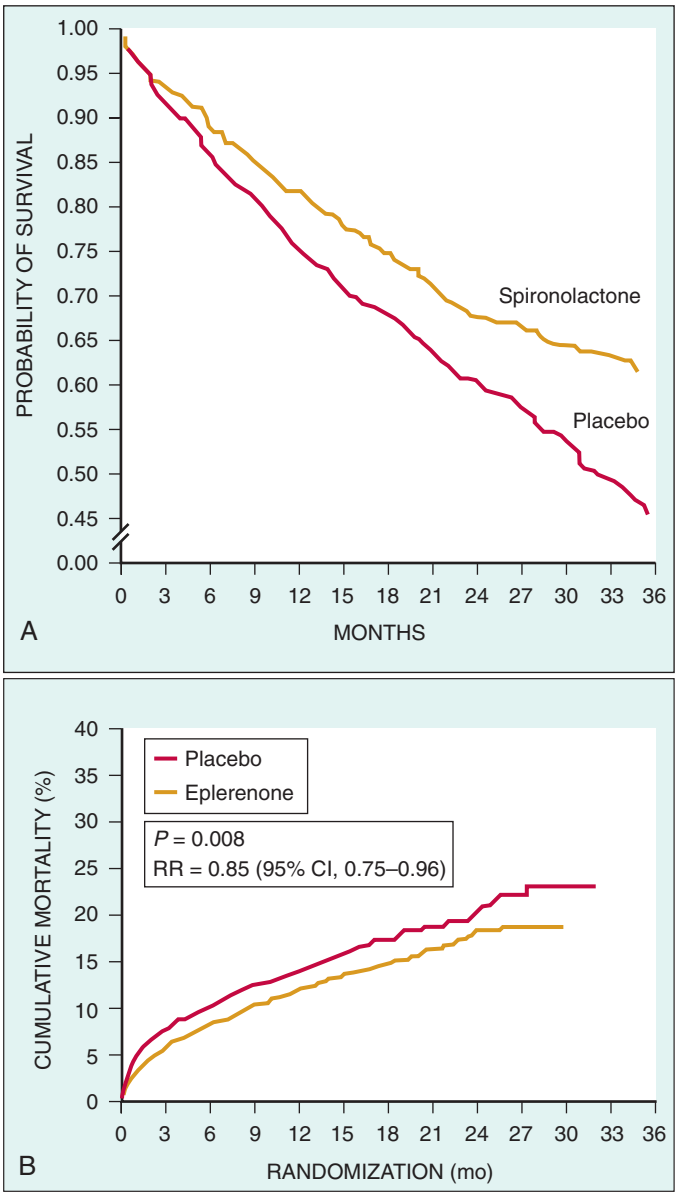

FIGURE 28-11 Kaplan-Meier analysis of the probability of survival in patients in the placebo and treatment groups in the RALES trial **(A)** with spironolactone, and probability of mortality in patients in the placebo and treatment groups in the EPHESUS **(B)** trial using eplerenone. *(Modified from Pitt B, Zannad F, Remme WJ, et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 341:709, 1999; and 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 348:1309, 2003.)*

epithelial cells of the distal convoluted tubule and collecting duct. These cytosolic receptors are ligand-dependent transcription factors, which, on binding of the ligand (e.g., aldosterone), translocate to the nucleus, where they bind to hormone response elements present in the promoter of some genes, including several involved in vascular and myocardial fibrosis, inflammation, and calcification. The first evidence that aldosterone antagonists could produce a major clinical benefit was shown by the Randomized Aldactone Evaluation Study (RALES) trial,[20] which evaluated spironolactone (25 mg/day initially, titrated to 50 mg/day for signs of worsening HF) versus placebo in NYHA Class III or IV HF patients with a LVEF lower than 35%, who were being treated with an ACEI, loop diuretic and, in most cases, digoxin. The primary endpoint was death from all causes. As shown in Figure 28-11A, spironolactone led to a 30% reduction in total mortality when compared with placebo ($P = 0.001$), which was attributed to a lower risk of death from progressive pump failure and sudden death. The frequency of hospitalization for worsening was also 35% lower in the spironolactone group than in the placebo group. In addition, patients who received spironolactone had a significant improvement in NYHA functional class ($P < 0.001$). Although the mechanism for the beneficial effect of spironolactone has not been fully elucidated, prevention of extracellular matrix remodeling (see Chap. 25) and prevention of hypokalemia are plausible mechanisms. In RALES, the serum potassium levels were 0.3 mEq/liter higher in the spironolactone group than in the placebo group ($P = 0.001$), which could have played a major role in reducing sudden or even pump failure-related deaths. Although spironolactone was well tolerated in RALES, gynecomastia was reported in 10% of men who were treated with spironolactone, as compared with 1% of men in the placebo group ($P < 0.001$). In the RALES trial, the incidence of serious hyperkalemia was minimal in both groups of patients; however, there have been several subsequent reports of severe hyperkalemia. In addition to the RALES trial, which was confined to patients with NYHA Classes III and IV HF, a retrospective analysis of a cohort of patients with mild to moderate HF suggested a favorable trend toward improved mortality when spironolactone was added to the HF regimen.

The second line of evidence that aldosterone antagonists could produce a major clinical benefit independent of the their diuretic effects came from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS; see Fig. 28-11B), a double-blind, placebo-controlled study that evaluated the effect of eplerenone on morbidity and mortality in patients with acute MI (AMI) complicated by LV dysfunction and HF. Patients were randomly assigned to eplerenone (25 mg/day initially, titrated to a maximum of 50 mg/day) or placebo in addition to optimal medical therapy. The primary end points were death from any cause and death from cardiovascular causes or hospitalization for HF, AMI, stroke, or ventricular arrhythmia. As shown in Figure 28-11B, there was a significant decrease in all-cause death in the patients randomized to receive eplerenone (relative risk [RR], 0.83; 95% CI, 0.72 to 0.94; $P = 0.005$). The rate of the other primary endpoint, death from cardiovascular causes or hospitalization for cardiovascular events, was reduced by eplerenone (RR, 0.85; 95% CI, 0.75 to 0.96; $P = 0.006$), as was the secondary endpoint of death from any cause or any hospitalization. There was also a reduction in the rate of sudden death from cardiac causes.[21] The role of eplerenone in mild HF (NYHA Class II) is being examined prospectively in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial (ClinicalTrials.gov identifier, NCT00232180). This trial was halted prematurely on May 27, 2010, because the trial had met its primary endpoints, which was cardiovascular death or HF hospitalization.

POTASSIUM-SPARING DIURETICS. Triamterene and amiloride are referred to as potassium-sparing diuretics. These agents share the common property of causing a mild increase in NaCl excretion, as well as having antikaluretic properties. Triamterene is a pyrazinoylguanidine derivative, whereas amiloride is a pteridine. Both drugs are organic bases that are transported into the proximal tubule, where they block Na^+ reabsorption in the late distal tubule and collecting duct. However, because Na^+ retention occurs in more proximal nephron sites in HF, neither amiloride nor triamterene is effective in achieving a net negative Na^+ balance when given alone in HF patients. Both amiloride and triamterene appear to share a similar mechanism of action. Considerable evidence suggests that amiloride blocks Na^+ channels in the luminal membrane of the principal cells in the late distal tubule and collecting duct, perhaps by competing with Na^+ for negatively charged areas within the pore of the Na^+ channel. Blockade of Na^+ channels leads to hyperpolarization of the luminal membrane of the tubule, which reduces the electrochemical gradient that provides the driving force for K^+ secretion into the lumen. Amiloride and its congeners also inhibit Na^+-H^+ antiporters in renal epithelial cells and in many other cell types, but only at concentrations higher than those used clinically.

CARBONIC ANHYDRASE INHIBITORS. The zinc metalloenzyme carbonic anhydrase plays an essential role in the $NaHCO_3$ resorption and acid secretion in the proximal tubule. Although weak diuretics, carbonic anhydrase inhibitors (see Table 28-7) such as acetazolamide potently inhibit carbonic anhydrase, resulting in almost complete loss of $NaHCO_3$ resorption in the proximal tubule. The use of these agents in patients with HF is confined to temporary administration to correct the metabolic alkalosis that occurs as a contraction phenomenon in response to the administration of other diuretics. When used

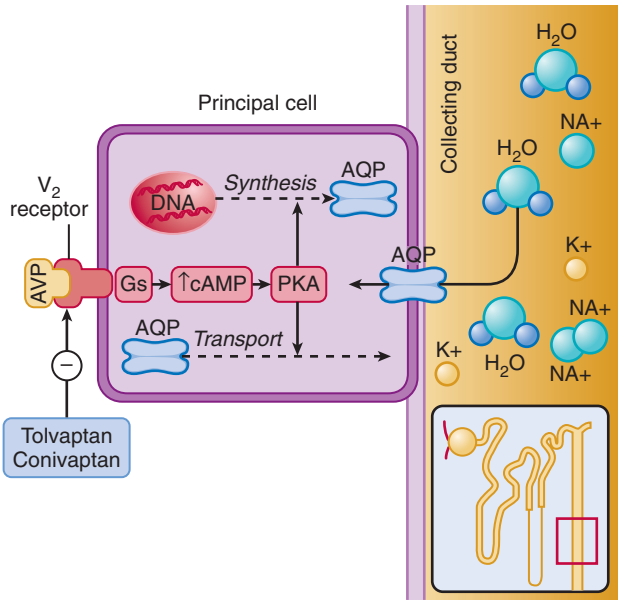

FIGURE 28-12 Mechanism of action of vasopressin antagonists. The binding of AVP to V_2 receptors stimulates the synthesis of aquaporin-2 (AQP) water channel proteins and promotes their transport to the apical surface. At the cell membrane, aquaporin-2 permits selective free water reabsorption down the medullary osmotic gradient, ultimately decreasing serum osmolarity and increasing fluid balance. V_2 antagonists work by preventing AVP from binding to its cognate receptor. *(Modified from deGoma EM, Vagelos RH, Fowler MB, Ashley EA: Emerging therapies for the management of decompensated heart failure: From bench to bedside. J Am Coll Cardiol 48:2397, 2006.)*

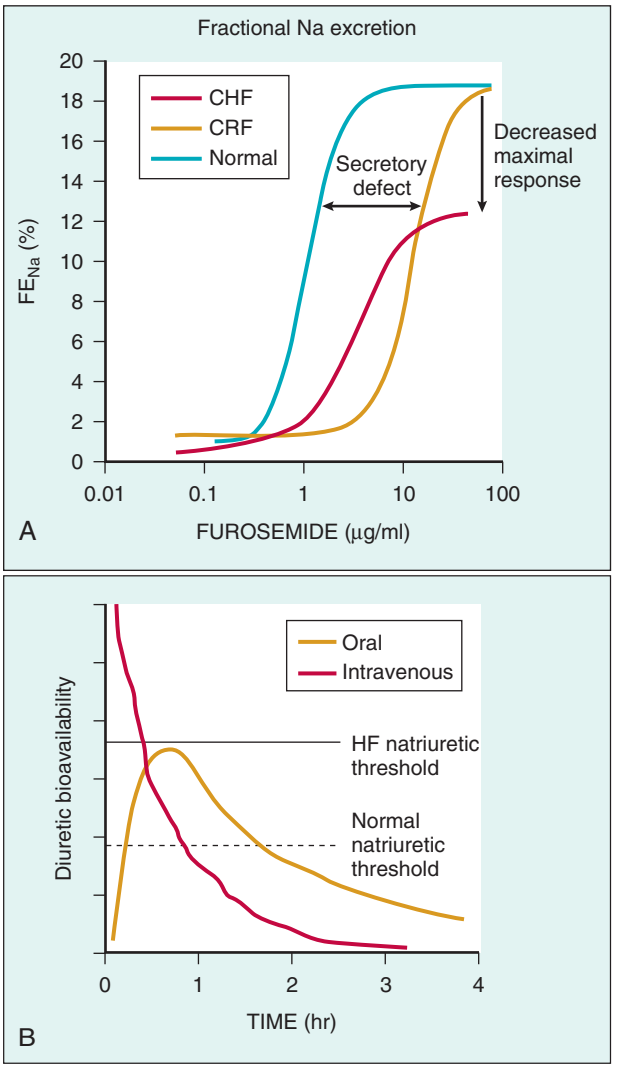

FIGURE 28-13 Dose-response curves for loop diuretics. **A,** Fractional Na excretion (FE_{Na}) as a function of loop diuretic concentration. Compared with normal patients, patients with chronic renal failure (CRF) show a rightward shift in the curve because of impaired diuretic secretion. The maximal response is preserved when expressed as FE_{Na}, but not when expressed as absolute Na excretion. Patients with HF demonstrate a rightward and downward shift, even when the response is expressed as FE_{Na}, and thus are relatively diuretic-resistant. **B,** Comparison of the response to intravenous and oral doses of loop diuretics in normal subjects and HF patients. Diuretic bioavailability is shown for normal and HF patients. The natriuretic threshold necessary to produce a diuresis is shown for normal subjects (dotted line) and for HF patients (solid line). In a normal individual, an oral dose may be as effective as an intravenous dose because the diuretic bioavailability (area under the curve) above the natriuretic threshold for intravenous and oral diuretics is approximately equal. However, if the natriuretic threshold increases in a patient with HF, the oral dose may not provide a high enough serum level to elicit a significant natriuresis. *(Modified from Ellison DH: Diuretic therapy and resistance in congestive heart failure. Cardiology 96:132, 2001.)*

repeatedly, these agents can lead to metabolic acidosis and severe hypokalemia.

VASOPRESSIN ANTAGONISTS. As discussed in Chap. 25, increased circulating levels of the pituitary hormone AVP contribute to the increased systemic vascular resistance and positive water balance in HF patients. The cellular effects of AVP are mediated by interactions with three types of receptors, V_{1a}, V_{2a}, and V_2. Selective V_{1a} antagonists block the vasoconstricting effects of AVP in peripheral vascular smooth muscle cells, whereas V_2 selective receptor antagonists inhibit recruitment of aquaporin water channels into the apical membranes of collecting duct epithelial cells, thereby reducing the ability of the collecting duct to resorb water (**Fig. 28-12**). Combined V_{1a}/V_2 antagonists lead to a decrease in systemic vascular resistance and prevent the dilutional hyponatremia that occurs in HF patients.[22]

The AVP antagonists, or vaptans, (see Table 28-7) were developed to block the V_2 receptors (e.g., tolvaptan, lixivaptan, satavaptan) selectively or nonselectively block both the V_{1a} and V_2 receptors (e.g., conivaptan). All four AVP antagonists increase urine volume, decrease urine osmolarity, and have no effect on 24-hour sodium excretion (see Chap. 27).[22] Long-term therapy with the V_2 selective vasopressin antagonist tolvaptan did not improve mortality but appeared to be safe in patients with advanced HF (see Chap. 27).[23] Currently, two vasopressin antagonists are U.S. Food and Drug Administration (FDA)–approved (conivaptan and tolvaptan) for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum $Na^+ \leq 125$ mEq/liter) that is symptomatic and resisted correction with fluid restriction. However, neither of these agents is currently approved for the treatment of HF. Use of these agents is appropriate after traditional measures to treat hyponatremia have been tried, including water restriction and maximization of medical therapies such as ACEIs or angiotensin receptor blockers (ARBs), which block or decrease angiotensin II. Lixivaptan is currently being evaluated in a phase II study in hypervolemic HF patients (ClinicalTrials.gov identifier, NCT01055912).

DIURETIC TREATMENT OF HEART FAILURE. Patients with evidence of volume overload or a history of fluid retention should be treated with a diuretic to relieve their symptoms. In symptomatic patients, diuretics should always be used in combination with neurohormonal antagonists known to prevent disease progression (see later, Table 28-9). When patients have moderate to severe symptoms or renal insufficiency, a loop diuretic is generally required. Diuretics should be initiated in low doses (see Table 28-7) and then titrated upward to relieve signs and symptoms of fluid overload. A typical starting dose of furosemide for patients with systolic HF and normal renal function is 40 mg, although doses of 80 to 160 mg are often necessary to achieve adequate diuresis. Because of the steep dose-response curve and effective threshold for loop diuretics (**Fig. 28-13**), it is critical to find an

adequate dose of loop diuretic that leads to a clear-cut diuretic response. One commonly used method for finding the appropriate dose is to double the dose until the desired effect is achieved or the maximal dose of diuretic is reached. Once patients have achieved an adequate diuresis, it is important to document their dry weight and make certain that patients weigh themselves daily to maintain their dry weight.

Although furosemide is the most commonly used loop diuretic, the oral bioavailability of furosemide is approximately 40% to 79%. Therefore, bumetanide or torsemide may be preferable because of their increased bioavailability. With the exception of torsemide, the commonly used loop diuretics are short acting (<3 hours). For this reason, loop diuretics usually need to be given at least twice daily. Some patients may develop hypotension or azotemia during diuretic therapy. Although the rapidity of diuresis should be slowed in these patients, diuretic therapy should be maintained at a lower level until the patient becomes euvolemic, insofar as persistent volume overload may compromise the effectiveness of some neurohormonal antagonists. Intravenous administration of diuretics may be necessary to relieve congestion acutely (see Fig. 25-13B and Chap. 27), and can be done safely in the outpatient setting. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even three times per day will provide more diuresis with less physiologic perturbation than larger single doses. Once the congestion has been relieved, treatment with diuretics is continued to prevent the recurrence of salt and water retention to maintain the patient's ideal dry weight.

COMPLICATIONS OF DIURETIC USE. Patients with HF who are receiving diuretics should be monitored for complications of diuretics on a regular basis. The major complications of diuretic use include electrolyte and metabolic disturbances, volume depletion, and worsening azotemia. The interval for reassessment should be individualized based on severity of illness and underlying renal function, use of concomitant medications such as ACEIs, ARBs, and aldosterone antagonists, past history of electrolyte imbalances, and/or need for more aggressive diuresis.

Electrolyte and Metabolic Disturbances

Diuretic use can lead to potassium depletion, which can predispose the patient to significant cardiac arrhythmia. Renal potassium losses from diuretic use can also be exacerbated by the increase in circulating levels of aldosterone observed in patients with advanced HF, as well by the marked increases in distal nephron Na^+ delivery that follows the use of loop or distal nephron diuretics. The level of dietary salt intake may also contribute to the extent of renal K^+ wasting with diuretics.

