Chapter 36: Chronic Heart Failure

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UPDATE SUMMARY

Update Summary

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The following sections, tables, and figures were updated following publication of the ACC Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction:

- Key concepts 4 and 8 were updated to reflect new guidance on the role of SGLT2 inhibitors for the treatment of HFpEF.
- Pharmacologic Therapy for HFpEF section was updated to reflect new guidance on the role of SGLT2 inhibitors, ARNI, ARB, and aldosterone antagonist.
- Table 36-10 was updated to include the DELIVER trial.

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 9, Heart Failure.

KEY CONCEPTS

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1 Heart failure (HF) is a clinical syndrome associated with symptoms due to abnormalities in cardiac structure and/or function substantiated by the presence of increased natriuretic peptide plasma concentrations or objective evidence of pulmonary or systemic congestion of cardiogenic origin. The left ventricular ejection fraction (LVEF) is used to classify patients into four different types of HF, the two primary classifications being heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). Patients with HFrEF or HFpEF commonly present with signs and symptoms of fluid overload.

2 With HFpEF, systolic function is preserved, but the heart does not relax nor fill sufficiently resulting in compromised diastolic function. Despite the activation of similar neurohormonal systems as HFrEF, patients with HFpEF are often treated differently than those with HFrEF. Most of the pharmacotherapies known to benefit patients with HFrEF have been less beneficial in HFpEF. Targeting the underlying cause, most commonly uncontrolled hypertension, has been the primary strategy for managing patient with HFpEF. However, recent trials have identified new therapies that benefit patients with HFpEF.

3 In HFrEF, systolic dysfunction results in a decline in cardiac output leading to the activation of a number of neurohormonal compensatory responses that attempt to maintain adequate cardiac output. These responses include activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) and other systems. These compensatory mechanisms play an important role in ventricular

remodeling and contribute to the progression of HF. Importantly, pharmacotherapy targeted at antagonizing this neurohormonal activation slows the progression of HFrEF and improves survival.

4 Most patients with HFrEF should be routinely treated with guideline-directed medical therapy (GDMT)—medications known to reduce mortality in these patients. GDMT includes four medication classes: an angiotensin receptor II receptor blocker/neprilysin inhibitor (ARNI) or angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), an evidence-based β-blocker, an aldosterone antagonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor. In patients with HFrEF, GDMT dosing should be titrated to achieve target doses known to be effective in randomized clinical trials. In contrast, all patients with HFpEF benefit from a SGLT2 inhibitor and select patients with HFpEF may benefit from an ARNI, ARB, and aldosterone antagonist.

5 The ARNI, sacubitril/valsartan, is approved to treat patients with HFrEF and many with HFpEF. In patients with HFrEF, ARNI is preferred over either ACE inhibitors or ARBs to improve survival, slow disease progression, reduce hospitalizations, and improve quality of life. Patients receiving ACE inhibitors or ARBs can be switched to ARNI or ARNI can be used as initial treatment in patients with newly detected HFrEF without previous exposure to ACE inhibitors or ARBs. The doses for these agents should be targeted at those shown in clinical trials to improve survival.

6 The β-blockers carvedilol, metoprolol succinate, and bisoprolol prolong survival, decrease hospitalizations, reduce the need for transplantation, and promote “reverse remodeling” of the left ventricle. These agents are recommended for all patients with HFrEF unless contraindicated. Therapy must be instituted at low doses, with slow upward titration to the target dose.

7 The aldosterone antagonists prolong survival and decrease hospitalizations in patients with HFrEF. These agents may be used provided that potassium and renal function can be carefully monitored. The aldosterone antagonists may be considered to reduce the risk of hospitalization in patients with HFpEF.

8 The SGLT2 inhibitors dapagliflozin or empagliflozin reduce the risk of cardiovascular death, hospitalization, and worsening HF in patients with HFrEF. In addition, dapagliflozin and empagliflozin improve composite outcomes in patients with HFpEF. In both HFrEF and HFpEF, these benefits were demonstrated in patients with and without type 2 diabetes. SGLT2 inhibitors require assessment of renal function prior to initiation.

9 Although chronic loop diuretic therapy frequently is used in patients with HFrEF or HFpEF, it is not mandatory. Diuretic therapy is required only in those patients with peripheral edema and/or pulmonary congestion. Many patients will need continued diuretic therapy to maintain euvolemia after fluid overload is resolved.