In the absence of formal guidelines with respect to the level of maintenance of serum K^+ levels in HF patients, many experienced HF clinicians have advocated that the serum K^+ level be maintained between 4.0 and 5.0 mEq/liter because HF patients are often treated with pharmacologic agents likely to provoke proarrhythmic effects in the presence of hypokalemia (e.g., digoxin, type III antiarrhythmics, beta agonists, phosphodiesterase inhibitors). Hypokalemia can be prevented by increasing the oral intake of KCl. The normal daily dietary K^+ intake is approximately 40 to 80 mEq. Therefore, to increase this by 50% requires 20 to 40 mEq K^+ daily. However, in the presence of alkalosis, hyperaldosteronism, or Mg^{2+} depletion, hypokalemia is unresponsive to increased dietary intake of KCl, and more aggressive replacement is necessary. If supplementation is necessary, oral potassium supplements in the form of KCl extended-release tablets or liquid concentrate should be used whenever possible. Intravenous potassium is potentially hazardous and should be avoided except in emergencies. Where appropriate, the use of an aldosterone receptor antagonist may also prevent the development of hypokalemia.

The use of aldosterone receptor antagonists is often associated with the development of life-threatening hyperkalemia, particularly when they are combined with ACEIs and/or ARBs.[24] Potassium supplementation is generally stopped after the initiation of aldosterone antagonists, and patients should be counseled to avoid high potassium-containing foods. However, patients who have required large amounts of potassium supplementation may need to continue receiving supplementation, albeit at a lower dose, particularly when previous episodes of hypokalemia have been associated with ventricular arrhythmias. Diuretics may be associated with a number of other metabolic and electrolyte disturbances, including hyponatremia, hypomagnesemia, metabolic alkalosis, hyperglycemia, hyperlipidemia, and hyperuricemia. Hyponatremia is usually observed in HF patients with a very high degree of RAS activation and/or AVP levels. Aggressive diuretic use can also lead to hyponatremia. Hyponatremia can generally be treated by more stringent water restriction. Both loop and thiazide diuretics can cause hypomagnesemia, which can aggravate muscle weakness and cardiac arrhythmias. Magnesium replacement should be administered for signs or symptoms of hypomagnesemia (e.g., arrhythmias, muscle cramps), and can be routinely given, with uncertain benefit, to all subjects receiving large doses of diuretics or requiring large amounts of K^+ replacement. The modest hyperglycemia and/or hyperlipidemia produced by thiazide diuretics is not usually clinically important, and blood glucose and lipid levels are usually easily controlled with the use of standard practice guidelines. Metabolic alkalosis can generally be treated by increasing KCl supplementation, lowering diuretic doses, or transiently using acetazolamide.

Hypotension and Azotemia

The excessive use of diuretics can lead to decreased blood pressure, decreased exercise tolerance, and increased fatigue, as well as impaired renal function. Hypotensive symptoms usually resolve after a decrease in the dose or frequency of diuretics in patients who are volume-depleted. However, in most cases, the use of diuretics is associated with the decrease in blood pressure and/or mild azotemia that do not lead to patient symptoms. In this case, reductions in the diuretic dose are not necessary, particularly if the patient remains edematous. In some patients with advanced chronic HF, elevated blood urea nitrogen (BUN) and creatinine concentrations may be necessary to maintain control of congestive symptoms.

Neurohormonal Activation

Diuretics may increase the activation of endogenous neurohormonal systems in HF patients, which can lead to disease progression unless patients are receiving treatment with a concomitant neurohormonal antagonist (e.g., ACEI or beta blocker).

Ototoxicity

Ototoxicity, which is more frequent with ethacrynic acid than the other loop diuretics, can manifest as tinnitus, hearing impairment, and deafness. Hearing impairment and deafness are usually, but not invariably, reversible. Ototoxicity occurs most frequently with rapid intravenous injections, and least frequently with oral administration.

DIURETIC RESISTANCE AND MANAGEMENT. One of the inherent limitations of diuretics is that they achieve water loss via excretion of solute at the expense of glomerular filtration, which in turn activates a set of homeostatic mechanisms that ultimately limit their effectiveness. In normal subjects, the magnitude of natriuresis following a given dose of diuretic declines over time as a result of the so-called braking phenomenon (**Fig. 28-14**). Studies have shown that the time-dependent decline in natriuresis for a given diuretic dose is critically dependent on reduction of the extracellular fluid volume, which leads to an increase in solute and fluid reabsorption in the proximal tubule. In addition, contraction of the extracellular volume can lead to stimulation of efferent sympathetic nerves, which reduces urinary Na^+ excretion by reducing renal blood flow, stimulating renin (and ultimately aldosterone) release, which in turn stimulates Na^+ reabsorption along the nephron (see Chap. 25). The magnitude of the natriuretic effect of potent loop diuretics may also decline in HF patients, particularly as HF progresses. Although the bioavailability of these diuretics is generally not decreased in HF, the potential delay in their rate of absorption may result in peak drug levels in the tubular lumen in the ascending loop of Henle that are insufficient to induce maximal natriuresis (see Fig. 28-13). The use of intravenous formulations may obviate this

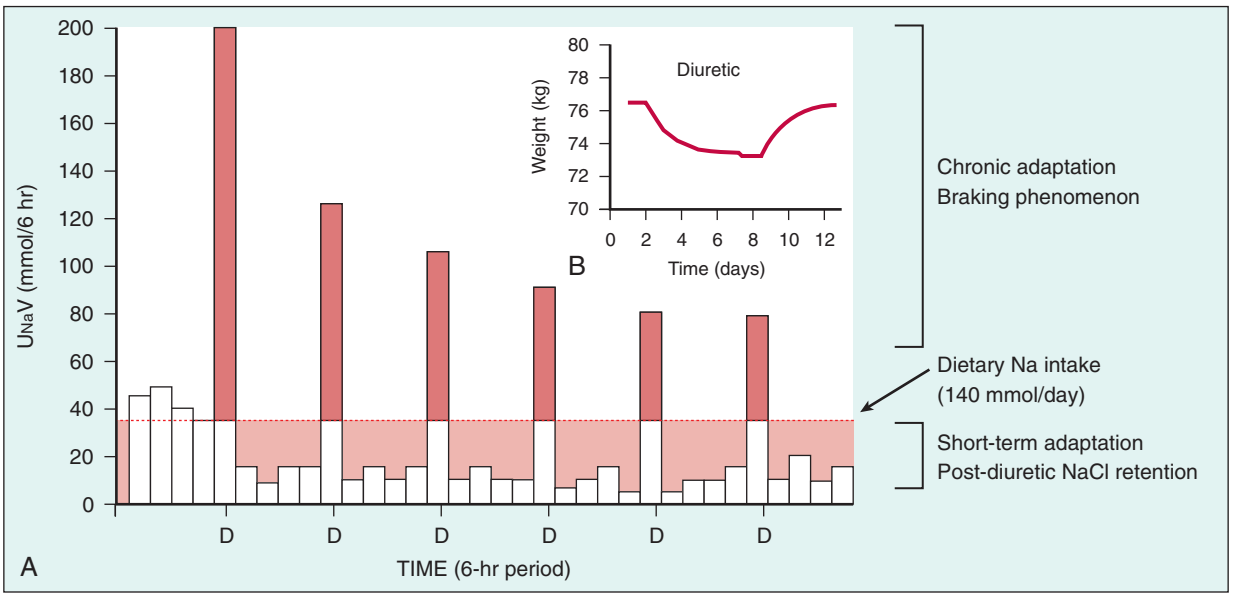

FIGURE 28-14 Effects of diuretics on urinary Na excretion and extracellular fluid (ECF) volume. **A,** Effects of a loop diuretic on urinary Na excretion ($U_{Na}V$). Bars represent 6-hour periods of Na balance before and after doses of loop diuretic (D). The dashed line indicates dietary Na intake. The shaded portion of the bars indicates the amount whereby Na excretion exceeds intake during natriuresis. The solid shaded area beneath the dashed line indicates the amount of positive Na balance after the diuretic effect has worn off. Net Na balance during 24 hours is the difference between the shaded area beneath the dashed line (postdiuretic NaCl retention) and the shaded portion within the bars. (diuretic-induced natriuresis). Chronic adaptation is indicated by progressively smaller peak natriuretic effects (the braking phenomenon) and is mirrored by a return to neutral balance. **Inset (B),** Effect of a diuretic on body weight, taken as an index of ECF volume. Note that a steady state is reached within 6-8 days despite continued diuretic administration. *(Modified from Ellison DH: Diuretic therapy and resistance in congestive heart failure. Cardiology 96:132, 2001.)*

problem (see Chap. 27). However, even with intravenous dosing, a rightward shift of the dose-response curve is observed between the diuretic concentration in the tubular lumen and its natriuretic effect in HF (see Fig. 28-13A). Moreover, the maximal effect (ceiling) is lower in HF. This rightward shift has been referred to as diuretic resistance and is likely caused by several factors in addition to the braking phenomenon described. First, most loop diuretics, with the exception of torsemide, are short-acting drugs. Accordingly, after a period of natriuresis, the diuretic concentration in plasma and tubular fluid declines below the diuretic threshold. In this situation, renal Na^+ reabsorption is no longer inhibited and a period of antinatriuresis or postdiuretic NaCl retention ensues. If dietary NaCl intake is moderate to excessive, postdiuretic NaCl retention may overcome the initial natriuresis in patients, with excessive activation of the adrenergic nervous system and RAS. This observation forms the rationale for administering short-acting diuretics several times daily to obtain consistent daily salt and water loss. Second, there is a loss of renal responsiveness to endogenous natriuretic peptides as HF advances (see Chap. 25). Third, diuretics increase solute delivery to distal segments of the nephron, causing epithelial cells to undergo hypertrophy and hyperplasia. Although the diuretic-induced signals that initiate changes in distal nephron structure and function are not well understood, chronic loop diuretic administration increases the Na^+,K^+-ATPase activity in the distal collecting duct and cortical collecting tubule, and increases the number of thiazide-sensitive NaCl cotransporters in the distal nephron, which increases the solute resorptive capacity of the kidney as much as threefold.

In patients with HF, an abrupt decline in cardiac and/or renal function or patient noncompliance with the diuretic regimen or diet may lead to diuretic resistance. Apart from these more obvious causes, it is important to query the patient about the use of concurrent use of drugs that adversely affect renal function (e.g., NSAIDs and COX inhibitors; see Table 28-6). The insulin-sensitizing thiazolidinediones (TZDs) have also been linked to increased fluid retention in patients with HF, although the clinical significance of this finding is unknown. It has been suggested that thiazolidinediones activate proliferator-activated receptor gamma expression in the renal collecting duct, which enhances the expression of cell surface epithelial Na^+ channels. Moreover, studies in healthy men have shown that pioglitazone stimulates plasma renin activity that may contribute to increased Na^+ retention. Rarely, drugs such as probenecid or high plasma concentrations of some antibiotics may compete with the organic ion transporters in the proximal tubule responsible for the transfer of most diuretics from the recirculation into the tubular lumen. The use of increasing doses of vasodilators, with or without a marked decline in intravascular volume as a result of concomitant diuretic therapy, may lower renal perfusion pressure below that necessary to maintain normal autoregulation and glomerular filtration in patients with renal artery stenosis from atherosclerotic disease. Accordingly, a reduction in renal blood flow may occur, despite an increase in cardiac output, thereby leading to a decrease in diuretic effectiveness.

A patient with HF may be considered to be resistant to diuretic drugs when moderate doses of a loop diuretic do not achieve the desired reduction of the extracellular fluid volume. In outpatients, a common and useful method for treating the diuretic-resistant patient is to administer two classes of diuretic concurrently. Adding a proximal tubule diuretic or a distal collecting tubule diuretic to a regimen of loop diuretics is often dramatically effective. As a general rule, when adding a second class of diuretic, the dose of loop diuretic should not be altered because the shape of the dose-response curve for loop diuretics is not affected by the addition of other diuretics, and the loop diuretic must be given at an effective dose for it to be effective. The combination of loop and distal collecting tubule diuretics has been shown to be effective through several mechanisms.[25] One is that distal collecting tubule diuretics have longer half-lives than loop diuretics and may thus prevent or attenuate postdiuretic NaCl retention. A second mechanism whereby distal collecting tubule diuretics potentiate the effects of loop diuretics is by inhibiting Na^+ transport along the proximal tubule, insofar as most thiazide diuretics also inhibit carbonic anhydrase, and by inhibiting NaCl transport along the distal renal tubule, which may counteract the increased solute resorptive effects of the hypertrophied and hyperplastic distal epithelial cells.

The selection of which distal collecting tubule diuretic to use as a second diuretic is a matter of choice. Many clinicians choose metolazone because its half-life is longer than that of some other distal collecting tubule diuretics, and because it has been reported to remain effective even when the glomerular filtration rate is low. However, direct comparisons between metolazone and several traditional thiazides have shown little difference in natriuretic potency when they are included in a regimen with loop diuretics in HF patients.[25] Distal

collecting tubule diuretics may be added in full doses (50 to 100 mg/day hydrochlorothiazide or 2.5 to 10 mg/day metolazone; see Table 28-7) when a rapid and robust response is needed. However, such an approach is likely to lead to excessive fluid and electrolyte depletion if patients are not followed up extremely closely. One reasonable approach to combination therapy is to achieve control of fluid overload by initially adding full doses of distal collecting tubule diuretic on a daily basis and then decreasing the dose of the distal collecting tubule diuretic to three times weekly to avoid excessive diuresis. An alternative strategy in hospitalized patients is to administer the same daily parenteral dose of a loop diuretic by continuous intravenous infusion, which leads to sustained natriuresis because of the continuous presence of high drug levels within the tubular lumen (see Chap. 27), and avoids postdiuretic (rebound) resorption of Na^+ (see Fig. 28-14B). This approach requires the use of a constant infusion pump but permits more precise control of the natriuretic effect achieved over time, particularly in carefully monitored patients. It also diminishes the potential for a too rapid decline in intravascular volume and hypotension, as well as the risk of ototoxicity in patients given large bolus intravenous doses of a loop diuretic. A typical continuous furosemide is initiated with a 20- to 40-mg intravenous loading dose as a bolus injection, followed by a continuous infusion of 5 to 10 mg/hr for a patient who had been receiving 200 mg of oral furosemide/day in divided doses. The usefulness of continuous versus bolus IV furosemide was evaluated in the National Heart, Lung and Blood Institute (NHLBI)–sponsored phase IV DOSE (Diuretic Optimal Strategy Evaluation in Acute Heart Failure) study (ClinicalTrials.gov identifier, NCT00577135). The provisional results of this study suggest that high-dose IV q12hr dosing and continuous IV dosing appear to be equivalent (see Chap. 27).

Another common reason for diuretic resistance in advanced HF is the development of the cardiorenal syndrome, which is recognized clinically as worsening renal function that limits diuresis in patients with obvious clinical volume overload.[26] In patients with advanced HF, the cardiorenal syndrome is frequently present in patients who have repeated HF hospitalizations, and in whom adequate diuresis is difficult to obtain because of worsening indices of renal function. This impairment in renal function often is dismissed as prerenal; however, when measured carefully, neither cardiac output nor renal perfusion pressure have been shown to be reduced in diuretic-treated patients who develop the cardiorenal syndrome. Importantly, worsening indices of renal function contribute to longer hospital stays, and predict higher rates of early rehospitalization and death (see Fig. 28-5). The mechanisms for and treatment of the cardiorenal syndrome remain poorly understood.

DEVICE-BASED THERAPIES FOR MANAGEMENT OF FLUID STATUS. The use of mechanical methods of fluid removal, such as extracorporeal ultrafiltration, may be needed to achieve adequate control of fluid retention, particularly in patients who become resistant and/or refractory to diuretic therapy (see Chap. 27). Extracorporeal ultrafiltration (UF) removes salt and water isotonically by driving the patient's blood through a highly permeable filter via an extracorporeal circuit in an arteriovenous or venovenous mode. Alternative extracorporeal methods include continuous hemofiltration, continuous hemodialysis, and continuous hemodiafiltration. With slow continuous UF, the patient's intravascular fluid volume remains stable as fluid shifts from the extravascular space into the intravascular space, so there is no deleterious activation of neurohormonal systems. UF has been shown to reduce right atrial and pulmonary artery wedge pressures and increase cardiac output, diuresis, and natriuresis without changes in heart rate, systolic blood pressure, renal function, electrolytes, or intravascular volume.[27]

The Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial, which was the first randomized controlled trial of UF for acute decompensated HF, enrolled 40 patients who were randomized to receive usual care (diuretic) or a single 8-hour UF (using a proprietary device) in addition to usual care.[27] The primary endpoint was weight loss 24 hours after enrollment. Fluid removal after 24 hours was approximately twofold greater in the UF group. The Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) compared the long-term safety and efficacy of ultrafiltration therapy (using a proprietary device) with intravenous diuretics in a multicenter trial involving 200 patients, who were assessed at entry and at intervals up to 90 days.[28] The primary endpoint of the trial was total weight loss during the first 48 hours of randomization and change in dyspnea score during the first 48 hours of randomization. Although the two treatments were similar in their ability to relieve dyspnea, UF was associated with significantly greater fluid loss over 48 hours and a lower rate of rehospitalization during the next 90 days. The use of UF in patients who are developing the cardiorenal syndrome is being explored in the NHLBI-sponsored CARRESS trial (Cardiorenal Rescue Study in Acute Decompensated HF; ClinicalTrials.gov identifier, NCT00608491).

Given the cost, need for venous access, and nursing support necessary to implement UF, this intervention will require additional studies to determine its role in the management of volume overload in HF patients. In addition to extracorporeal methods for relieving volume overload, peritoneal dialysis can be used as a viable alternative therapy for the short-term management of refractory congestive symptoms in patients for whom vascular access cannot be obtained, or for whom appropriate extracorporeal therapies are not available.

Preventing Disease Progression

Drugs that interfere with the excessive activation of renin angiotensin-aldosterone system and the adrenergic nervous system can relieve the symptoms of HF with a depressed EF by stabilizing and/or reversing cardiac remodeling (see Chap. 25; **Table 28-8**). In this regard ACEIs, ARBs, and beta blockers have emerged as cornerstones of modern HF therapy for patients with a depressed EF.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. There is overwhelming evidence that ACEIs should be used in symptomatic and asymptomatic patients with a reduced EF (<40%). ACEIs interfere with the RAS by inhibiting the enzyme that is responsible for the conversion of angiotensin I to angiotensin II (see Chap. 25). However, because ACEIs also inhibit kininase II, they may lead to the upregulation of bradykinin, which may further enhance the effects of angiotensin suppression. ACEIs stabilize LV remodeling, improve patient symptoms, prevent hospitalization, and prolong life. Because fluid retention can attenuate the effects of ACEIs, it is preferable to optimize the dose of diuretic first, before starting the ACEI. However, it may be necessary to reduce the dose of diuretic during the initiation of an ACEI to prevent symptomatic hypotension. ACEIs should be initiated in low doses, followed by increments in dose if lower doses have been well tolerated. Titration is generally achieved by doubling the dosage every 3 to 5 days. The dose of ACE inhibitor should be increased until the doses used are similar to those that have been shown to be effective in clinical trials (see Table 28-8). Higher doses are more effective than lower doses in preventing hospitalization. For stable patients, it is acceptable to add therapy with beta-blocking agents before full target doses of ACEIs are reached. Blood pressure (including postural changes), renal function, and potassium level should be evaluated within 1 to 2 weeks after initiation of ACEIs, especially in patients with preexisting azotemia, hypotension, hyponatremia, or diabetes mellitus, or in those taking potassium supplements. Abrupt withdrawal of treatment with an ACEI may lead to clinical deterioration and should therefore be avoided in the absence of life-threatening complications (e.g., angioedema, hyperkalemia).

The efficacy of ACEIs has been consistently demonstrated in clinical trials with patients with asymptomatic and symptomatic LV dysfunction (**Fig. 28-15**).[29,30] These trials recruited a broad variety of patients, including women and older patients, as well as patients with a wide range of causes and severity of LV dysfunction. The consistency of data from the SOLVD Prevention Trial, Survival and Ventricular Enlargement (SAVE), and Trandolapril Cardiac Evaluation (TRACE) has shown that asymptomatic patients with LV dysfunction will have less development of symptomatic

TABLE 28-8 Drugs for the Prevention and Treatment of Chronic Heart Failure

AGENTS	INITIATING DOSAGE	MAXIMAL DOSAGE
Angiotensin-Converting Enzyme Inhibitors		
Captopril	6.25 mg tid	50 mg tid
Enalapril	2.5 mg bid	10 mg bid
Lisinopril	2.5-5.0 mg qd	20 mg qd
Ramipril	1.25-2.5 mg qd	10 mg qd
Fosinopril	5-10 mg qd	40 mg qd
Quinapril	5 bid	40 mg bid
Trandolapril	0.5 mg qd	4 mg qd
Angiotensin Receptor Blockers		
Valsartan	40 mg bid	160 mg bid
Candesartan	4-8 mg qd	32 mg qd
Losartan	12.5-25 mg qd	50 mg qd
Beta Receptor Blockers		
Carvedilol	3.125 mg bid	25 mg bid (50 mg bid if body weight > 85 kg)
Carvedilol-CR	10 mg qd	80 mg qd
Bisoprolol	1.25 mg bid	10 mg qd
Metoprolol succinate CR	12.5-25 mg qd	200 mg qd
Aldosterone Antagonists		
Spironolactone	12.5-25 mg qd	25-50 mg qd
Eplerenone	25 mg qd	50 mg qd
Other Agents		
Combination of hydralazine/ isosorbide dinitrate	10-25 mg/10 mg tid	75 mg/40 mg tid
Fixed dose of hydralazine/ isosorbide dinitrate	37.5 mg/20 mg (one tablet) tid	75 mg/40 mg (two tablets) tid
Digoxin*	0.125 mg qd	≤0.375 mg/day†

*Dosing should be based on ideal body weight, age and renal function
†Trough level should be 0.5-1 ng/mL, although absolute levels have not been established.
Modified from Mann DL: Heart failure and cor pulmonale. *In* Kasper DL, Braunwald E, Fauci AS, Hauser SL, et al (eds): Harrison's Principles of Internal Medicine. 17th ed. New York, McGraw-Hill, 2007, p 1449.

HF and fewer hospitalizations when treated with an ACEI. ACEIs have also consistently shown benefit for patients with symptomatic LV dysfunction. As shown in **Table 28-9**, all placebo-controlled chronic HF trials have demonstrated a reduction in mortality. Furthermore, the absolute benefit is greatest in patients with the most severe HF. The patients with NYHA Class IV HF in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I) had a much larger effect size than the SOLVD Treatment Trial, which in turn had a larger effect size than the SOLVD Prevention Trial. Although only three placebo-controlled mortality trials have been conducted in patients with chronic HF, the aggregate data suggest that ACEIs reduce mortality in direct relation to the degree of severity of chronic HF. The Vasodilator in Heart Failure II (V-HeFT-II) trial provided evidence that ACEIs improve the natural history of HF through mechanisms other than vasodilation, inasmuch as subjects treated with enalapril had significantly lower mortality than subjects treated with the vasodilatory combination of hydralazine plus isosorbide dinitrate, which does not directly inhibit neurohormonal systems. Although enalapril is the only ACEI that has been used in placebo-controlled mortality trials in chronic HF, as shown in Table 28-9, a number of ACEIs have proven to be more or less equally effective when administered orally within the first week of the ischemic event in MI trials. ACEIs markedly enhance survival in patients with signs or symptoms of HF after MI. In addition to these effects on mortality, ACEIs improve the functional status of patients with HF. In contrast, ACEIs only produce small benefits in exercise capacity. Taken together, these observations support the conclusion that the effects of ACEIs on the natural history of chronic HF, post-MI LV dysfunction, or patients at high risk of developing HF represent a class effect of these agents. Nonetheless, it should be emphasized that patients with low blood pressure (<90 mm Hg systolic) or impaired renal function (serum creatinine level > 2.5 mg/mL) were not recruited and/or represent a small proportion of patients who participated in these trials. Thus, the efficacy of these agents for this latter patient population is less well established.

Complications of Angiotensin-Converting Enzyme Inhibitor Use

Most adverse effects of ACEIs are related to suppression of the RAS. The decreases in blood pressure and mild azotemia often seen during the initiation of therapy are, in general, well tolerated and do not require a decrease in the dose of the ACEI. However, if hypotension is accompanied by dizziness or if the renal dysfunction becomes severe, it may be necessary to decrease the dose of the diuretic if significant fluid retention is not present or, alternatively, decrease the dose of the ACEI if significant fluid retention is present. Potassium retention may also become problematic if the patient is receiving potassium supplements or a potassium-sparing diuretic. Potassium retention that is not responsive to these measures may require a reduction in the dose of ACEI. The side effects of ACEIs that are related to kinin potentiation include a nonproductive cough (10% to 15% of patients) and angioedema (1% of patients). In patients who cannot tolerate ACEIs because of cough or angioedema, ARBs are the next recommended line of therapy. Patients intolerant to ACEIs because of hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. The combination of hydralazine and an oral nitrate should be considered for these latter patients (see Table 28-8).

ANGIOTENSIN RECEPTOR BLOCKERS. ARBs are well tolerated in patients who are intolerant of ACEIs because of the development of cough, skin rash, and angioedema and should therefore be used in symptomatic and asymptomatic patients with an EF less than 40% who are ACE-intolerant for reasons other than hyperkalemia or renal insufficiency (see Table 28-9). Although ACEIs and ARBs inhibit RAS, they do so by a different mechanism. Whereas ACEIs block the enzyme responsible for converting angiotensin I to angiotensin II, ARBs block the effects of angiotensin II on the angiotensin type 1 receptor, the receptor subtype responsible for almost all the adverse biologic effects relevant to angiotensin II on cardiac remodeling (see Chap. 25). ARBs approved for the treatment of hypertension are now available to clinicians. Three of these, losartan, valsartan and candesartan, have been extensively evaluated in the setting of HF (see Table 28-8). Some clinical trials have demonstrated that ARBs are as effective as ACEIs in reversing the process of LV remodeling, improving patient symptoms, preventing hospitalization, and prolonging life. Moreover, several studies have shown that there is added therapeutic benefit for the addition of ARB to an ACEI in patients with chronic HF. ARBs should be initiated with the starting doses shown in Table 28-8, which can be uptitrated every 3 to 5 days by doubling the dose of ARB. As with ACEIs, blood pressure, renal function, and potassium level should be reassessed within 1 to 2 weeks after initiation and followed closely after changes in dosage.

In studies of symptomatic HF patients who were intolerant to ACEIs, the aggregate clinical data suggest that ARBs are as effective as ACEIs in reducing HF morbidity and mortality.[30] Candesartan significantly reduced all-cause mortality, cardiovascular death, and/or hospital admission in the Candesartan Heart Failure: Assessment of Reduction in Mortality and Morbidity trial (CHARM-Alternative Trial; **Fig. 28-16A**).[31] Importantly, candesartan reduced all-cause mortality, irrespective of background ACEI or beta blocker therapy. Similar findings were shown with valsartan in the small subgroup of patients not receiving an ACEI in the Valsartan Heart Failure Trial (Val-HeFT).[32] A direct comparison of ACEIs and ARBs was assessed in the Losartan Heart Failure Survival Study (ELITE-II), which showed that losartan was not associated with improved survival in older HF patients when compared with captopril, but was significantly better tolerated. Two trials have compared ARBs with ACEIs in post-MI patients

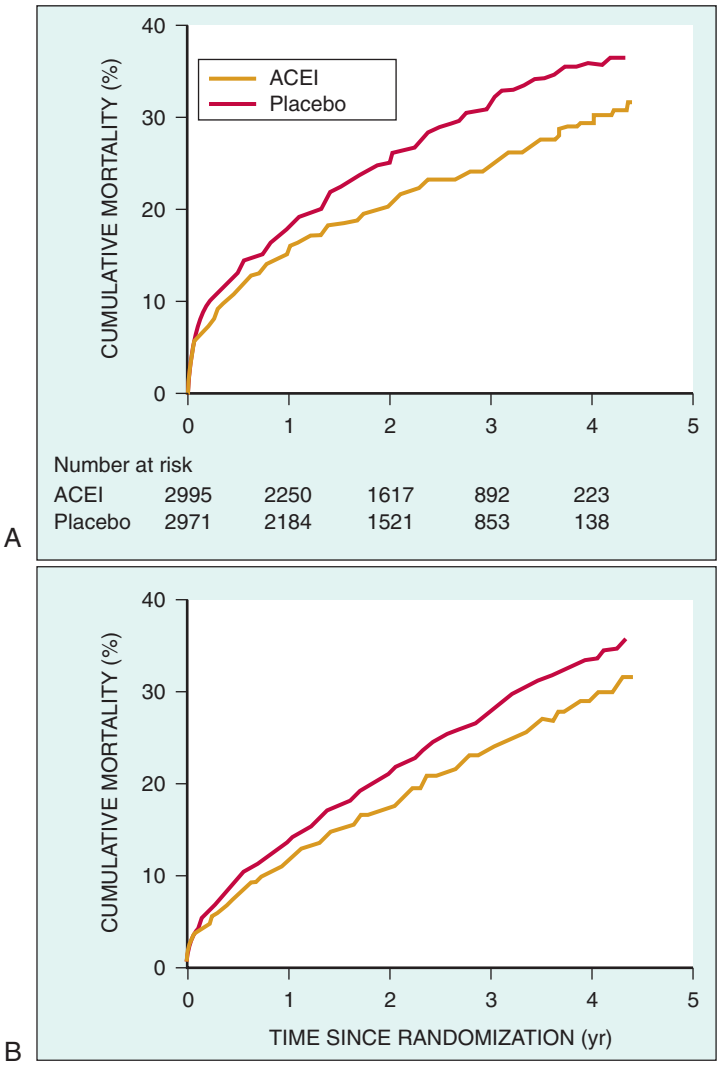

FIGURE 28-15 Meta-analysis of ACE inhibitors in HF patients with a depressed EF. **A,** Kaplan-Meier curves for mortality for HF patients with a depressed EF treated with an ACEI following an acute AMI (three trials). **B,** Kaplan-Meier curves for mortality for HF patients with a depressed EF treated with an ACEI in five clinical trials, including postinfarction trials. The benefits of ACEIs were observed early and persisted long term. *(Modified from Flather MD, Yusuf S, Kober L, et al: Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: A systematic overview of data from individual patients. Lancet 355:1575, 2000.)*

who developed LV dysfunction or signs of HF. The direct comparison of losartan with captopril indicated that losartan is not as effective as captopril on all-cause mortality, whereas valsartan was shown to be noninferior to captopril on all-cause mortality in the Valsartan in Acute Myocardial Infarction Trial (VALIANT).[33] The combination of captopril and valsartan produced no further reduction in mortality in VALIANT, although the number of adverse events increased. When given in addition to ACEIs in general cohorts of patients with symptomatic HF, the ARBs were shown to have a modest beneficial effect in the CHARM-Added trial (see Fig. 28-16B).[34] However, the addition of valsartan to ACEIs had no beneficial effect on mortality in Val-HeFT, although the combined endpoint of mortality and morbidity was significantly lower (13.2%) with valsartan than with placebo because of a reduction in the number of patients hospitalized for HF.[32] The question of high-dose versus low-dose angiotensin receptor antagonism on clinical outcomes was evaluated in the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial.[35] This study showed that the use of high-dose losartan was not associated with a significant reduction in the primary endpoint of all-cause death or admission for heart failure (HR, 0.94; 95% CI, 0.84 to 1.04; $P = 0.24$) when compared to low-dose losartan, but was associated with a significant reduction in HF admissions (HR, 0.94; 95% CI, 0.84 to 1.04; $P = 0.24$), suggesting that uptitration of ARBs may confer clinical benefit.

Although one meta-analysis has suggested that ARBs and ACEIs have similar effects on all-cause mortality and heart failure hospitalizations,[36] and although ARBs may be considered as initial therapy rather than ACEIs following MI, the general consensus is that ACEIs remain first-line therapy for the treatment of HF, whereas ARBs are recommended for ACE-intolerant patients (see Chap. 30, Guidelines).

Complications of Angiotensin Receptor Blocker Use

Both ACEIs and ARBs have similar effects on blood pressure, renal function, and potassium levels. Therefore, the problems of symptomatic hypotension, azotemia, and hyperkalemia will be similar for both these agents. Although angioedema is less frequent than with ACEIs, it has also been reported in some patients who receive ARBs. In patients who are intolerant to ACEIs and ARBs, the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option (see Table 28-8). However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions.

RENIN INHIBITORS. Aliskiren is an orally active renin inhibitor that appears to suppress RAS to a similar degree as ACE-inhibitors. Aliskiren is a nonpeptide inhibitor that binds to the active site (S1/S3 hydrophobic binding pocket) of renin, preventing the conversion of angiotensinogen to angiotensin I (see Fig. 25-4). The Aliskiren Observation of Heart Failure Treatment (ALOFT) study evaluated aliskiren in addition to an ACEI in patients with NYHA Classes II to IV heart failure. The primary endpoint was the change from baseline to 3 months in N-terminal pro BNP (NT-proBNP). In this study, NT-proBNP was significantly ($P < 0.01$) lower in patients who were randomized to aliskiren when compared with placebo.[37] Aliskiren is currently being evaluated in a phase III study that will evaluate the efficacy and safety of both aliskiren monotherapy and aliskiren-enalapril combination therapy as compared with enalapril monotherapy in regard to cardiovascular death and heart failure hospitalizations in NYHA Classes II to IV HF patients in the ATMOSPHERE (Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbi-mortality in Patients With Chronic Heart Failure) study (ClinicalTrials.gov identifier, NCT00853658).

BETA-ADRENERGIC RECEPTOR BLOCKERS. Beta blocker therapy represents a major advance in the treatment of HF patients with a depressed EF. Beta blockers interfere with the harmful effects of sustained activation of the nervous system by competitively antagonizing one or more adrenergic receptors (alpha$_1$, beta$_1$, and beta$_2$). Although there are a number of potential benefits to blocking all three receptors, most of the deleterious effects of sympathetic activation are mediated by the beta$_1$-adrenergic receptor.[38] When given in concert with ACEIs, beta blockers reverse the process of LV remodeling, improve patient symptoms, prevent hospitalization, and prolong life. Therefore, beta blockers are indicated for patients with symptomatic or asymptomatic HF and a depressed EF (<40%). Three beta blockers have been shown to be effective in reducing the risk of death in patients with chronic HF; bisoprolol and sustained-release metoprolol succinate both competitively block the beta$_1$-adrenergic receptor, and carvedilol competitively blocks the alpha$_1$-, beta$_1$-, and beta$_2$-adrenergic receptors. Analogous to the use of ACEIs, beta blockers should be initiated in low doses (see Table 28-8), followed by gradual increments if lower doses have been well tolerated. The dose of beta blocker should be increased until the doses used are similar to those that have been reported to be effective in clinical trials. However, unlike ACEIs, which may be uptitrated relatively rapidly, the dose titration of beta blockers should proceed no sooner than at 2-week intervals, because the initiation and/or increased dosing of these agents may lead to worsening fluid retention because of the abrupt withdrawal of adrenergic support to the heart and the circulation. Therefore, it is important to optimize the dose of diuretic before starting therapy with beta blockers. If worsening fluid retention

TABLE 28-9 Mortality Rates in Placebo-Controlled Trials*

TRIAL NAME	AGENT	NYHA CLASS	NO. OF PATIENTS IN STUDY	12-MO PLACEBO MORTALITY (%)	12-MO EFFECT SIZE (%)	*P* VALUE AT 12 MO (FULL FOLLOW-UP)
ACEIs						
HF						
CONSENSUS-1	Enalapril	IV	253	52	↓31	0.01(0.0003)
SOLVD-Rx	Enalapril	I-III	2569	15	↓21	0.02 (0.004)
SOLVD-Asx	Enalapril	I, II	4228	5	0	0.82 (0.30)
Post-MI						
SAVE	Captopril	—	2231	12	↓18	0.11 (0.02)
AIRE	Ramipril	—	1986	20	↓22	0.01 (0.002)
TRACE	Trandolapril	—	1749	26	↓16	0.046 (0.001)
ARBs						
HF						
VAL-HeFT	Valsartan	II-IV	5010	9	0	NS (0.80)
CHARM-Alternative	Candesartan	II-IV	2028	8	↓14	NS
CHARM-Added	Candesartan	II-IV	2548	8	↓12	NS
Aldosterone Antagonists						
HF						
RALES	Spironolactone	III, IV	1663	24	↓25	NS (<0.001)
Post-MI						
EPHESUS	Eplerenone	I	6632	12	↓15	NS (0.005)
Beta Blockers						
HF						
CIBIS-I	Bisoprolol	III, IV	641	21	↓20†	NS (0.22)
U.S. Carvedilol	Carvedilol	II, III	1094	8	↓66†	NS (< 0.001)
ANZ-Carvedilol	Carvedilol	I-III	415	NS	NS	NS (>0.1)
CIBIS-II	Bisoprolol	III, IV	2647	12	↓34†	NS (0.001)
MERIT-HF	Metoprolol CR	II-IV	3991	10	↓35†	NS (0.006)
BEST	Bucindolol	III, IV	2708	23	↓10†	NS (0.16)
COPERNICUS	Carvedilol	Severe	2289	28	↓38†	NS (0.0001)
Post-MI						
CAPRICORN	Carvedilol	I	1959		↓23†	NS (0.03)
BEAT	Bucindolol	I	343	NS	↓12†	NS (0.06)

NOTE: Twelve-month mortality rates were taken from the survival curves when data were not directly available in published material.

*Conducted in patients with chronic HF (EF < 40%) or patients with AMI or at risk for HF.

†Effect size at the conclusion of the trial.