10 The combination of hydralazine and nitrates improves the composite endpoint of mortality, hospitalizations for HF, and quality of life in Black patients receiving GDMT for HFrEF. Hydralazine and nitrates should be used in Black patients with persistent symptoms despite GDMT. Hydralazine and a nitrate might be reasonable in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or possibly hypotension.

11 Other therapies including digoxin, ivabradine, and vericiguat may be used in select patients with HFrEF to improve symptoms or reduce the risk of hospitalization.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video by Osmosis regarding congestive heart failure (CHF)—systolic, diastolic, left side, right side, and symptoms. This video provides an overview of the pathophysiology of heart failure due to both systolic and diastolic dysfunction. It also explains how heart failure symptoms relate to the underlying pathophysiology. A thorough understanding of heart failure pathophysiology and symptoms is key for students to learn how pharmacotherapy affects symptoms and improves overall outcomes. This will assist students in understanding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

1 Heart failure (HF) is a clinical syndrome associated with symptoms and/or signs due to abnormalities in cardiac structure and/or function substantiated by the presence of increased natriuretic peptide plasma concentrations or objective evidence of pulmonary or systemic congestion of cardiogenic origin.[1] HF is the final common pathway for numerous cardiac disorders including those affecting the pericardium, heart valves, and myocardium. HF may be caused by an abnormality that affects cardiac systolic function, diastolic function, or both. Making the distinction is important because the treatment of HF may be quite different depending on whether the predominant mechanism of the disorder is systolic (ie, reduced left ventricular ejection fraction [LVEF]), now referred to as heart failure with reduced ejection fraction (HFrEF) or diastolic dysfunction (HF with normal LVEF, termed heart failure with preserved ejection fraction, HFpEF). Approximately 50% of patients with HF have HFpEF with disturbances in relaxation (lusitropic) properties of the heart or diastolic dysfunction.[2] However, regardless of the etiology of HF, the principal clinical manifestations (fatigue, dyspnea, and often volume overload) are similar and appear to be independent of the initial cause. This chapter focuses on the treatment of patients with chronic HFrEF and HFpEF. Chapter 37, "Acute Decompensated Heart Failure," discusses the treatment of acute decompensated HF.

EPIDEMIOLOGY

HF is an epidemic public health problem in the United States.[2] Approximately 6 million Americans have HF with 1,000,000 new cases diagnosed each year.[2] Unlike most other cardiovascular diseases, the incidence and prevalence of HF are increasing and are expected to continue to increase over the next few decades as the population ages. A large majority of patients with HF are elderly, with multiple comorbid conditions that influence morbidity and mortality.[2] Improved survival from the treatment of comorbidities such as hypertension and coronary artery disease as well as the more widespread use of device therapy including implantable cardioverter-defibrillators and cardiac resynchronization therapy are likely contributors to the increased incidence and prevalence of HF.[2,3] Annual hospital discharges for HF are approximately 800,000, and HF is a common hospital discharge diagnosis in individuals over age 65 years.[2] The disorder also has a tremendous economic impact, with this expected to increase markedly as the baby-boom generation ages. The annual expenditures for HF were over $30 billion, with estimates approaching $70 billion by 2030.[2] Thus, HF is a major medical problem, with a substantial economic impact that is expected to become even more significant as the population ages.

Marked racial and ethnic disparities in the epidemiology and clinical outcomes of HF exist.[2,4] Black patients are at the highest risk of developing and dying from HF (HFrEF or HFpEF) and are hospitalized at higher rates than White patients.[2,4] The reasons for these differences are multifactorial and represent a complex mix of higher prevalence of cardiovascular risk factors (hypertension, diabetes, obesity, chronic kidney disease), genetic susceptibility, access to care, socioeconomic factors and other social determinants of health, and implicit biases in healthcare providers and systems.[4]

Despite prodigious advances in our understanding of the etiology, pathophysiology, and pharmacotherapy of HF, the prognosis for patients with this disorder remains grim. Although the mortality rates have declined over the last 50 years, the overall 5-year survival remains approximately 42% for all patients with a diagnosis of HF, with mortality increasing with symptom severity.[2] Death is classified as sudden in about 40% of patients, implicating serious ventricular arrhythmias as the underlying cause. Factors affecting the prognosis of patients with HF include, but are not limited to, age, gender, LVEF, renal function, natriuretic peptide plasma concentrations, diabetes, metabolic syndrome, the extent of underlying coronary artery disease, blood pressure (BP), HF etiology, and medical or device therapies.[2] Models incorporating these and other factors enable clinicians to develop reliable estimates of an individual patient's prognosis.[5–7]