AIRE = Acute Infarction Ramipril Efficacy; BEAT = Bucindolol Evaluation in Acute Myocardial Infarction Trial; BEST = Beta Blocker Evaluation of Survival Trial; CAPRICORN = Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CHARM = Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity; CIBIS = Cardiac Insufficiency Bisoprolol Study; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; MERIT-HF = Metoprolol CR/XL Randomized Interventional Trial in Congestive Heart Failure; NS = not specified; RALES = Randomized Aldactone Evaluation Study; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction; TRACE = Trandolapril Cardiac Evaluation; Val-HeFT = Valsartan Heart Failure Trail.

Modified from Bristow MR, Linas S, Port DJ: Drugs in the treatment of heart failure. *In* Zipes DP, Libby P, Bonow RO, Braunwald E (eds): Braunwald's Heart Disease. 7th ed. Philadelphia, Elsevier, 2004, p 573.

does occurs, it is likely to occur within 3 to 5 days of initiating therapy, and will be manifested as an increase in body weight and/or symptoms of worsening HF. The increased fluid retention can usually be managed by increasing the dose of diuretics. Patients need not be taking high doses of ACEIs before being considered for treatment with a beta blocker, because most patients enrolled in the beta blocker trials were not taking high doses of ACEIs. Furthermore, in patients taking a low dose of an ACEI, the addition of a beta blocker produces a greater improvement in symptoms and reduction in the risk of death than an increase in the dose of the ACEI. It has been shown that beta blockers can be safely started before discharge, even in patients hospitalized for HF, provided that the patient is stable and does not require intravenous HF therapy. Contrary to early reports, the aggregate results of clinical trials suggest that beta blocker therapy is well tolerated by the great majority of HF patients (>85%), including patients with comorbid conditions such as diabetes mellitus, chronic obstructive lung disease, and peripheral vascular disease. Nonetheless, there is a subset of patients (10% to 15%) who remain intolerant to beta blockers because of worsening fluid retention or symptomatic hypotension.

The first placebo-controlled multicenter trial with a beta-blocking agent was the Metoprolol in Dilated Cardiomyopathy (MDC) trial, which used the shorter-acting tartrate preparation at a target dose of 50 mg three times daily in symptomatic HF patients with idiopathic dilated cardiomyopathy. Metoprolol tartrate at an average dose of 108 mg/day reduced the prevalence of the primary endpoint of death or need for cardiac transplantation by 34%, which did not quite reach statistical significance ($P = 0.058$). The benefit was entirely the result of a reduction in the morbidity component of the primary endpoint by metoprolol, with no favorable trends in the mortality component of the primary endpoint. A more efficacious formulation of metoprolol was subsequently developed, metoprolol succinate CR/XL, which has a better pharmacologic profile than metoprolol tartrate because of its controlled-release profile and longer half-life. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), metoprolol CR/XL provided a significant relative risk reduction of 34% reduction in mortality in subjects with mild to moderate HF and moderate to severe systolic dysfunction when compared with the placebo group (**Fig. 28-17**).[30] Importantly, metoprolol CR/X reduced mortality from both sudden death and progressive pump failure. Furthermore, mortality was reduced across most demographic groups, including older versus younger subjects, nonischemic versus ischemic cause, and lower versus higher ejection fractions.

Bisoprolol is a second-generation $beta_1$ receptor–selective blocking agent, with approximately 120-fold higher affinity for human $beta_1$ versus $beta_2$ receptors. The first trial performed with bisoprolol was the Cardiac Insufficiency Bisoprolol Study I (CIBIS-I) trial, which examined the

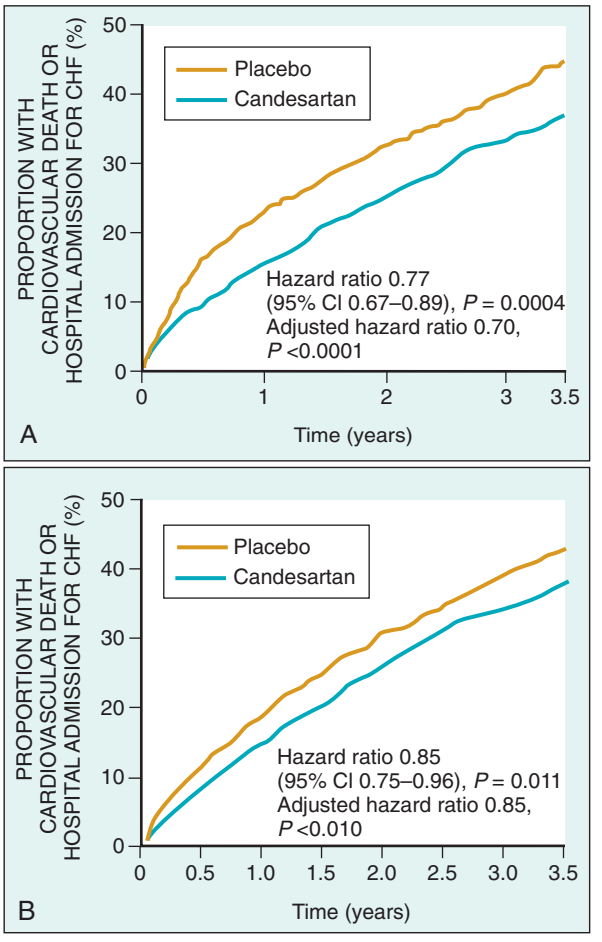

FIGURE 28-16 Effect of candesartan on cardiovascular mortality or hospital admission for heart failure in the CHARM-Alternative trial **(A)** and the CHARM-Added trial **(B)**. Two groups of patients who were randomized to candesartan or placebo are depicted—patients who were not receiving an ACEI **(A)** and patients who were receiving an ACEI **(B)**. The effect size of candesartan was reduced in the group of patients who were receiving an ACEI. *(Modified from Granger CB, McMurray JJ, Yusuf S, et al: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-Alternative trial. Lancet 362:772, 2003; and McMurray JJ, Ostergren J, Swedberg K, et al: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: The CHARM-Added trial. Lancet 362:767, 2003.)*

effects of bisoprolol on mortality in subjects with symptomatic ischemic or nonischemic cardiomyopathy. CIBIS-I showed a nonsignificant (P = 0.22) 20% risk reduction for mortality at 2-year follow-up. Because the sample size for CIBIS-I was based on an unrealistically high expected event rate in the control group, a follow-up trial with more conservative effect size estimates and sample size calculations was conducted. In CIBIS-II, bisoprolol reduced all-cause mortality by 32% (11.8% versus 17.3%; P = 0.002), sudden cardiac death by 45% (3.6% versus 6.4%; P = 0.001), HF hospitalizations by 30% (11.9% bisoprolol versus 17.6% placebo; P < 0.001), and all-cause hospitalizations by 15% (33.6% versus 39.6%; P = 0.002; see Fig. 28-17). The CIBIS-III trial addressed the important question of whether an initial treatment strategy using the beta blocker bisoprolol was noninferior to a treatment strategy of using an ACEI (enalapril) first in patients with newly diagnosed mild to moderate HF. The two strategies were compared in a blinded manner with regard to the combined primary endpoint of all-cause mortality or hospitalization, and with regard to each of the components of the primary endpoint individually. In the per-protocol primary endpoint analysis (the most conservative approach with regard to noninferiority), death or rehospitalization occurred in 32.4% of the bisoprolol-first strategy and 33.1% of the enalapril-first strategy (HR, 0.97; 95% CI, 0.78 to 1.21; P = 0.046 for noninferiority), which missed the prespecified criteria for noninferiority of an

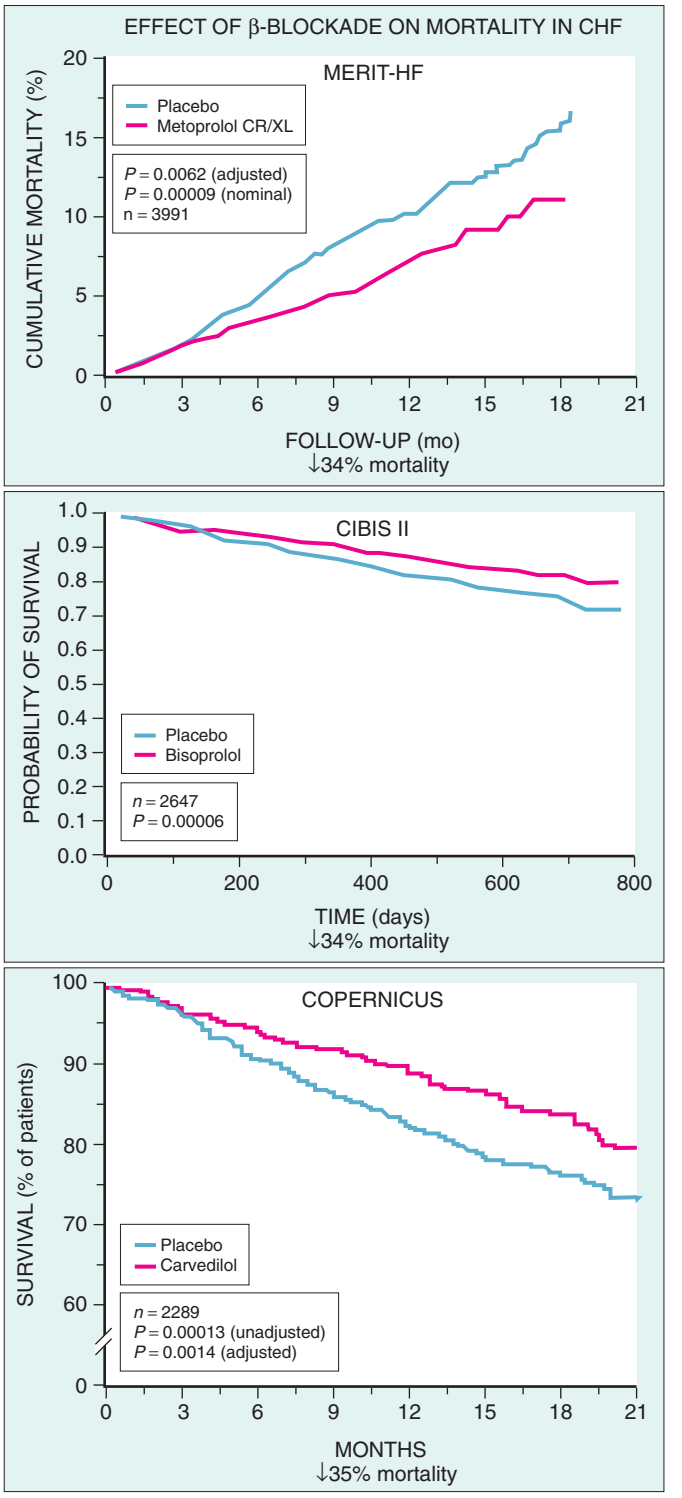

FIGURE 28-17 Kaplan-Meier analysis of the probability of survival in patients in the placebo and beta blocker groups in the MERIT-HF (top), CIBIS II (middle), and COPERNICUS (bottom) trials. CHF = chronic heart failure. *(Data from The Cardiac Insufficiency Bisoprolol Study II [CIBIS-II]: A randomised trial. Lancet 353:9, 1999; Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure [MERIT-HF]. Lancet 353:2001, 1999; and Packer M, Coats AJ, Fowler MB, et al: Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 344:1651, 2001.)*

HR 1.17. However, when the data were analyzed using an intent to treat analysis, bisoprolol was shown to be noninferior to enalapril (HR, 0.94; 95% CI, 0.77 to 1.16; $P = 0.019$ for noninferiority). Although CIBIS-III did not provide clear-cut evidence to justify starting with a beta blocker first, the overall safety profile of the two strategies was similar. Current guidelines continue to recommend starting with an ACEI first, followed by the subsequent addition of a beta blocker.

Of the three beta blockers that are approved for the treatment of HF, carvedilol has been studied most extensively (see Table 28-9). The phase III U.S. Trials Program, composed of four individual trials managed by a single Steering and Data and Safety Monitoring Committee, was stopped prematurely because of a highly significant ($P < 0.0001$) 65% reduction in mortality by carvedilol observed across all four trials. This was followed by a second study, the Australia-New Zealand Heart Failure Research Collaborative Group Carvedilol Trial (ANZ-Carvedilol), which showed that there was a significant improvement in LVEF ($P < 0.0001$) and a significant reduction ($P = 0.0015$) in LV end-diastolic volume index in the carvedilol-treated group at 12 months, as well as a significant relative risk reduction of 26% in the clinical composite of death or hospitalization for the carvedilol group at 19 months. Rates of hospitalization were also significantly lower for patients treated with carvedilol (48%) compared with placebo (58%). The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study extended these benefits to patients with more advanced HF. In COPERNICUS patients with advanced HF, symptoms had to be clinically euvolemic and the LVEF less than 25%. When compared with placebo, carvedilol reduced the mortality risk at 12 months by 38% (see Table 28-9) and the relative risk of death or HF hospitalization by 31% (see Fig. 28-17). Carvedilol has also been evaluated in a post-MI trial in which patients had to exhibit LV dysfunction. The Carvedilol Post-Infarct Survival Controlled Evaluation (CAPRICORN) trial was a randomized, placebo-controlled trial designed to test the long-term efficacy of carvedilol on morbidity and mortality in patients with post-MI LV dysfunction already treated with ACEIs.[39] Although carvedilol did not reduce the prespecified primary end point of mortality plus cardiovascular hospitalization, it did significantly reduce total mortality by 23% ($P = 0.03$), cardiovascular mortality by 25% ($P < 0.05$), and nonfatal MI by 41% ($P = 0.014$). Finally, in the Carvedilol or Metoprolol European Trial (COMET), carvedilol (target dose, 25 mg twice daily) was compared with immediate-release metoprolol tartrate (target dose, 50 mg twice daily) with respect to the primary endpoint of all-cause mortality. In COMET, carvedilol was associated with a significant 33% reduction in all-cause mortality when compared with metoprolol tartrate (33.9% versus 39.5%; HR, 0.83; 95% CI, 0.74 to 0.93; $P = 0.0017$).[40] Based on the results of the COMET trial, short-acting metoprolol tartrate is not recommended for use in the treatment of HF. The results of the COMET trial emphasize the importance of using doses and formulations of beta blockers that have been shown to be effective in clinical trials. There have been no trials to ascertain whether the survival benefits of carvedilol are greater than those of metoprolol succinate CR/XL when both drugs are used at the appropriate target doses.

Not all studies with beta blockers have been universally successful, suggesting that the effects of beta blockers should not necessarily be viewed broadly as a class effect. Early studies with the first generation of non-specific $beta_1$ and $beta_2$ receptors without ancillary vasodilating properties (e.g., propranolol) resulted in significant worsening of HF and death. The Beta blocker Evaluation of Survival Trial (BEST) evaluated the third-generation beta-blocking agent bucindolol, which is a completely nonselective $beta_1$ and $beta_2$ blocker with some $alpha_1$ receptor blockade. In the BEST trial, bucindolol produced a statistically nonsignificant ($P = 0.10$) 10% reduction in total mortality that was heterogeneous with respect to race. That is, the 76% of subjects in BEST who were not black had a statistically significant ($P = 0.01$), 19% reduction in mortality, whereas the 24% who were black had a nonsignificant trend for an increase (by 17%) in mortality (interaction P value < 0.05). The differential response of bucindilol in white patients has been suggested to be secondary to a polymorphism (arginine 389) in the $beta_1$-adrenergic receptor (see Chap. 33).[41] Bucindolol is not currently approved for clinical use at this time.

Furthermore, not all antiadrenergic strategies are beneficial in HF patients. For example, moxonidine is a centrally acting imidazoline receptor antagonist that powerfully lowers adrenergic activity. In the Moxonidine in Heart Failure (MOXCON) trial, moxonidine SR or matching placebo was titrated to a target dose of 1.5 mg twice daily.[42] This trial was stopped prematurely because of early increase in death rate (~50% increase) and adverse events in the moxonidine SR group when compared with placebo. Analysis of norepinephrine (NE) levels showed that NE levels were significantly less in the moxonidine treatment arm, suggesting that generalized sympathetic inhibition (withdrawal) may be deleterious in patients with HF. Nebivolol is a selective $beta_1$ receptor antagonist, not yet approved for the treatment of HF, with ancillary vasodilatory properties that are mediated, at least in part, by nitric oxide. In the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS), nebivolol significantly (HR, 0.86; 95% CI, 0.74 to 0.99; $P < 0.04$) reduced the composite outcome of death or cardiovascular hospitalizations in older patients comparing nebivolol with placebo ($P < 0.04$) with a known EF ≤ 35% or a previous hospitalization for HF within 1 year (35% had an EF > 35%).[43] In a prespecified subgroup analysis, the effects of nebivolol versus placebo on death or cardiovascular hospitalizations were found to be of similar magnitude in HF patients with depressed and preserved EF.

Side Effects of Beta Blockers

The adverse affects of beta blockers are generally related to the predictable complications that arise from interfering with the adrenergic nervous system. These reactions generally occur within several days of initiating therapy and are generally responsive to adjusting concomitant medications (see earlier). The problem of fluid retention has been discussed. Treatment with a beta blocker can be accompanied by feelings of general fatigue or weakness. In most cases, the increased fatigue spontaneously resolves within several weeks or months; however, in some patients, it may be severe enough to limit the dose of beta blocker or require the withdrawal or reduction of treatment. Therapy with beta blockers can lead to bradycardia and/or exacerbate heart block. Moreover, beta blockers (particularly those that block the $alpha_1$ receptor) can lead to vasodilatory side effects. Accordingly, the dose of beta blockers should be decreased if the heart rate decreases to less than 50 beats/min and/or second- or third-degree heart block or symptomatic hypotension develops. Beta blockers are not recommended for patients with asthma with active bronchospasm

ALDOSTERONE ANTAGONISTS. Although classified as potassium-sparing diuretics, drugs that block the effects of aldosterone (e.g., spironolactone) have beneficial effects that are independent of the effects of these agents on sodium balance (see Fig. 28-11). Although ACEIs may transiently decrease aldosterone secretion, with chronic therapy there is a rapid return of aldosterone to levels similar to those before ACEIs. The administration of an aldosterone antagonist is recommended for patients with NHA Class III (previously Class IV) or IV HF who have a depressed EF (<35%), and are receiving standard therapy, including diuretics, ACEIs, and beta blockers.[30] It is possible that the indications for the use of aldosterone antagonists will be expanded when the results of the EMPHASIS-HF trial are published. The dose of aldosterone antagonist should be increased until the doses used are similar to those that have been shown to be effective in clinical trials (see Table 28-8). Spironolactone should be initiated at a dose of 12.5 to 25 mg daily or, occasionally, on alternate days. Eplerenone was used after MI in one study at doses of 25 mg/day, increasing to 50 mg daily (see Table 28-9). As noted, potassium supplementation is generally stopped after the initiation of aldosterone antagonists, and patients should be counseled to avoid high potassium-containing foods. Potassium levels and renal function should be rechecked within 3 days and again at 1 week after initiation of an aldosterone antagonist. Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status but should be done at least monthly for the first 6 months.

Side Effects of Aldosterone Antagonists

The major problem with the use of aldosterone antagonists is the development of life-threatening hyperkalemia, which is more prone to occur in patients who are receiving potassium supplements or who have underlying renal insufficiency. Aldosterone antagonists are not recommended when the serum creatinine level is higher than 2.5 mg/dL (or creatinine clearance < 30 mL/min) or the serum potassium level is higher than 5.5 mmol/liter. The development of worsening renal function should lead to consideration of stopping aldosterone antagonists because of the potential risk of hyperkalemia. Painful gynecomastia may develop in 10% to 15% of patients who use spironolactone, in which case eplerenone may be substituted.

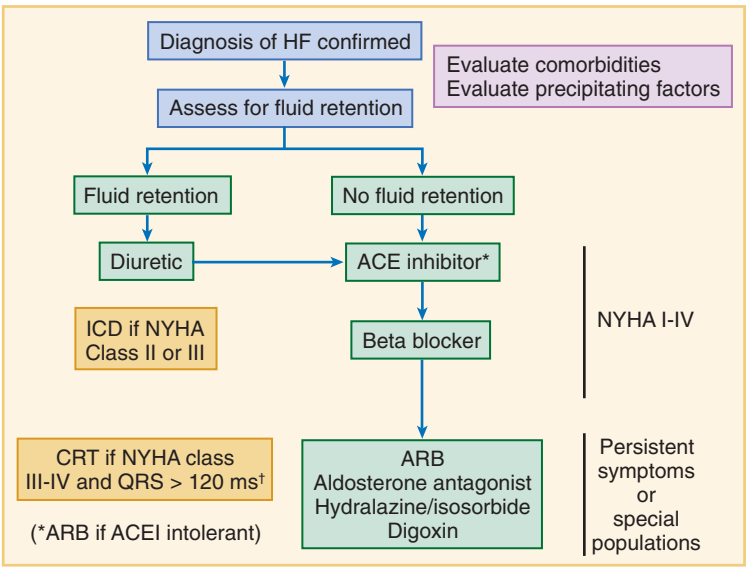

FIGURE 28-18 Treatment algorithm for patients with chronic heart failure with a reduced EF. After the clinical diagnosis of HF is made, it is important to treat the fluid retention that the patient experienced before starting an ACEI (or an ARB if the patient is ACEI-intolerant). Beta blockers should be started after the fluid retention has been treated and/or the ACEI has been uptitrated. If the patient remains symptomatic, an ARB or aldosterone antagonist or digoxin can be added as triple therapy. The fixed-dose combination of hydralazine and isosorbide dinitrate should be added to an ACEI and beta blocker in African American patients with NYHA Classes II-IV HF. Device therapy should be considered in addition to pharmacologic therapy in appropriate patients. †The Centers for Medicare & Medicaid Services (CMS) has expanded the coverage for CRT-defibrillators (CRT-D) to include patients with left bundle branch block with a QRS ≥130 ms, an EF ≤30% and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure. Updated practice guidelines will likely reflect the expanded CMS indications for use of CRT-D. *(Modified from Mann DL: Heart failure and cor pulmonale.* In *Kasper DL, Braunwald E, Fauci AS, et al: Harrison's Principles of Internal Medicine. 17th ed. New York, McGraw-Hill, 2007, p 1450.)*

Management of Patients Who Remain Symptomatic

As noted, an ACEI (or an ARB) plus a beta blocker should be standard background therapy for HF patients with a depressed LVEF. Additional pharmacologic therapy (polypharmacy) or device therapy (see later) should be considered in patients who have persistent symptoms or progressive worsening despite optimized therapy with an ACEI and beta blocker (**Fig. 28-18**; see Table 28-9). Agents that may be considered as part of additional therapy include an ARB (NYHA Classes II to IV), spironolactone (NYHA Classes III to IV), the combination of hydralazine and isosorbide dinitrate (NYHA Classes III to IV), or digitalis.[30] The optimal choice of additional drug therapy to improve outcome further in patients has not been firmly established. Thus, the choice of specific agent will be influenced by clinical considerations, including renal function, serum potassium concentration, blood pressure, and race (see later). The triple combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended because of the risk of hyperkalemia. Digoxin is recommended for patients with symptomatic LV systolic dysfunction who have concomitant atrial fibrillation, and should be considered for patients who have signs or symptoms of HF while receiving standard therapy, including ACEIs and beta blockers.

CARDIAC GLYCOSIDES. Digoxin and digitoxin are the most frequently used cardiac glycosides. Given that digoxin is most commonly used, and is the only glycoside that has been evaluated in placebo-controlled trials, there is little reason to prescribe other cardiac glycosides for the management of patients with chronic HF. Digoxin exerts its effects by inhibiting the Na^+,K^+-ATPase pump in cell membranes, including the sarcolemmal Na^+,K^+-ATPase pump of cardiac myocytes (see Chap. 25). Inhibition of the Na^+,K^+-ATPase pump leads to an increase in intracellular calcium and hence increased cardiac contractility, which has led to the suggestion that beneficial effects of digoxin are secondary to its inotropic properties. However, the more likely mechanism of digoxin in HF patients is to sensitize Na^+,K^+-ATPase activity in vagal afferent nerves, leading to an increase in vagal tone that counterbalances the increased activation of the adrenergic system in advanced HF. Digoxin also inhibits Na^+,K^+-ATPase activity in the kidney and may therefore blunt renal tubular resorption of sodium. Therapy with digoxin is commonly initiated and maintained at a dose of 0.125 to 0.25 mg daily. For most patients, the dose should be 0.125 mg daily and the serum digoxin level should be less than 1.0 ng/mL, especially in older patients, patients with impaired renal function, and patients with a low lean body mass. Higher doses (e.g., digoxin > 0.25 mg daily) are rarely used and/or not recommended for the management of HF patients in sinus rhythm or those who have atrial fibrillation. Further details about digitalis, including details about mechanism of action, pharmacokinetics, and interaction with other commonly used drugs can be found in the online supplement (see digitalis supplement on the website).

Although clinicians have used cardiac glycosides to treat patients with chronic HF for more than 200 years, there is still considerable debate regarding the effectiveness of the cardiac glycosides for HF patients. Whereas small and medium-sized trials conducted in the 1970s and 1980s yielded equivocal results, two relatively large digoxin withdrawal studies in the early 1990s, the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) and the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED), provided strong support for clinical benefit from digoxin.[44] In these studies, worsening HF and HF hospitalizations developed in more patients who were withdrawn from digoxin than in patients who were maintained on digoxin.

Insofar as withdrawal studies are difficult to interpret with respect to the efficacy of a given therapeutic agent, the Digoxin Investigator Group (DIG) trial was conducted to address the role of digitalis in chronic HF prospectively. Although the DIG trial showed that digoxin had a neutral effect on the primary endpoint of mortality, digoxin reduced hospitalizations and favorably affected the combined endpoints of death or hospitalization caused by worsening HF. Data from the DIG trial have indicated a strong trend ($P = 0.06$) toward a decrease in deaths secondary to progressive pump failure, which was offset by an increase in sudden and other non–pump failure cardiac deaths ($P = 0.04$). One of the most important findings to emerge from the DIG trial was that mortality is directly related to the digoxin serum level.[44] In men enrolled in the DIG trial, trough levels between 0.6 and 0.8 ng/mL were associated with decreased mortality, suggesting that trough levels of digitalis should be maintained between 0.5 and 1.0 ng/mL. There is also evidence that digoxin may be potentially harmful in women. In a post hoc multivariable analysis of the DIG trial, digoxin was associated with a significantly higher risk (23%) of death from any cause among women, but not men, possibly because of the relatively lower body weights in women, who were prescribed doses of digoxin on the basis of a nomogram rather than on trough levels.[45] The DIG trial was conducted prior to the widespread use of beta blockers, and no large trial of digoxin in addition to therapy with both ACEIs and beta blockers is available.

Complications of Digoxin Use

The principal adverse effects of digoxin are as follows: (1) cardiac arrhythmias, including heart block (especially in older patients) and ectopic and reentrant cardiac rhythms; (2) neurologic complaints such as visual disturbances, disorientation, and confusion; and (3) gastrointestinal symptoms such as anorexia, nausea, and vomiting. As noted, these side effects can generally be minimized by maintaining trough levels of 0.5 to 1.0 ng/mL. In patients with HF, overt digitalis toxicity tends to emerge at serum concentrations greater than 2.0 ng/mL; however, digitalis toxicity may occur with lower digoxin levels, particularly if hypokalemia or hypomagnesemia coexist. Oral potassium administration is often useful for atrial, AV junctional, or ventricular ectopic rhythms, even when the serum potassium level is in the normal range, unless high-grade AV block is also present. However, serum K^+ levels must be monitored carefully to avoid hyperkalemia,

especially in patients with renal failure or those taking aldosterone receptor antagonists. Potentially life-threatening digoxin toxicity can be reversed by antidigoxin immunotherapy using purified Fab fragments (see website for details). The concomitant use of quinidine, verapamil, spironolactone, flecainide, propafenone, and/or amiodarone can increase serum digoxin levels and may increase the risk of adverse reactions (see website). Patients with advanced heart block should not be given digitalis unless a pacemaker is in place.

N-3 POLYUNSATURATED (OMEGA-3) FATTY ACIDS. There is a large body of experimental evidence suggesting that n-3 polyunsaturated fatty acids (n-3 PUFAs; omega-3 fatty acids) have favorable effects on inflammation, including a reduction of endothelial activation and production of inflammatory cytokines, platelet aggregation, autonomic tone, blood pressure, heart rate, and LV function. The GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure) study has shown that long-term administration of 1 g/day of omega-3 fatty acids results in a significant reduction in both all-cause mortality (adjusted HR, 0.91; 95.5% CI, 0.83 to 0.99; $P = 0.041$) and all-cause mortality and cardiovascular admissions (adjusted HR, 0.92; 99% CI, 0.85 to 0.99; $P = 0.009$) in all the predefined subgroups, including HF patients with nonischemic cardiomyopathy.[46] Although omega-3 fatty acids are not endorsed by current practice guidelines, their use may be considered for patients who remain symptomatic despite optimal medical therapy.

Management of Atherosclerotic Disease

The clinical evaluation of atherosclerotic cardiovascular heart disease in HF patients is discussed in Chap. 26. In patients with a prior MI and HF without angina, the use of ACEIs and beta blockers has been shown to decrease the risk of reinfarction and death. Although aspirin has been shown to reduce the risk of major ischemic events in patients without HF, the role of aspirin in patients with HF has not been clearly established.[30] Prior studies have suggested that the use of aspirin may attenuate the beneficial effects of ACEIs in HF patients. For these reasons, the role of aspirin in preventing ischemic events in patients with chronic HF remains controversial. Alternative antiplatelet agents (e.g., clopidogrel) may not interact adversely with ACEIs and may have superior effects in preventing clinical events; however, their ability to affect outcomes favorably in HF has not been demonstrated. Although some clinicians recommend the use of coronary revascularization in patients with HF and CAD who do not have symptoms of angina, coronary revascularization has not been shown to improve cardiac function or symptoms or prevent reinfarction or death in HF patients without angina. In contrast, coronary artery bypass grafting has been shown to improve symptoms and survival in patients with modestly reduced EF and angina, although patients with clinical HF or markedly depressed ventricular function have generally been excluded from these studies. To this end, an ongoing National Institutes of Health–funded trial is evaluating the usefulness of surgical revascularization in such patients (see Chap. 31). Until the results of randomized clinical trials are forthcoming, it is reasonable to consider coronary artery revascularization with coronary artery bypass surgery or percutaneous coronary intervention for HF patients who have suitable coronary anatomy and angina or for patients who have demonstrable evidence of myocardial viability in areas of significant obstructive coronary disease and/or the presence of inducible ischemia.[30] The surgical management of patients with CAD disease and HF is discussed in Chap. 31.

Special Populations

WOMEN. Although women account for a significant proportion of those affected by the growing heart failure epidemic, they have been poorly represented in clinical trials (see Chap. 81). Women with heart failure are more likely to be older (see Fig. 28-1) and to have a preserved HF (see Chap. 30) and nonischemic cause for their HF. Although clinical trials have demonstrated improved outcomes among HF patients with a depressed EF, they have mainly included men and have been often been powered inadequately to detect a benefit in women. Nonetheless, pooled analyses of several large-scale prospective clinical trials with beta blockers and ACEIs have suggested that these agents provide similar survival benefits in women with systolic dysfunction, as in men.[47] In addition, some studies have suggested that ARBs may result in improved survival in women when compared with ACEIs.

RACE. Epidemiologic (see earlier) and clinical trial data have raised awareness of potential areas of concern regarding the evaluation and treatment of HF in blacks (see Chap. 2). A retrospective analysis, the Vasodilator in Heart Failure Trial I (V-HeFT I) has suggested that overall mortality and HF hospitalization are significantly reduced in black patients who receive combination therapy with hydralazine and isosorbide, whereas white patients show no treatment effect when compared with placebo. In contrast, in V-HeFT II, only white patients showed a significant mortality reduction from ACEI therapy (enalapril) when compared with treatment with hydralazine and isosorbide, whereas black patients had no apparent treatment benefit from ACEIs.[7] To address the role of hydralazine plus isosorbide treatment in blacks, the African-American Heart Failure Trial (A-HeFT) compared the adjunctive use of a proprietary formulation of isosorbide dinitrate and hydralazine to a standard HF regimen of ACEIs, beta blockers, and diuretics in blacks with NYHA Class III or IV HF.[48] The primary endpoint was a composite score made up of weighted values for death from any cause, a first hospitalization for HF, and change in the quality of life. The study was terminated early because there was a significant 43% reduction in the rate of death from any cause (see Fig. 2-6). and a significant 33% relative reduction in the rate of first hospitalization for HF. The mechanism for the beneficial effect of the hydralazine and isosorbide regimen may be related to improved nitric oxide bioavailability; however, the combination therapy group also had a small (but significant) effect of blood pressure lowering. The effect of this combination of isosorbide dinitrate and hydralazine in other HF patients who are being treated with standard therapy is not known because the population studied in A-HeFT was limited to blacks. However, there is no reason to believe that this benefit is limited to blacks. The results of the A-HeFT trial have suggested that the addition of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACEIs and beta blockers, is reasonable and can be effective in blacks with NYHA functional Class III or IV HF (see Fig. 28-18). The emerging field of genomic medicine has begun to suggest that important variances in the expression of certain high-risk, single-nucleotide polymorphisms may be evident along racial lines and may provide a physiologic basis for differences in the natural history of HF and in drug responsiveness (see Chaps. 10 and 33).

OLDER PATIENTS. As noted, the prevalence of HF increases with age (see Fig. 28-1) and is the most common reason for hospitalization in older patients (see Chap. 80). Of note, the presentation of HF may differ in older patients. Although they commonly present with the classic symptoms of dyspnea and fatigue, they are more likely than younger patients to present with atypical symptoms such as altered mental status, depression, or poor executive functioning.[49] The therapeutic approach to HF with a reduced EF in older patients should be, in principal, identical to that in younger patients with respect to the choice of pharmacologic therapy. However, altered pharmacokinetic and pharmacodynamic properties of cardiovascular drugs in older patients may require that these therapies be applied more cautiously, with reductions in drug dosages when appropriate. Other complicating factors may include blunting of baroreceptor function and orthostatic dysregulation of blood pressure, which may make it difficult to use target doses of some neurohormonal antagonists. Multidisciplinary HF programs have been successful in decreasing the rate of readmission and associated morbidity in older patients (see later).

CANCER PATIENTS. Patients with cancer are particularly predisposed to the development of HF as a result of the cardiotoxic effects of many cancer chemotherapeutic agents. The management of these patients is discussed in Chap. 90.

Anticoagulation and Antiplatelet Therapy

Patients with HF have an increased risk for arterial or venous thromboembolic events. In clinical HF trials, the rate of stroke ranges from 1.3% to 2.4%/year. Depressed LV function is believed to promote relative stasis of blood in dilated cardiac chambers with increased risk of thrombus formation. Treatment with warfarin (goal international normalized ratio [INR] = 2.0 to 3.0) is recommended for all patients with HF and chronic or paroxysmal atrial fibrillation and a history of systemic or pulmonary emboli, including stroke or transient ischemic attack. Patients with symptomatic or asymptomatic ischemic cardiomyopathy and a documented, recent, large anterior MI or recent MI with documented LV thrombus should be treated with warfarin (goal INR, 2.0 to 3.0) for the initial 3 months after MI unless there are contraindications. In the absence of these indications, the optimal strategy to prevent stroke in individuals with HF is less certain.

Although warfarin was associated with a reduction in cardiovascular events and death in a retrospective analysis of the SOLVD studies, no difference in antiplatelet or anticoagulant therapy has been observed in other retrospective analyses. To date, two prospective randomized trials of anticoagulation in HF have been published; however, both of these trials were underpowered to show a difference in clinical outcomes. The Warfarin/Aspirin Study in Heart Failure (WASH) showed no differences in the combined primary outcomes of death, MI, or stroke for HF patients who were randomized to receive warfarin (INR target, 2.5), 300 mg aspirin, or no treatment.[50] In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, patients with symptomatic heart failure and reduced EF were randomized to aspirin, 162 mg/day, clopidogrel, 75 mg/day, or open-label warfarin to achieve an INR of 2.5 to 3.[50] There was no difference in the primary outcome measure of death, nonfatal MI, or nonfatal stroke, although warfarin was associated with fewer nonfatal strokes compared with aspirin or clopidogrel. To address this important question more effectively, the National Institutes of Neurological Disorders and Stroke (NINDS) is conducting the WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) trial (ClinicalTrials.gov identifier, NCT00041938), to determine whether there are differences between warfarin (INR = 2.5 to 3) and aspirin (325 mg) with respect to event-free survival for the composite endpoint of all-cause mortality and stroke or stroke (ischemic or hemorrhagic). At present, in the absence of strong data, the decision to anticoagulate must be an individual one in patients with dilated cardiomyopathy and EF ≤35%. Currently, aspirin is recommended in HF patients with ischemic heart disease for the prevention of MI and death. However, lower doses of aspirin (75 or 81 mg) may be preferable because of the concern of worsening of HF at higher doses, as noted above.