CLASSIFICATION AND ETIOLOGY

1 The LVEF is used to classify patients with HF as it identifies specific groups in which guideline-directed medical therapy (GDMT) improves key clinical outcomes such as mortality, hospitalization, and symptoms. Four classifications of HF are proposed: (1) HFrEF; (2) HF with mildly reduced ejection fraction (HFmrEF); (3) HFpEF; and (4) HF with improved EF (HFimpEF) (Table 36-1).[1]

TABLE 36-1

Classification of Heart Failure According to Left Ventricular Ejection Fraction

HF with reduced EF (HFrEF)	HF with LVEF ≤40% (0.4)
HF with mildly reduced EF (HFmrEF)	HF with LVEF 41%-49% (0.41-0.49)
HF with preserved EF (HFpEF)	HF with LVEF ≥50% (0.5)
HF with improved EF (HFimpEF)	HF with baseline LVEF ≤40% (0.4), a ≥10 point increase from baseline LVEF, and a second measurement of LVEF >40% (0.4)

HF, heart failure; LVEF, left ventricular ejection fraction.

Data from Reference 1.

HF can result from any disorder that affects the ability of the heart to contract (systolic function) and/or relax (diastolic dysfunction); common causes of HF are shown in Table 36-2.[8] HFrEF is the classic, more familiar form of the disorder although up to 50% of patients with HF have preserved left ventricular systolic function with presumed diastolic dysfunction, now termed HFpEF.[9] Patients with HFpEF typically are elderly, female, and obese, and have hypertension (HTN), atrial fibrillation, or diabetes.[2,10] Mortality is lower in patients with HFpEF compared to patients with HFrEF, despite HFpEF patients being older.[10]

TABLE 36-2

Common Causes of Chronic Heart Failure

Heart failure with reduced ejection fraction (HFrEF)

- Coronary artery disease (eg, myocardial infarction or ischemia)
- Dilated cardiomyopathies (eg, drug-induced, viral infections, postpartum)
- Pressure overload (eg, systemic or pulmonary hypertension, or aortic valve or pulmonic valve stenosis)
- Volume overload (eg, valvular regurgitation, shunts, high-output states)

Heart failure with preserved ejection fraction (HFpEF)

- Increased ventricular stiffness
  - Ventricular hypertrophy (eg, hypertrophic cardiomyopathy, hypertension)
  - Infiltrative myocardial diseases (eg, amyloidosis, sarcoidosis, endomyocardial fibrosis)
  - Myocardial infarction or ischemia
- Mitral or tricuspid valve stenosis
- Pericardial disease (eg, pericarditis, pericardial tamponade)

Data from Reference 8.

Patients with LVEF between the HFrEF and HFpEF range are considered as "HF with mid-range EF" or "HF with mildly-reduced EF" (HFmrEF).[1] HFmrEF may represent patients with prior HFrEF but with improved LVEF or patients with deterioration in LVEF possibly progressing to HFrEF. To improve the specificity of diagnosing HFmrEF and HFpEF, the clinical diagnosis of HF in these EF categories should be further supported by objective measures. In addition, patients with HF with baseline LVEF <40% (0.4) who experience a greater than 10 point increase from baseline LVEF and a subsequent measurement of LVEF >40% (0.4) may be classified as HFimpEF. Both characteristics of and optimal management of patients with HFmrEF and HFimpEF are areas of ongoing investigations.

Coronary artery disease is the most common cause of HFrEF, accounting for up to 75% of cases.[8] Myocardial infarction (MI) leads to a reduction in muscle mass due to the death of affected myocardial cells. The degree to which contractility is impaired depends on the size of the infarction. To attempt to maintain cardiac output (CO), the surviving myocardium undergoes a compensatory remodeling, thus beginning the maladaptive process that initiates the HF syndrome and leads to further injury to the heart. This is discussed in greater detail in the "Pathophysiology" section. Myocardial ischemia and infarction also affect the diastolic properties of the heart by increasing ventricular stiffness and slowing ventricular relaxation. Thus, MI frequently results in systolic and diastolic dysfunctions.