Management of Cardiac Arrhythmias

The management of atrial arrhythmias is discussed in detail in Chaps. 39 and 40. Briefly, atrial fibrillation occurs in 15% to 30% of patients with HF, and is a frequent cause of cardiac decompensation (see Table 28-6). Most antiarrhythmic agents, with the exception of amiodarone and dofetilide, have negative inotropic effects and are proarrhythmic. Amiodarone is a Class III antiarrhythmic that has little or no negative inotropic and/or proarrhythmic effects, and is effective against most supraventricular arrhythmias. Amiodarone is the preferred drug for restoring and maintaining sinus rhythm, and may improve the success of electrical cardioversion in patients with HF. Amiodarone increases the level of phenytoin and digoxin and will prolong the INR in patients taking warfarin. Therefore, it is often necessary to reduce the dose of these drugs by as much as 50% when initiating therapy with amiodarone. The risk of adverse events such as hyperthyroidism, hypothyroidism, pulmonary fibrosis, and hepatitis is relatively low, particularly when lower doses of amiodarone are used (100 to 200 mg/day). Dronedarone is a novel antiarrhythmic drug that reduces the incidence of atrial fibrillation and atrial flutter and has electrophysiologic effects similar to those of amiodarone but does not contain iodine, and thus does not cause iodine-related adverse reactions. Although dronedarone was significantly more effective than placebo in maintaining sinus rhythm in several studies, the ANDROMEDA trial (European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure) had to be terminated prematurely because of a twofold increase in mortality (HR, 2.13; 95% CI, 1.07 to 4.25; $P = 0.167$) in the dronedarone-treated HF patients.[51] The excess mortality was predominantly related to worsening of heart failure. As a result of this study, dronedarone is contraindicated in patients with Class IV heart failure or those with Class II or III heart failure who have had a recent heart failure decompensation. Because of the risk of proarrhythmic effects of antiarrhythmic agents in patients with LV dysfunction, it is preferable to treat ventricular arrhythmias with implantable cardiac defibrillators (ICDs), either alone or in combination with amiodarone (see Chap. 29).

Device Therapy

CARDIAC RESYNCHRONIZATION. Cardiac resynchronization therapy (CRT) is discussed in detail in Chaps. 29 and 38. When CRT is added to optimal medical therapy in patients in sinus rhythm, there is a significant decrease in patient mortality and hospitalization, a reversal of LV remodeling, and improved quality of life and exercise capacity.[52] Implantation of a biventricular pacing device should be considered for patients with NYHA Class III or IV HF with a depressed EF (<30% to 35%) who are already on optimal background therapy, including an ACEI, ARB, beta blocker, or aldosterone antagonist for several months (see Fig. 28-18).

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS. ICDs are discussed in detail in Chaps. 29, 38, and 41. Briefly, the prophylactic implantation of ICDs in patients with mild to moderate HF (NYHA Class II or III) has been shown to reduce the incidence of sudden cardiac death in patients with ischemic or nonischemic cardiomyopathy. Accordingly, implantation of an ICD should be considered for patients with NYHA Class II or III HF with a depressed EF (<30% to 35%) who are already on optimal background therapy including an ACEI, ARB, beta blocker, or aldosterone antagonist for several months, and who have a reasonable expectation of survival with good functional status for longer than 1 year (see Fig. 28-18).

Sleep-Disordered Breathing

The general topic of sleep disorders in cardiovascular disease is discussed in detail in Chap. 79. HF patients with a reduced EF (<40%) commonly exhibit sleep-disordered breathing; approximately 40% of patients exhibit central sleep apnea (CSA), commonly referred to as Cheyne-Stokes breathing (see Chap. 26), whereas another 10% exhibit obstructive sleep apnea (OSA). CSA associated with Cheyne-Stokes respiration is a form of periodic breathing in which central apnea and hypopnea alternate with periods of hyperventilation that have a waxing-waning pattern of tidal volume. Risk factors for the development of CSA in HF patients include male gender, age older than 60 years, presence of atrial fibrillation, and hypocapnia.[53] **Figure 28-19** illustrates the proposed mechanisms that underlie periodic oscillations in ventilation in HF. The main clinical significance of CSA in HF is its association with increased mortality. Whether this is because Cheyne-Stokes respiration with CSA is a reflection of advanced disease with poor LV function or whether its presence constitutes a separate additional adverse influence on outcomes is not clear. Nevertheless, multivariate analyses have suggested that CSA remains an independent risk factor for death or cardiac transplantation, even after controlling for potentially confounding risk factors. The potential mechanism(s) for adverse outcomes in HF patients with CSA may be attributed to marked neurohumoral activation, especially norepinephrine. Studies have suggested that Cheyne-Stokes respirations can resolve with proper treatment of HF. However, if the patient continues to have symptoms related to sleep-disordered breathing (sleep onset or sleep maintenance insomnia), despite optimization of HF therapies (see Fig. 28-19), the patient should undergo a comprehensive overnight sleep study (polysomnography).

At present, there is no consensus as to how CSA should be treated, or whether CSA should be treated at all. Insofar as CSA is to some extent a manifestation of advanced HF, the first consideration is to optimize drug therapy, including aggressive diuresis to lower cardiac filling

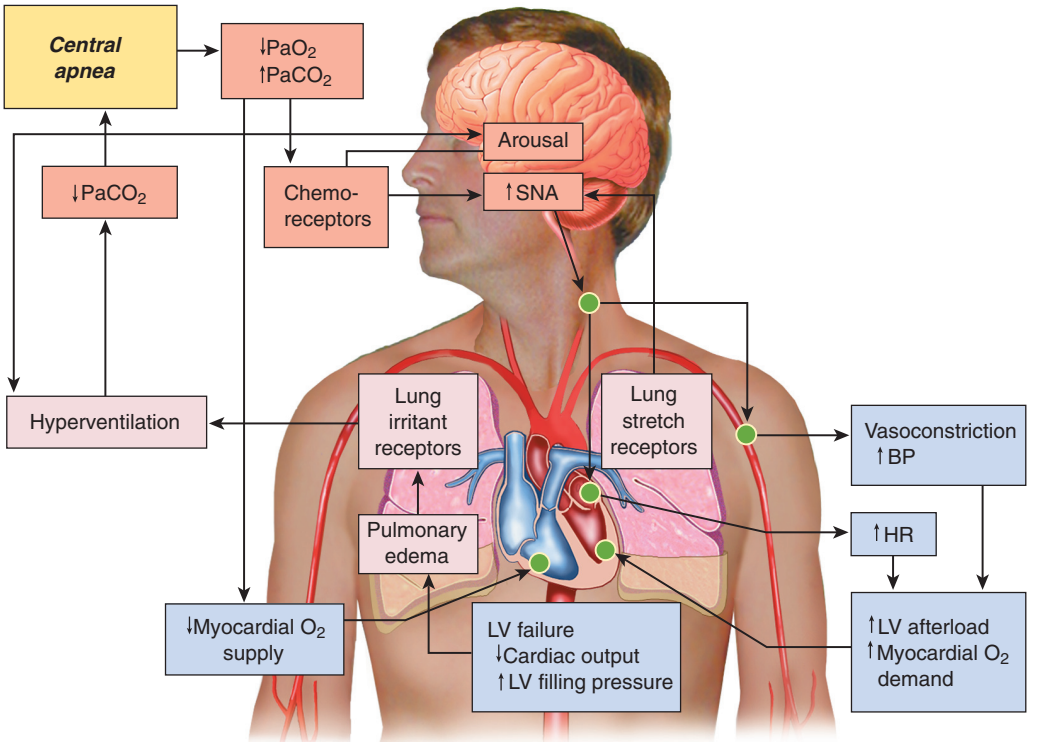

FIGURE 28-19 Pathophysiology of CSA and Cheyne-Stokes respiration in HF. HF leads to increased LV filling pressure. The resulting pulmonary congestion activates lung vagal irritant receptors, which stimulate hyperventilation and hypocapnia. Superimposed arousals cause further abrupt increases in ventilation and drive the partial pressure of carbon dioxide in arterial blood ($Paco_2$) below the threshold for ventilation, triggering a central apnea. CSAs are sustained by recurrent arousal resulting from apnea-induced hypoxia and the increased effort to breathe during the ventilatory phase because of pulmonary congestion and reduced lung compliance. Increased sympathetic activity causes increases in blood pressure (BP) and heart rate (HR) and increases myocardial oxygen (O_2) demand in the presence of reduced supply. Pao_2 = partial pressure of oxygen in arterial blood; SNA = sympathetic nervous system activity. *(Modified from Bradley TD, Floras JS: Sleep apnea and heart failure. Part II: Central sleep apnea. Circulation 107:1822, 2003.)*

pressure, along with the use of ACEIs, ARBs, and beta blockers, which may lessen the severity of CSA. In some cases, however, metabolic alkalosis arising from diuretic use may predispose to CSA by narrowing the difference between the circulating $PaCO_2$ level and the $PaCO_2$ threshold necessary for apnea to develop.[53] The use of nocturnal oxygen and devices that provide continuous positive airway pressure has been reported to alleviate CSA, abolish apnea-related hypoxia, decrease nocturnal norepinephrine levels, and produce symptomatic and functional improvement in HF patients when used in the short term (up to 1 month). However, the effects of supplemental oxygen on cardiovascular endpoints over more prolonged periods have not been assessed. Although there is no direct evidence that treatment of sleep-disturbed breathing prevents the development of HF, treatment of established LV dysfunction with continuous positive airway pressure (CPAP) breathing has been shown to improve LV structure and function in patients with OSA or CSA disturbed breathing syndrome. Despite these objective measurements of improvement with CPAP, this treatment modality did not lead to a prolongation of life in the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial.[54] In CANPAP, patients with HF and central sleep apnea were randomly assigned to receive CPAP or no CPAP for a mean duration of 2 years. The trial was discontinued early after the event rate for death or transplantation observed in the trial was too low to detect a difference based on the expected event rate used to determine the sample size for the trial. There was no difference in the primary endpoint of death or transplantation ($P = 0.54$), nor was there a significant difference in the frequency of hospitalization between groups (0.56 versus 0.61 hospitalizations/patient year; $P = 0.45$). Additional studies will be needed to evaluate the efficacy of these types of interventions in HF patients.

Disease Management

Despite the compelling scientific evidence that ACEIs, ARBs, beta blockers, and aldosterone antagonists reduce hospitalizations and mortality in patients with HF, these life-prolonging therapies continue to be underused outside the highly artificial environment of clinical trials. Numerous studies in a variety of different clinical settings have documented that a significant proportion of patients with HF are not receiving treatment with guideline-recommended, evidence-based therapies.[55] The failure to deliver optimal medical care to HF patients is almost certainly multifactorial, as for other complex chronic conditions that have substantial morbidity and mortality. Furthermore, because many HF patients are older and often have a myriad of comorbidities, health care providers face a special challenge. Optimal HF care includes the following: (1) a trained network of providers for the delivery of HF management and interventions, including nurses, case managers, physicians, pharmacists, case workers, dietitians, physical therapists, psychologists, and information systems specialists; (2) a method for communicating this knowledge to the patient, including patient education, education of caregivers and family members, medication management, peer support, or some form of postacute care; (3) a method of ensuring that the patient has received and understood the knowledge; and (4) a system for encouraging adherence to the recommended regimen and patient compliance. Studies have shown that many of the challenges to delivering optimal care to HF patients can be met through an integrated, specialized HF clinical approach that uses nurse and physician extenders to deliver and ensure the implementation of care.[56] Technology-driven strategies that use low-cost telemonitoring also appear promising in terms of improving HF management and outcomes (see Chap. 29),[57] emphasizing the importance of team management in the care of these complex patients. A disease management approach to HF has been shown to reduce hospitalizations and increase the percentage of patients who receive ideal guideline-recommended therapy.[58] Recent studies have demonstrated that disease management programs need not be confined to the outpatient setting; hospital-based disease management systems can also improve medical care and education of hospitalized

HF patients and accelerate the use of evidence-based guideline-recommended therapies by administering them before hospital discharge.[30] Although disease management strategies can lead to improved survival, it is not clear that these strategies are necessarily more cost-effective. Accordingly, the biggest challenge to disease management programs will be to determine how to support the additional personnel required to implement this model of care.

Patients with Refractory End-Stage Heart Failure (Stage D)

Most patients with HF caused by reduced LVEF respond well to evidence-based pharmacologic and nonpharmacologic treatments, and enjoy a good quality of life with a meaningful prolongation. However, for reasons that are not clear, some patients do not improve or will experience a rapid recurrence of symptoms, despite optimal medical and device therapies. These individuals represent the most advanced stage of HF (stage D) and should be considered for specialized treatment strategies, such as mechanical circulatory support (see Chap. 32), continuous intravenous positive inotropic therapy, referral for cardiac transplantation (see Chap. 31), or hospice care. However, before a patient is considered to have refractory HF, physicians should identify any contributing conditions (see Table 28-6) and ensure that all conventional medical strategies have been optimally used (see Fig. 28-18). When no further therapies are appropriate, careful discussion of the prognosis and options for end-of-life care should be initiated (see Chap. 34).

Future Perspectives

As noted, ACEIs, ARBs, aldosterone antagonists, beta blocker therapy, and cardiac devices have substantially improved quality and quantity of life for patients with HF with a reduced EF. Unfortunately, we appear to be limited with regard to further antagonism of neurohormonal-cytokine systems inasmuch as most trials attempting to add additional neurohormonal-cytokine inhibition to the background therapy of ACE inhibition and beta blockade have been unsuccessful. These failures include certain endothelin antagonists, tumor necrosis factor antagonists, and neutral endopeptidase inhibitors, which indicates the potential limits of neurohormonal inhibitory strategies and strongly signals that different drug development approaches are needed. Currently, these approaches are underway, with newer small molecules, cell replacement therapy (see Chap. 11), and gene therapy (see Chap. 33), accompanied by growing appreciation of the role of pharmacogenetics (see Chaps. 10 and 33). Further refinement of device technology and appropriate patient selection may allow device therapies, especially CRT, to be extended to more eligible patients. It is likely that one or more of these therapies that target maladaptive mechanisms and/or cardiac remodeling will soon be successful.

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GUIDELINES

DOUGLAS L. MANN

Management of Heart Failure

A joint task force of the American College of Cardiology and the American Heart Association (ACC/AHA) published guidelines for the evaluation and management of heart failure in 2005[1] and subsequently updated them in 2009.[2] These guidelines superseded previous sets of recommendations issued by the ACC/AHA in 2001[3] and 1995[4] as well as guidelines from the Agency for Health Care Policy and Research in 1994[5] and the Heart Failure Society of America in 1999.[6] New guidelines from the Heart Failure Society were published in 2006,[7] and a complete revision of the Heart Failure Society guidelines will be published in 2010. The most recent European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of chronic heart failure were published in 2008.[8] The current ACC/AHA guidelines classify patients according to four stages, which reflects the growing appreciation for the importance of the prevention of heart failure:

Stage A: patients at high risk for developing heart failure but without structural disorders of the heart

Stage B: patients with a structural disorder of the heart but no symptoms of heart failure

Stage C: patients with past or current symptoms of heart failure associated with underlying structural heart disease

Stage D: patients with end-stage disease who require specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care

The advantage of the four-stage system is that it recommends interventions for asymptomatic patients with the goal of preventing signs or symptoms of heart failure. In contrast, the traditional New York Heart Association (NYHA) functional classification system primarily gauges the severity of symptoms in patients who are in stage C or stage D. **Figure 28G-1** summarizes the guideline recommendations for therapy by stage.

Like other ACC/AHA guidelines, these recommendations classify interventions into one of three classes as follows, including two levels of the intermediate group:

Class I: conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective

Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy

Class IIa: weight of evidence and opinion in favor of usefulness/efficacy

Class IIb: usefulness/efficacy is less well established by evidence and opinion

Class III: conditions for which there is evidence and/or general agreement that a procedure or therapy is not useful or effective and in some cases may be harmful

The ACC/AHA guidelines also adopt a convention for rating levels of evidence on which recommendations have been based. Level A recommendations are derived from data from multiple randomized clinical trials; level B recommendations are derived from a single randomized trial or nonrandomized studies; and level C recommendations are based on the consensus opinion of experts. The guidelines emphasize that the strength of evidence does not necessarily reflect the strength of a recommendation. A treatment may be controversial despite having been evaluated in controlled clinical trials; conversely, a strong recommendation may be supported only by historical data or by no data at all.

INITIAL PATIENT EVALUATION

The ACC/AHA guidelines state that a complete history and physical examination should be the first step in the evaluation of patients with heart failure (**Table 28G-1**). This evaluation may provide insight into the cause of the patient's heart failure and the presence or absence of structural cardiovascular abnormalities. Other issues to be addressed include the presence or absence of history of diabetes, rheumatic fever, chest irradiation, or exposure to cardiotoxic drugs and the use or abuse of alcohol, illicit drugs, or alternative therapies. The patient's functional and hemodynamic status should also be evaluated to assess prognosis and to guide management.

The guidelines recommend that the initial evaluation include a complete blood count; urinalysis; serum electrolyte determinations, plus calcium and magnesium concentrations; renal and hepatic function tests; fasting blood glucose concentration and HbA1c level; lipid profile; thyroid function tests; chest radiography; 12-lead electrocardiography; two-dimensional echocardiography with Doppler study; and coronary arteriography in patients with angina or significant ischemia (unless the patient is ineligible for revascularization).

Measurements of serum ferritin level and transferrin saturation are considered potentially useful for the detection of hemochromatosis because this condition is a treatable cause of heart failure. Screening for the human immunodeficiency virus, sleep-disturbed breathing, connective tissue diseases, amyloidosis, or pheochromocytoma is also reasonable in selected patients.

The updated guidelines reflect recent research on B-type natriuretic peptide (BNP). In the 2009 guidelines, the ACC/AHA supports its use in the urgent care setting when the diagnosis of heart failure is uncertain as well as for risk stratification but does not recommend that BNP be used to guide therapy.

Echocardiography to assess left ventricular function and to detect underlying myocardial, valvular, or pericardial disease is considered a more valuable initial test than radionuclide ventriculography or magnetic resonance imaging.

Screening for and assessment of coronary artery disease in patients with heart failure are given considerable attention in these guidelines, reflecting the frequent coexistence of these conditions and the survival benefit of revascularization of patients with severe coronary disease and left ventricular dysfunction. Coronary arteriography is recommended (Class I indication) for patients with angina or significant ischemia and heart failure unless they are not eligible for revascularization. For patients who have chest pain and heart failure, the guidelines provide support for bypassing the step of noninvasive testing and proceeding directly to coronary angiography (Class IIa indication). For patients without chest pain, the guidelines consider coronary angiography "reasonable" for excluding the diagnosis of coronary disease. Maximal exercise testing is

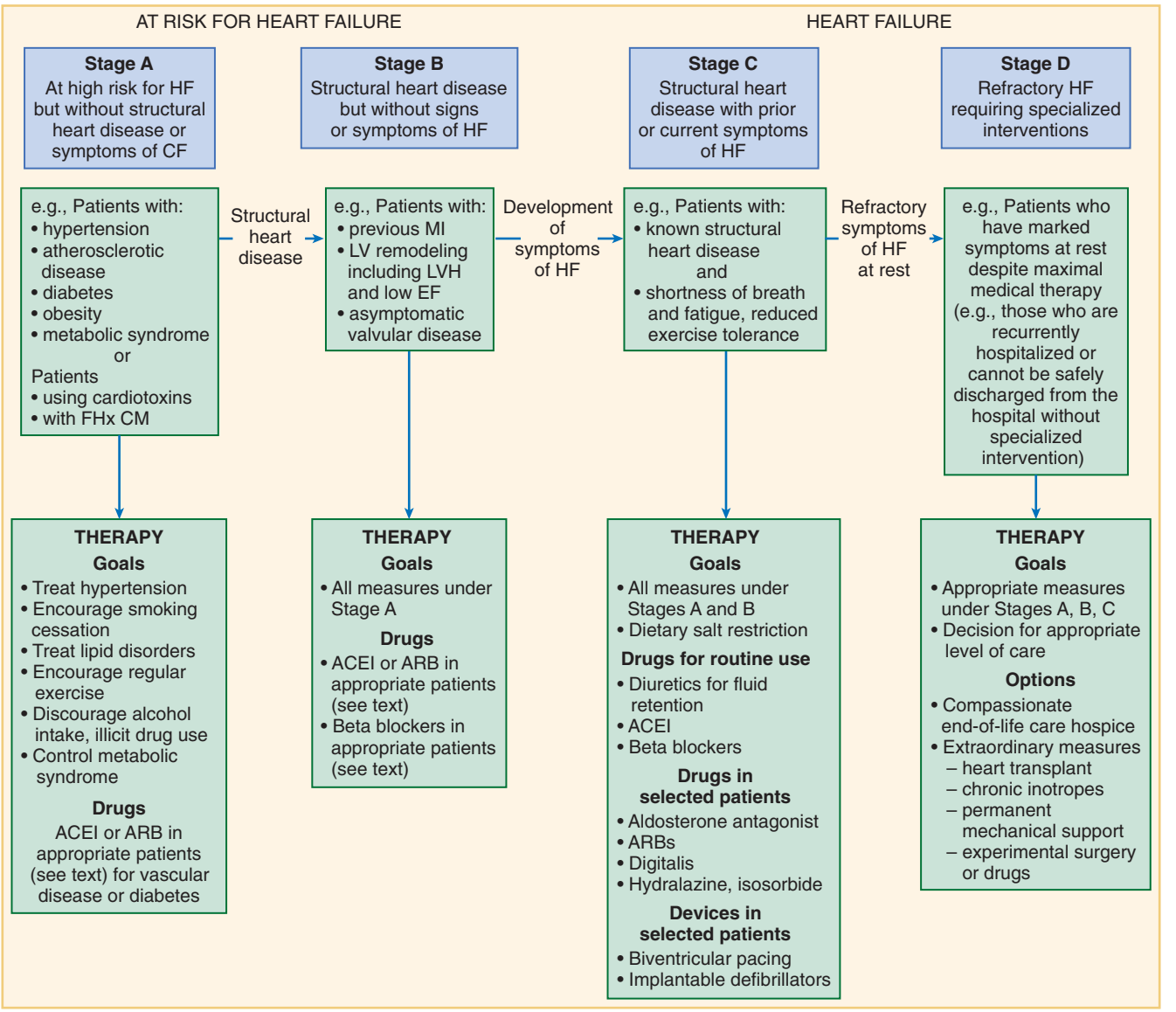

FIGURE 28G-1 Stages in the evolution of heart failure (HF) and recommended therapy by stage. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; EF = ejection fraction; FHx CM = family history of cardiomyopathy; IV = intravenous; LV = left ventricular; LVH = left ventricular hypertrophy; MI = myocardial infarction. *(From Hunt SA, Baker DW, Chin MH, et al: ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure]. J Am Coll Cardiol 104:2996, 2001.)*

recommended to help determine if heart failure is the cause of exercise limitation or to identify high-risk patients with heart failure who may be candidates for cardiac transplantation or other advanced therapy.

The guidelines offered only weak support for noninvasive testing to define the likelihood of coronary artery disease in patients with heart failure and left ventricular dysfunction and for Holter monitoring in patients with a history of myocardial infarction who might be susceptible to ventricular tachycardia.

Routine use of endomyocardial biopsy or signal-averaged electrocardiography and routine measurement of circulating levels of neurohormones such as norepinephrine and endothelin are not recommended.

ONGOING ASSESSMENT OF PATIENTS WITH HEART FAILURE

The guidelines support routine assessment of functional and volume status in patients with heart failure along with assessment of potentially harmful behaviors or habits (see Table 28G-1). They discourage routine serial measurement of ejection fraction at regular intervals and instead recommend that ejection fraction be reassessed if patients have had a change in clinical status, recovered from a significant clinical event, or received treatment that might affect left ventricular function. The value of serial measurements of BNP remains uncertain.

TREATMENT OF PATIENTS AT HIGH RISK OF DEVELOPING HEART FAILURE (STAGE A)

The ACC/AHA guidelines provide strong recommendations (Class I) for control of risk factors for coronary disease and other causes of cardiomyopathy, including hypertension, hyperlipidemia, diabetes, alcohol abuse, cigarette smoking, supraventricular tachycardia, and thyroid disorders (**Table 28G-2**). Patients at risk for heart failure should also be assessed frequently for evidence that this condition is developing, particularly those with a strong family history of cardiomyopathy and those receiving cardiotoxic interventions. Attention should be paid to secondary prevention efforts in patients with atherosclerotic vascular disease.

The guidelines suggest a low threshold for use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (Class IIa). The ACC/AHA Task Force recommends advising patients not to use nutritional supplements solely to prevent the development of heart failure.

TABLE 28G-1 ACC/AHA Guidelines for Initial and Serial Evaluation of Heart Failure

CLASS	INDICATION	LEVEL OF EVIDENCE*
	ACC/AHA Guidelines for initial Evaluation of Patients with Heart Failure	
I (indicated)	1. Thorough history and physical examination to identify cardiac and noncardiac disorders or behaviors that might cause heart failure or accelerate its development or progression	C
	2. Obtain a careful history of current and past use of alcohol, illicit drugs, current or past standard or "alternative therapies," and chemotherapy drugs	C
	3. Initial assessment of the patient's ability to perform routine and desired activities of daily living	C
	4. Initial examination should include assessment of volume status, orthostatic blood pressure changes, measurement of weight and height, and calculation of body mass index	C
	5. Initial laboratory evaluation should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, fasting blood glucose (glycohemoglobin), lipid profile, liver function tests, and thyroid-stimulating hormone	C
	6. Initial 12-lead electrocardiogram and chest radiograph (posteroanterior and lateral)	C
	7. Initial two-dimensional echocardiography with Doppler to assess left ventricular size and ejection fraction, wall thickness, and valve function; radionuclide ventriculography can be performed to assess left ventricular ejection fraction and volumes	C
	8. Coronary arteriography in patients with angina or significant ischemia except those who are not eligible for revascularization	B
IIa (good supportive evidence)	1. Coronary arteriography in patients with chest pain whose coronary anatomy has not been evaluated and who do not have contraindications to coronary revascularization	C
	2. Coronary arteriography in patients with known or suspected coronary artery disease but without angina except those who are not eligible for revascularization	C
	3. Noninvasive imaging to detect myocardial ischemia and viability in patients with known coronary artery disease and without angina except those who are not eligible for revascularization	B
	4. Maximal exercise testing with or without measurement of respiratory gas exchange and/or blood oxygen saturation to help determine whether heart failure is the cause of exercise limitation when the contribution of heart failure is uncertain	C
	5. Maximal exercise testing with measurement of respiratory gas exchange to identify high-risk patients who are candidates for cardiac transplantation or other advanced treatments	B
	6. Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus in selected patients	C
	7. Tests for rheumatologic diseases, amyloidosis, or pheochromocytoma in patients in whom there is a clinical suspicion of these diseases	C
	8. Endomyocardial biopsy in patients when a specific diagnosis is suspected that would influence therapy	C
	9. Measurement of B-type natriuretic peptide in the urgent care setting when the clinical diagnosis of heart failure is uncertain, as well as in prognostication	A
IIb (weak supportive evidence)	1. Noninvasive imaging to define the likelihood of coronary artery disease in patients with left ventricular dysfunction	C
	2. Holter monitoring in patients with a history of myocardial infarction who are being considered for electrophysiologic study to document inducibility of ventricular tachycardia	C
III (not indicated)	1. Routine evaluation with endomyocardial biopsy	C
	2. Routine use of signal-averaged electrocardiography	C
	3. Routine measurement of circulating levels of neurohormones (e.g., norepinephrine or endothelin)	C
	ACC/AHA Guidelines for Serial Clinical Assessment of Patients with Heart Failure	
I (indicated)	1. Assess at each visit the patient's ability to perform routine and desired activities of daily living	C
	2. Assess at each visit the patient's volume status and weight	C
	3. Ask at each visit about the patient's current use of alcohol, tobacco, illicit drugs, "alternative therapies," and chemotherapy drugs as well as about diet and sodium intake	C
IIa (good supportive evidence)	1. Repeat measurements of ejection fraction and structural remodeling in patients who have had a change in clinical status, who have experienced or recovered from a clinical event, or who have received treatment that might have had a significant effect on cardiac function	C
IIb (weak supportive evidence)	1. Serial measurement of B-type natriuretic peptide to guide therapy is not well established	C

*See guidelines text for definition of level of evidence categories.

TREATMENT OF PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION WHO HAVE NOT DEVELOPED SYMPTOMS (STAGE B)

In this population, the goal of therapy is to reduce the risk of further damage to the left ventricle and to minimize the rate of progression of left ventricular dysfunction. The same risk factor modifications supported for stage A patients are also recommended for stage B patients (**Table 28G-3**). As is true for virtually all patients with heart failure, no evidence was found to support the use of nutritional supplements.

In the absence of contraindications, beta blockers and ACE inhibitors (or angiotensin receptor blockers [ARBs] in those intolerant of ACE inhibitors) are recommended for all patients with histories of myocardial infarction, regardless of ejection fraction, and for all patients with diminished ejection fraction, regardless of history of myocardial infarction. In contrast, the guidelines discourage use of digoxin and calcium channel blockers with negative inotropic action in this population.

The guidelines support the use of coronary revascularization in appropriate patients as well as surgery to correct valvular disease in patients with hemodynamically significant valvular stenosis or regurgitation that causes heart failure.

The guidelines indicate that placement of an implantable cardioverter-defibrillator (ICD) is reasonable in patients with ischemic cardiomyopathy who have had a recent (>40 days) myocardial infarction, have compromised left ventricular ejection fraction, and have reasonable expectation of

TABLE 28G-2 ACC/AHA Guidelines for Treating Patients at High Risk of Developing Heart Failure (Stage A)

CLASS	INDICATION	LEVEL OF EVIDENCE*
I (indicated)	1. Control of systolic and diastolic hypertension in accordance with contemporary guidelines	A
	2. Treatment of lipid disorders in accordance with contemporary guidelines	A
	3. Control of blood glucose in patients with diabetes mellitus in accordance with contemporary guidelines	C
	4. Avoidance of behaviors that may increase the risk of heart failure, such as smoking, excessive alcohol consumption, and illicit drug use	C
	5. Control of ventricular rate or restoration of sinus rhythm in patients with supraventricular tachyarrhythmias	B
	6. Treatment of thyroid disorders in accordance with contemporary guidelines	C
	7. Perform periodic evaluation for signs and symptoms of heart failure in high-risk patients	C
	8. Follow current guidelines for secondary prevention for patients with known atherosclerotic vascular disease	C
	9. Noninvasive evaluation of left ventricular function in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions	C
IIa (good supportive evidence)	1. ACE inhibition in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors	A
	2. Angiotensin II receptor blockers in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors	C
III (not indicated)	1. Use of nutritional supplements to prevent the development of structural heart disease	C

*See guidelines text for definition of level of evidence categories.

TABLE 28G-3 ACC/AHA Guidelines for Treatment of Asymptomatic Left Ventricular Systolic Dysfunction (Stage B)

CLASS	INDICATION	LEVEL OF EVIDENCE*
I (indicated)	1. Apply all Class I recommendations for stage A	A, B, C
	2. Beta blockade and ACE inhibition in all patients with a recent or remote history of myocardial infarction regardless of ejection fraction or presence of heart failure	A
	3. Beta blockade in all patients without a history of myocardial infarction who have a reduced left ventricular ejection fraction but no heart failure symptoms	C
	4. ACE inhibition in patients with a reduced ejection fraction whether or not they have experienced a myocardial infarction	A
	5. Angiotensin II receptor blockers (ARBs) for post–myocardial infarction patients without heart failure but with a low left ventricular ejection fraction who are intolerant of ACE inhibitors	B
	6. Treat post–myocardial infarction patients according to contemporary guidelines	C
	7. Recommend coronary revascularization in accordance with contemporary guidelines	A
	8. Valve replacement or repair for patients with hemodynamically significant valvular stenosis or regurgitation	B
IIa (good supportive evidence)	1. ACE inhibition or ARBs for patients with hypertension and left ventricular hypertrophy	B
	2. ARBs for patients with low ejection fraction who are intolerant of ACE inhibitors	C
	3. Placement of an ICD in patients with ischemic cardiomyopathy who are at least 40 days post–myocardial infarction, have a left ventricular ejection fraction ≤30%, are NYHA functional Class I on chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year	A
III (not indicated)	1. Use of digoxin in patients with low ejection fraction, sinus rhythm, and no history of heart failure symptoms (risk of harm not balanced by known benefit)	C
	2. Use of nutritional supplements to treat structural heart disease or to prevent the development of symptoms of heart failure	C
	3. Calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low left ventricular ejection fraction after myocardial infarction	C

*See guidelines text for definition of level of evidence categories.

survival with good functional status for more than 1 year. There was less support for ICD placement in similar patients with nonischemic cardiomyopathy, although the recently completed MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), which demonstrated beneficial outcomes in patients with NYHA Class I heart failure (ejection fraction <30%) and prolonged QRS duration (>130 milliseconds) who received an ICD with cardiac resynchronization therapy (CRT), may lead to stronger recommendation in subsequent guidelines to implant ICD/CRT in patients with less symptomatic heart failure.[9]

TREATMENT OF PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AND CURRENT OR PRIOR SYMPTOMS (STAGE C)

Application of the same measures recommended for preventing or minimizing progression of left ventricular dysfunction for stage A and stage B patients is supported for stage C patients who have current or prior symptoms attributable to left ventricular dysfunction (**Table 28G-4**). However, in contrast to the recommendations for stage B patients, the guidelines support use of moderate sodium restriction as well as daily measurement of weight.

Physical activity is recommended for stage C patients. More detailed recommendations are provided in an AHA Scientific Statement on Exercise and Heart Failure, published in 2003.[10] The updated guidelines also reflect the results of the recent HF-ACTION trial, in which exercise training did not have a favorable impact on all-cause mortality or heart failure hospitalization (see Fig. 28-9). Maximal exercise testing with or without measurement of respiratory gas exchange to facilitate an appropriate exercise program has been changed from a Class I recommendation to a Class IIa indication.

The 2009 ACC/AHA updated guidelines support the use of beta blockers (bisoprolol, carvedilol, and sustained-release metoprolol succinate) and ACE inhibitors (ARBs for patients who cannot tolerate ACE inhibitors) for all stage C patients, in the absence of contraindications, and the use of diuretics for patients with fluid overload. Addition of an aldosterone antagonist is recommended in selected patients who can be carefully monitored for preserved renal function and normal potassium concentration. The use of hydralazine was recommended in patients who

TABLE 28G-4 ACC/AHA Guidelines for Treatment of Symptomatic Left Ventricular Systolic Dysfunction (Stage C)

CLASS	INDICATION	LEVEL OF EVIDENCE*
I (indicated)	1. Apply all Class I recommendations for Stage A	A, B, C
	2. Diuretics and salt restriction in patients with evidence of fluid retention	C
	3. ACE inhibition in all patients unless contraindicated	A
	4. Beta blockade with one of the three proven to reduce mortality (bisoprolol, carvedilol, or sustained-release metoprolol succinate) in all patients unless contraindicated	A
	5. Angiotensin II receptor blockers approved for the treatment of heart failure (candesartan or valsartan) in patients who cannot tolerate ACE inhibitors	A
	6. Avoid or withdraw drugs known to adversely affect heart failure whenever possible, such as nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs	B
	7. Exercise training as an adjunctive approach to improve clinical status in ambulatory patients	B
	8. Placement of an implantable cardioverter-defibrillator (ICD) for secondary prevention to prolong survival in patients with a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia	A
	9. ICD therapy to prevent sudden cardiac death in patients with ischemic heart disease who are at least 40 days post–myocardial infarction, have a left ventricular ejection fraction ≤35%, with NYHA functional Class II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival for more than 1 year with good functional status	A
	10. ICD therapy to prevent sudden cardiac death in patients with nonischemic cardiomyopathy who are at least 40 days post–myocardial infarction, have a left ventricular ejection fraction ≤35%, with NYHA functional Class II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival for more than 1 year with good functional status	B
	11. Cardiac resynchronization therapy in patients with cardiac dyssynchrony (a QRS duration > 0.12 msec), a left ventricular ejection fraction ≤35% who are in sinus rhythm and are in NYHA functional Class III or ambulatory Class IV in spite of optimal medical therapy, unless contraindicated	A
	12. Addition of an aldosterone antagonist in selected patients who can be carefully monitored for preserved renal function and normal potassium concentration; creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women and potassium should be ≤5.0 mEq/L.	B
IIa (good supportive evidence)	1. ARBs are a reasonable alternative to ACE inhibitors as first-line therapy, especially for patients already taking ARBs for other indications	A
	2. Digitalis to decrease hospitalizations for heart failure	B
	3. The addition of a combination of hydralazine and a nitrate for patients who have persistent symptoms in spite of already taking an ACE inhibitor and beta blocker	A
	4. In patients with cardiac dyssynchrony (a QRS duration > 0.12 msec), a left ventricular ejection fraction ≤35%, and atrial fibrillation, cardiac resynchronization therapy with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV patients on optimal medical therapy	B
IIb (weak supportive evidence)	1. A combination of hydralazine and a nitrate in patients who cannot tolerate an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency	C
	2. Adding an ARB in persistently symptomatic patients who are already being treated with conventional therapy	B
III (not indicated)	1. Routinely combining an ACE inhibitor, an ARB, and an aldosterone antagonist	C
	2. Routine use of calcium channel blocking drugs	A
	3. Long-term use of an infusion of a positive inotropic drug may be harmful and is not recommended except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment	C
	4. Use of nutritional supplements as treatment for heart failure	C
	5. Hormonal therapies other than to replete deficiencies may be harmful	C

*See guidelines text for definition of level of evidence categories.

are intolerant of an ACE inhibitor or an ARB. A new Class I recommendation in the updated guidelines is the use of hydralazine isosorbide in self-identified African Americans who remain symptomatic despite optimal therapy.