Impaired systolic function is a cardinal feature of dilated cardiomyopathies. Although the cause of reduced contractility frequently is unknown, abnormalities such as interstitial fibrosis, cellular infiltrates, cellular hypertrophy, and myocardial cell degeneration are seen commonly on histologic examination. Inherited forms of dilated as well as hypertrophic cardiomyopathies may also occur.[8]

Pressure or volume overload causes ventricular hypertrophy, which attempts to return contractility to a near-normal state. If the pressure or volume overload persists, the remodeling process results in alterations in the geometry of the hypertrophied myocardial cells and is accompanied by increased collagen deposition in the extracellular matrix. Thus, both systolic and diastolic functions may be impaired.[11] Examples of pressure overload include systemic or pulmonary HTN and valvular heart disease.

HTN remains an important cause and/or contributor to both HFrEF and HFpEF in many patients, particularly women, the elderly, and African Americans.[2,4,8] The role of HTN should not be underestimated because it is an important risk factor for ischemic heart disease and is present in a high percentage of patients with coronary artery disease. HF is a largely preventable disorder; control of lifestyle risk factors (eg, HTN, coronary heart disease, smoking, obesity, physical inactivity, diabetes) is key to minimizing the risk of HF development. Two causes of HF that have been increasingly recognized include amyloidosis and cardiotoxicity with cancer therapies.

PATHOPHYSIOLOGY

Normal Cardiac Function

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

$$CO = HR \times SV$$CO=HR×SV

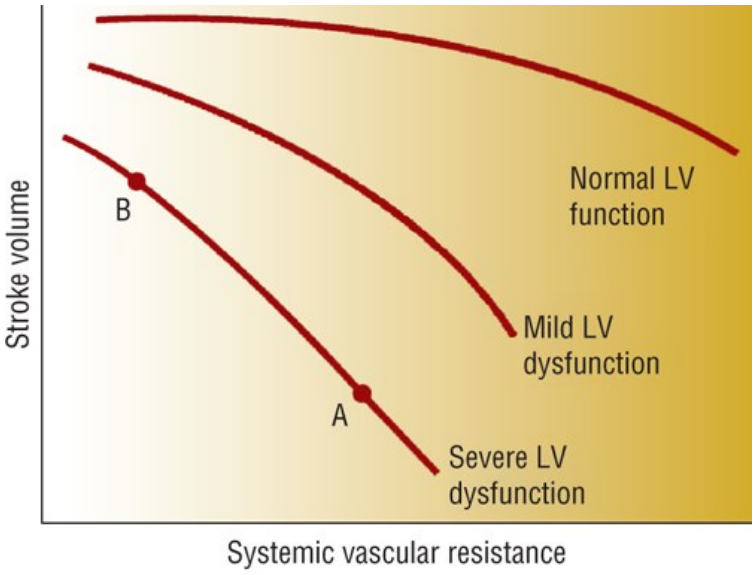
The relationship between CO and mean arterial pressure (MAP) is as follows:

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

HR is controlled by the autonomic nervous system. The volume of blood ejected during systole, or stroke volume, depends on preload, afterload, and contractility.[11] As defined by the Frank-Starling mechanism, the ability of the heart to alter the force of contraction depends on changes in preload. As myocardial sarcomere length is stretched, the number of cross-bridges between thick and thin myofilaments increases, resulting in an increase in the force of contraction. The length of the sarcomere is determined primarily by the volume of blood in the ventricle; therefore, left ventricular end-diastolic volume (LVEDV) is the primary determinant of preload. In normal hearts, the preload response is the primary compensatory mechanism such that a small increase in end-diastolic volume results in a large increase in CO. Because of the relationship between pressure and volume in the heart, left ventricular end-diastolic pressure (LVEDP) is often used in the clinical setting to estimate preload. The hemodynamic measurement used to clinically estimate LVEDP is the pulmonary capillary wedge pressure (PCWP) also known as the pulmonary artery occlusion pressure (PAOP). Afterload is a more complex physiologic concept that can be viewed pragmatically as the sum of forces preventing the active forward ejection of blood by the ventricle. Major components of afterload are ejection impedance, wall tension, and regional wall geometry. In patients with left ventricular systolic dysfunction, an inverse relationship exists between afterload (estimated clinically by SVR) and SV such that increasing afterload causes a decrease in SV (Fig. 36-1). Contractility is the intrinsic property of cardiac muscle describing fiber shortening and tension development.

FIGURE 36-1

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

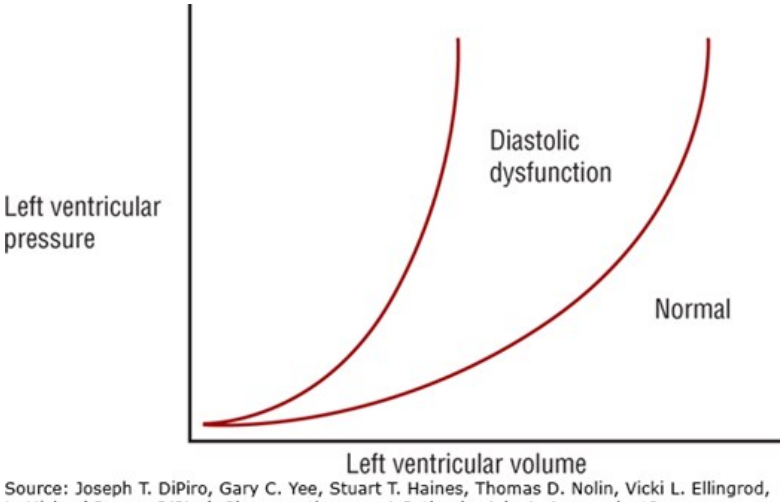


Heart Failure with Preserved Ejection Fraction

This disorder can be defined as a condition in which myocardial relaxation and filling are impaired and incomplete. The ventricle is unable to accept an adequate volume of blood from the venous system, does not fill at low pressure, and/or is unable to maintain normal SV. In its most severe form, HFpEF results in overt symptoms of HF. In modest HFpEF, symptoms of dyspnea and fatigue occur only during stress or activity, when HR and end-diastolic volume increase. In its mildest form, HFpEF can be manifested as a slow or delayed pattern of relaxation and filling with little or no elevation in diastolic pressure and few or no cardiac symptoms. The congestive symptoms that occur with HFpEF are a manifestation of increased pulmonary venous pressures. HFpEF is caused by impaired myocardial relaxation and/or increased diastolic stiffness. When HF is caused by a predominant abnormality in diastolic function, the ventricular chamber is not enlarged, and EF may be normal or even elevated.[12] Figure 36-2 shows the pressure-volume relationship in a patient with normal versus abnormal diastolic function. The changes in the myocardium are associated with a shift upward and to the left of the pressure-volume curve so that for any increase in LV volume, diastolic pressure rises to a much greater level than normally would occur. Clinically, patients present with reduced exercise tolerance and dyspnea when they have elevated LV diastolic pressures. Patients with HFpEF have a predominant abnormality in diastolic function, whereas patients with HFrEF have a predominant abnormality in the systolic function of the LV.

FIGURE 36-2

Diastolic pressure-volume relationship in a normal patient (right trace) and a patient with diastolic dysfunction (left trace).



HFpEF may represent a collection of syndromes because there is significant variability in morphology and functional presentation.[13] Some feel that a systemic inflammatory state and microvascular endothelial dysfunction play a role.[9] Although CAD is a common comorbidity, HF symptoms are often disproportionate to the severity of coronary artery disease. Obesity, HTN, and diabetes are proinflammatory and are frequent comorbidities in patients with HFpEF. During physical exertion, CO increases through integrated enhancements in venous return, contractility, HR, and peripheral vasodilation. The vasodilation that normally occurs during exercise is impaired in HFpEF.[13] Pulmonary HTN is also a common finding. Abnormalities in each of these components of normal exercise reserve function have been identified in HFpEF and all may contribute to pathophysiology in individual patients.[9,12]

Heart Failure with Reduced Ejection Fraction

HFrEF is a progressive disorder initiated by any event that impairs the ability of the heart to contract and sometimes relax resulting in a decrease in CO. The index event may have an acute onset, as with MI, or the onset may be slow, as with long-standing HTN. Regardless of the index event, a decrease in CO results in the activation of compensatory responses to maintain circulation.[11,14] These compensatory responses include: (a) tachycardia and increased contractility through sympathetic nervous system (SNS) activation, (b) the Frank-Starling mechanism, whereby an increase in preload results in an increase in SV, (c) vasoconstriction, and (d) ventricular hypertrophy and remodeling. Compensatory responses evolved to provide short-term support to maintain circulatory homeostasis after acute reductions in BP or renal perfusion. However, the persistent decline in CO in HF triggers long-term activation of these compensatory responses resulting in the complex functional, structural, biochemical, and molecular

changes important for the development and progression of HF. The beneficial and detrimental effects of these compensatory responses are described below and are summarized in Table 36-3.