The recommendations regarding the use of ICDs were simplified in the 2009 ACC/AHA updated guidelines and were harmonized with the 2008 ACC/AHA/Heart Rhythm Society Device-Based Therapy guidelines.[11,12] Class I recommendations support the use of ICDs in nonischemic dilated cardiomyopathy, ischemic cardiomyopathy at least 40 days after myocardial infarction, left ventricular ejection fraction <35% (previously 30%), and NYHA Class II-III symptoms despite optimal medical therapy. As in the 2005 ACC/AHA guidelines, Class I recommendations support the use of ICDs in stage C patients with a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia. Guidelines covering patient selection for CRT were published in 2005.[13] CRT is a Class I indication in patients with a left ventricular ejection fraction <35% who are in sinus rhythm and NYHA functional Class III or ambulatory Class IV despite optimal medical therapy. The 2009 updated ACC/AHA also consider CRT reasonable (Class IIa) in NYHA Class III-IV heart failure patients with an ejection fraction <35% who are in atrial fibrillation or who have a frequent dependence on ventricular pacing. As discussed in Chap. 29, the Centers for Medicare & Medicaid Services (CMS) has expanded the coverage for CRT-defibrillators (CRT-D) to include patients with left bundle branch block with a QRS ≥130 ms, an EF ≤30% and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure. It is anticipated that updated practice guidelines will reflect the expanded CMS indications for use of CRT-D in subsequent updates.

The guidelines offer qualified support (Class IIa) for the use of ARBs in place of ACE inhibitors as first-line therapy, especially in patients already taking an ARB for another indication. Digitalis is a reasonable approach to decrease hospitalizations in symptomatic patients.

The guidelines explicitly discourage the routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist; calcium channel blockers; long-term infusion of positive inotropic drugs (except as palliation in patients with end-stage disease; see Table 28G-10); nutritional supplements as treatment; and hormonal therapies other than those needed to replete deficiencies.

TREATMENT OF PATIENTS WITH REFRACTORY END-STAGE HEART FAILURE (STAGE D)

The ACC/AHA guidelines emphasize the importance of meticulous application of the measures listed as Class I recommendations for patients in stages A, B, and C (see Tables 28G-2 to 28G-4) and consider these patients

TABLE 28G-5 ACC/AHA Guidelines for Treatment of Patients with End-Stage Heart Failure (Stage D)

CLASS	INDICATION	LEVEL OF EVIDENCE*
I (indicated)	1. Meticulous identification and control of fluid retention	B
	2. Refer potentially eligible patient for cardiac transplantation	B
	3. Refer patients to a heart failure program with expertise in the management of refractory heart failure	A
	4. Discuss options for end-of-life care with the patient and family when severe symptoms persist despite application of all recommended therapies	C
	5. Offer patients with implantable defibrillators and end-stage disease the option to inactivate defibrillation	C
IIa (good supportive evidence)	1. Consider a left ventricular assist device as permanent or "destination" therapy in highly selected patients with refractory end-stage heart failure and an estimated 1-year mortality >50% with medical therapy	B
IIb (weak supportive evidence)	1. Pulmonary artery catheter placement to guide therapy in patients with persistently severe symptoms	C
	2. Mitral valve repair or replacement is not established for severe secondary mitral regurgitation	C
	3. Continuous intravenous infusion of a positive inotropic agent may be considered for palliation	C
III (not indicated)	1. Partial left ventriculectomy is not recommended in patients with nonischemic cardiomyopathy	C
	2. Routine intermittent infusions of positive inotropic agents are not recommended	A

*See guidelines text for definition of level of evidence categories.

TABLE 28G-6 ACC/AHA Guidelines: Indications for Cardiac Transplantation

Absolute Indications
For hemodynamic compromise due to heart failure
Refractory cardiogenic shock
Documented dependence on intravenous inotropic support to maintain adequate organ perfusion
Peak $\dot{V}O_2$ <10 mL/kg/min with achievement of anaerobic metabolism
Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention
Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities
Relative Indications
Peak $\dot{V}O_2$ 11 to 14 mL/kg/min (or 55% of predicted) and major limitation of the patient's daily activities
Recurrent unstable ischemia not amenable to other intervention
Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen
Insufficient Indications
Low left ventricular ejection fraction
History of functional Class III or IV symptoms of heart failure
Peak $\dot{V}O_2$ >15 mL/kg/min (and >55% of predicted) without other indications

$\dot{V}O_2$ = oxygen consumption per unit time.

candidates for specialized treatment strategies, such as referral for cardiac transplantation, mechanical circulatory support, continuous intravenous positive inotropic therapy, or hospice care (**Table 28G-5**). The guidelines also endorse the use of team management approaches, such as heart failure programs. Detailed specifications of the components of such heart failure programs are provided in an AHA Scientific Statement published in 2000.[14]

The guidelines include explicit cautionary notes about the use of ACE inhibitors and beta blockers in this population. Although consideration of these agents is supported, the guidelines state, "Treatment with either type of drug should not be initiated in patients who have systolic blood pressures less than 80 mm Hg or who have signs of peripheral hypoperfusion. In addition, patients should not be started on a beta blocker if they have significant fluid retention or if they recently required treatment with an intravenous positive inotropic agent." When these medications are used, very low doses should be prescribed at initiation, and patients should be monitored closely for evidence of intolerance. The guidelines note that spironolactone has been shown to be beneficial in patients with advanced heart failure, but they emphasize that these data are derived from patients with preserved renal function and that spironolactone may induce hyperkalemia in patients with impaired renal function.

According to the updated 2009 guidelines, there is limited evidence to support the placement of a pulmonary artery catheter to guide therapy or mitral valve repair or replacement for severe mitral regurgitation.

The ACC/AHA guidelines recognize the value of continuous intravenous inotropic support for some patients who require a "bridge" strategy while awaiting cardiac transplantation or who cannot otherwise be discharged from the hospital. However, the guidelines directly discourage routine intermittent intravenous infusion of inotropic agents. Similarly, the guidelines did not encourage use of partial left ventriculectomy.

The guidelines also include a summary of indications for cardiac transplantation (**Table 28G-6**). These indications make explicit that low left ventricular ejection fraction and poor functional status are insufficient indications in the absence of demonstrated peak oxygen consumption less than 15 mL/kg/min.

THE HOSPITALIZED PATIENT

The most significant addition to the 2009 ACC/AHA updated guidelines is inclusion of specific new recommendations regarding the hospitalized patient (**Table 28G-7**). Although a number of new Class I indications involve the diagnosis of heart failure, use of BNP and N-terminal pro-BNP (NT-proBNP), recognition of acute coronary syndromes, recognition of potential precipitating factors, use of supplemental oxygen, use of intravenous inotropic or pressure agents in patients with clinical evidence of hypotension with hypoperfusion, use of pulmonary artery catheters, and transition from intravenous to oral diuretics, the level of evidence supporting each of these recommendations is based on consensus opinion or standard use of care (i.e., level C). Stronger Class I recommendations (level of evidence B) are provided for the use of intravenous diuretics to decongest patients, initiation of ACE inhibitors/ARBs and beta blockers before hospital discharge, and postdischarge systems of care.

TABLE 28G-7 ACC/AHA Recommendations for the Hospitalized Patient

CLASS	INDICATION	LEVEL OF EVIDENCE*
I (indicated)	1. Evaluate for adequacy of systemic perfusion, volume status, the contribution of precipitating factors and/or comorbidities, and whether heart failure is associated with preserved ejection fraction	C
	2. B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) should be measured to evaluate dyspnea if the contribution of heart failure is not known	A
	3. Acute coronary syndromes precipitating hospitalization for heart failure should be promptly evaluated and treated	C
	4. Identify potential precipitating factors for acute heart failure	C
	5. Oxygen therapy should be administered to relieve symptoms related to hypoxemia	C
	6. Rapidly improve systemic perfusion in patients who present with rapid decompensation and hypoperfusion associated with decreasing urine output and other manifestations of shock	C
	7. Treatment of significant fluid overload with intravenous loop diuretics; the diuretic dose should be titrated to relieve symptoms and to reduce extracellular fluid volume excess	B, C
	8. Monitor the effects of therapy with careful measurement of fluid intake and output, vital signs, body weight, and symptoms of systemic perfusion and congestion	C
	9. Intensify the diuretic regimen (higher dose, add second diuretic, continuous infusion) when the diuresis is inadequate to relieve congestion	C
	10. Intravenous inotropic or vasopressor drugs should be administered to maintain systemic perfusion and preserve end-organ performance in patients with clinical evidence of hypotension associated with hypoperfusion and elevated cardiac filling pressures	C
	11. Invasive hemodynamic monitoring to guide therapy in patients who are in respiratory distress or with clinical evidence of impaired perfusion if filling pressures cannot be determined from clinical assessment	C
	12. Medications should be reconciled and adjusted as appropriate on admission to and discharge from the hospital	C
	13. Maintenance treatment with oral therapies known to improve outcomes (ACE inhibitors or ARBs and beta blocker therapy) in the absence of hemodynamic instability or contraindications	C
	14. Initiation of treatment with oral therapies known to improve outcomes (ACE inhibitors or ARBs and beta blocker therapy) in stable patients prior to hospital discharge	B
	15. During the transition from intravenous to oral diuretic therapy, the patient should be monitored carefully for supine and upright hypotension, worsening renal function, and heart failure signs or symptoms	C
	16. Comprehensive written discharge instructions for patients and their caregivers are strongly recommended	C
	17. Postdischarge systems of care, if available, should be used to facilitate the transition to effective outpatient care	B
IIa (good supportive evidence)	1. Urgent cardiac catheterization and revascularization in patients with acute heart failure with known or suspected acute myocardial ischemia due to occlusive coronary disease when there are signs and symptoms of inadequate systemic perfusion and revascularization is likely to prolong meaningful survival	C
	2. Intravenous nitroglycerin, nitroprusside, or nesiritide for patients with evidence of severely symptomatic fluid overload in the absence of systemic hypotension	C
	3. Ultrafiltration for patients with refractory congestion not responding to medical therapy	B
IIb (weak supportive evidence)	1. Intravenous inotropic drugs (dopamine, dobutamine, or milrinone) for patients presenting with documented severe systolic dysfunction, low blood pressure, and evidence of low cardiac output, with or without congestion, to maintain systemic perfusion and preserve end-organ performance	C
III (not indicated)	1. Use of parenteral inotropes in normotensive patients with acute decompensated heart failure without evidence of decreased organ perfusion	B
	2. Routine use of invasive hemodynamic monitoring in normotensive patients with acute decompensated heart failure and congestion with symptomatic response to diuretics and vasodilators	B

*See guidelines text for definition of level of evidence categories.

The updated guidelines offer qualified support (Class IIa) for the use of urgent catheterization and revascularization, the use of vasodilators (intravenous nitroglycerin, nitroprusside, nesiritide), invasive hemodynamic monitoring, and ultrafiltration. More muted support (Class IIb) is given to the use of inotropic agents (dopamine, dobutamine, or milrinone) in patients with severe left ventricular dysfunction, low blood pressure, and evidence of low cardiac output. In contrast, the use of inotropic agents in patients without evidence of decreased organ perfusion as well as the routine use of invasive hemodynamic monitoring is not recommended (Class III indication).

SPECIAL POPULATIONS AND CONCOMITANT DISORDERS

The ACC/AHA guidelines support consideration of patient-specific needs and coexisting medical conditions. Clinicians are reminded that even though heart failure has traditionally been considered to be a disease of men, women—particularly elderly women—make up the majority of the general population with heart failure. Yet women have not been included in sufficient numbers in most large trials to allow conclusions about the efficacy of the treatments under study. In addition, women, minorities, and the elderly are less likely to receive interventions supported by clinical trials, and differences in the natural history of heart failure and response to treatment exist among various patient subsets.

Patients from high-risk ethnic minority groups, such as blacks, as well as from groups underrepresented in clinical trials and those believed to be underserved should receive the same clinical screening and therapy as received by the broader population, in the absence of specific evidence to the contrary. As noted before, the 2009 update of the guidelines recommends the addition of a fixed dose of isosorbide dinitrate and hydralazine to a standard medical regimen for heart failure that includes ACE inhibition and beta blockade to improve outcomes for self-described African American patients who have NYHA functional Class III or IV heart failure (changed from a Class IIa to Class I indication). The guidelines acknowledge that other groups of patients may also benefit, but this has not been tested.

Specific clinical recommendations for the management of patients with concomitant disorders (**Table 28G-8**) emphasize the importance of meticulous management of hypertension, ischemic heart disease, anticoagulation, and supraventricular and ventricular arrhythmias. The use of digitalis, particularly in combination with a beta blocker, to control the ventricular response rate in patients with atrial fibrillation and of amiodarone to decrease the recurrence of atrial arrhythmias and the likelihood of an ICD discharge is considered reasonable. The updated 2009 guidelines suggest that although verapamil and diltiazem can effectively suppress the ventricular response during exercise, they should be avoided because of

TABLE 28G-8 ACC/AHA Guidelines for Management of Concomitant Diseases in Patients with Heart Failure

CLASS	INDICATION	LEVEL OF EVIDENCE*
I (indicated)	1. Apply all other recommendations in the absence of specific exceptions	C
	2. Control systolic and diastolic hypertension and diabetes mellitus in accordance with recommended guidelines	C
	3. Nitrates and beta blockers for the treatment of angina	B
	4. Coronary revascularization according to recommended guidelines in patients with both angina and heart failure	A
	5. Anticoagulants in patients with heart failure who have paroxysmal or persistent atrial fibrillation or a previous thromboembolic event	A
	6. Beta blockade (or amiodarone, if beta blockers are contraindicated or not tolerated) to control the ventricular response rate in patients with atrial fibrillation	A
	7. Treat patients with coronary artery disease and heart failure in accordance with recommended guidelines for chronic stable angina	C
	8. Antiplatelet agents for prevention of myocardial infarction and death in patients with heart failure and underlying coronary artery disease	B
IIa (good supportive evidence)	1. Digitalis to control the ventricular response rate in patients with heart failure and atrial fibrillation	A
	2. Amiodarone to decrease recurrence of atrial arrhythmias and recurrence of ICD discharge for ventricular arrhythmias	C
IIb (weak supportive evidence)	1. Current strategies to restore and to maintain sinus rhythm in patients with heart failure and atrial fibrillation are not well established	C
	2. Anticoagulation in patients with heart failure who do not have atrial fibrillation or a previous thromboembolic event is not well established	B
	3. Enhancing erythropoiesis in patients with heart failure and anemia is not established	C
III (not indicated)	1. Class I or III antiarrhythmic drugs are not recommended for the prevention of ventricular arrhythmias	A
	2. Antiarrhythmic medication is not indicated for primary treatment of asymptomatic ventricular arrhythmias or to improve survival	A

*See guidelines text for definition of level of evidence categories.

TABLE 28G-9 ACC/AHA Guidelines for Treatment of Patients with Heart Failure and Normal Left Ventricular Ejection Fraction

CLASS	INDICATION	LEVEL OF EVIDENCE*
I (indicated)	1. Control systolic and diastolic hypertension in accordance with published guidelines	A
	2. Control ventricular rate in patients with atrial fibrillation	C
	3. Diuretics to control pulmonary congestion and peripheral edema	C
IIa (good supportive evidence)	1. Coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function	C
IIb (weak supportive evidence)	1. Restoration and maintenance of sinus rhythm in patients with atrial fibrillation	C
	2. Use of beta blockade, ACE inhibitors, ARBs, or calcium antagonists may minimize heart failure symptoms	C
	3. Use of digitalis to minimize symptoms is not well established	C

*See guidelines text for definition of level of evidence categories.

their propensity to depress left ventricular function and to worsen heart failure.

There is insufficient evidence to recommend for or against the use of current strategies to restore and to maintain sinus rhythm in patients with atrial fibrillation, the usefulness of anticoagulation in patients without atrial fibrillation or a prior myocardial infarction, or the improvement of erythropoiesis in anemia patients.

The guidelines do not support routine use of Class I or III antiarrhythmic drugs, except amiodarone, or the use of antiarrhythmic drugs for primary treatment of asymptomatic ventricular arrhythmias.

DIASTOLIC DYSFUNCTION

Recommendations for management of patients with heart failure in the absence of left ventricular systolic dysfunction reflect the lack of conclusive data on effective therapies and are unchanged in the 2009 ACC/AHA update of the heart failure guidelines. The major strategies are control of hypertension, control of ventricular rate in patients with atrial fibrillation, and use of diuretics to control pulmonary congestion and peripheral edema (**Table 28G-9**). Because myocardial ischemia can cause diastolic dysfunction, the guidelines offer support for consideration of use of coronary revascularization in patients with coronary disease (Class IIa indication). Possibly useful therapies include restoration and maintenance of sinus rhythm in patients with atrial fibrillation and the use of beta blockers, ACE inhibitors, ARBs, or calcium channel blockers to minimize symptoms in patients with controlled hypertension.

END-OF-LIFE CARE

Despite significant advances in the diagnosis and management of heart failure, approximately half of individuals die within 5 years of its diagnosis. For many patients, there is an abrupt transition from the period of aggressive intervention to one of palliation and comfort. Addressing end-of-life issues relatively early in the course of heart failure, before the patient becomes unable to participate in decision making, is important for all involved (**Table 28G-10**). The guidelines recommend discussing treatment preferences, living wills, and advance directives, the formulation of which can be more difficult than for patients with cancer or other conditions. Heart failure can be characterized by periods of good quality of life even after hospitalization for intensive care or the approach of death. In addition to resuscitation, discussions should cover the possible deactivation of an ICD.

Hospice services, once available primarily for cancer patients, are being extended to those dying of heart failure. In such patients, compassionate care may include the use of intravenous diuretics and positive inotropic agents as well as pain medications.

TABLE 28G-10 ACC/AHA Guidelines on End-of-Life Care for Patients with Heart Failure

CLASS	INDICATION	LEVEL OF EVIDENCE*
I (indicated)	1. Ongoing education of the patient and family regarding prognosis for functional capacity and survival	C
	2. Patient and family education about options for formulating and implementing advance directives and the role of palliative and hospice care services with reevaluation for changing clinical status	C
	3. Discussion regarding the option of inactivating implantable cardioverter-defibrillators	C
	4. Ensure continuity of medical care between inpatient and outpatient settings	C
	5. Palliation at the end of life should include standard components of hospice care, such as opiates for pain control, and should not preclude the use of inotropes and intravenous diuretics	C
	6. Examine current end-of-life processes and work toward improvement in approaches to palliation and end-of-life care	C
III (not indicated)	1. Aggressive procedures performed within the final days of life (including intubation and implantation of a cardioverter-defibrillator in patients with NYHA functional Class IV symptoms who are not anticipated to experience clinical improvement from available treatments)	

*See guidelines text for definition of level of evidence categories.

The guidelines explicitly discourage the performance of aggressive procedures, such as intubation and ICD implantation, within the final days of life in patients with severe end-stage symptoms who are not expected to experience clinical improvements.

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