TABLE 36-3

Beneficial and Detrimental Effects of the Compensatory Responses in Heart

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

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

Tachycardia and Increased Contractility

The increase in HR and contractility that rapidly occurs in response to a drop in CO is primarily due to the release of norepinephrine (NE) from adrenergic nerve terminals, although parasympathetic nervous system activity is also diminished.[14] Loss of atrial contribution to ventricular filling also can occur (atrial fibrillation, ventricular tachycardia), reducing ventricular performance even more. Because ionized calcium is sequestered into the sarcoplasmic reticulum and pumped out of the cell during diastole, the shortened diastolic time with increases in HR also results in a higher average intracellular calcium concentration during diastole, increasing actin-myosin interaction, augmenting the active resistance to fibril stretch, and reducing lusitropy. Conversely, the higher average calcium concentration translates into greater filament interaction during systole, generating more tension.[11] Increasing HR also increases myocardial oxygen demand. If ischemia is induced or worsened, both diastolic and systolic functions may become impaired, and SV can drop precipitously.

Fluid Retention and Increased Preload

Augmentation of preload is another compensatory response that is rapidly activated in response to decreased CO. Renal perfusion in HF is reduced due to both depressed CO and redistribution of blood away from nonvital organs. The kidney interprets the reduced perfusion as an ineffective blood volume, resulting in activation of the renin-angiotensin-aldosterone system (RAAS) in an attempt to maintain BP and increase renal sodium and water retention. Reduced renal perfusion and increased sympathetic tone also stimulate renin release from juxtaglomerular cells in the kidney. As shown in Fig. 36-3, renin is responsible for the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-

converting enzyme (ACE). Angiotensin II may also be generated via non–ACE-dependent pathways. Angiotensin II stimulates aldosterone release from the adrenal gland, thereby providing an additional mechanism for renal sodium and water retention. As intravascular volume increases secondary to sodium and water retention, left ventricular volume and pressure (preload) increase, sarcomeres are stretched, and the force of contraction is enhanced.[11] While the preload response is the primary compensatory mechanism in normal hearts, the chronically failing heart usually has exhausted its preload response.[11] As shown in Fig. 36-4, increases in preload will increase SV only to a certain point. Once the flat portion of the curve is reached, further increases in preload will only lead to pulmonary or systemic congestion, a detrimental result.[11] Figure 36-4 also shows that the curve is flatter in patients with left ventricular dysfunction. Consequently, a given increase in preload in a patient with HF will produce a smaller incremental increase in SV than in an individual with normal ventricular function.

FIGURE 36-3

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

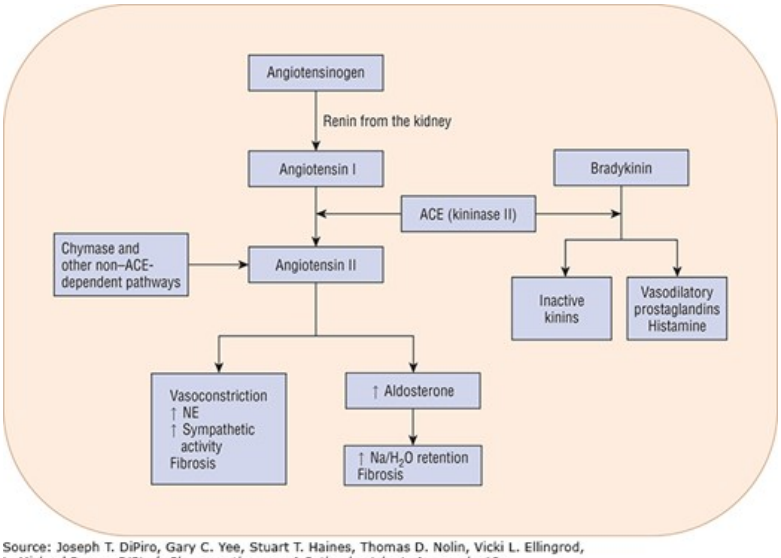
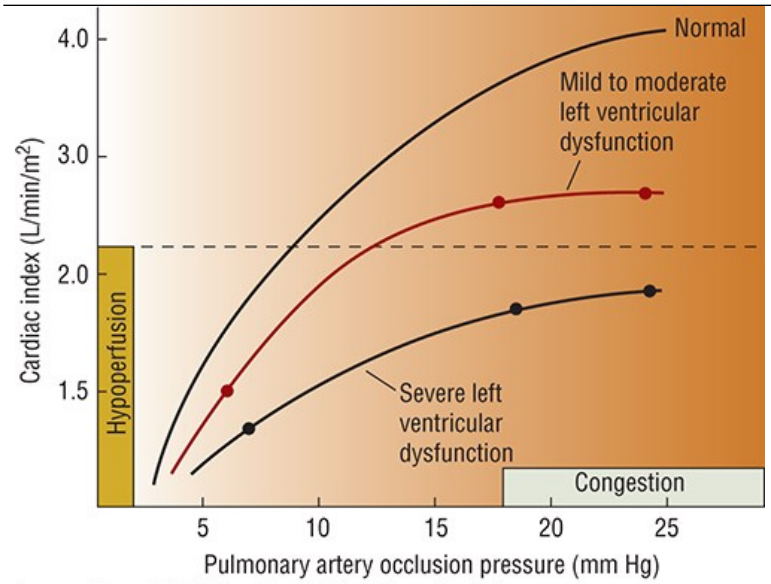


FIGURE 36-4

Relationship between cardiac output (shown as cardiac index which is CO/BSA) and preload (shown as pulmonary artery occlusion pressure).



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Vasoconstriction and Increased Afterload

Vasoconstriction occurs in patients with HFrEF to help redistribute blood flow away from nonessential organs to coronary and cerebral circulations which may be reduced secondary to a decrease in CO (MAP = CO × SVR).[11] A number of neurohormones likely contribute to the vasoconstriction, including NE, angiotensin II, endothelin-1 (ET-1), neuropeptide Y, urotensin II, and arginine vasopressin (AVP).[11,14] Vasoconstriction impedes forward ejection of blood from the ventricle, further depressing CO and heightening the compensatory responses. The failing ventricle is exquisitely sensitive to changes in afterload (**Fig. 36-1**). Thus, increases in afterload often potentiate a vicious cycle of continued worsening and downward spiraling of the HF state.

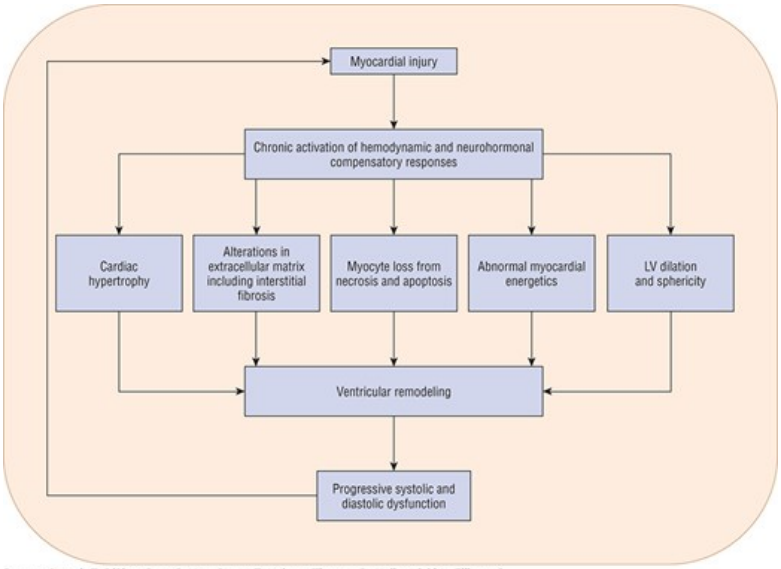
Ventricular Hypertrophy and Remodeling

3 While the signs and symptoms of HF are closely associated with the items described above, the progression of HF appears to be independent of the patient's hemodynamic status. It is now recognized that left ventricular hypertrophy and remodeling are key components in the pathogenesis of progressive myocardial failure.[11] *Ventricular hypertrophy* is a term used to describe an increase in ventricular muscle mass. *Cardiac or ventricular remodeling* is a broader term describing changes in both myocardial cells and the extracellular matrix that result in changes in the size, shape, structure, and function of the heart.[15] These progressive changes in ventricular structure and function ultimately result in a change in the shape of the left ventricle from an ellipse to a sphere. This change in ventricular size and shape serves to further depress the mechanical performance of the heart, increase regurgitant flow through the mitral valve, and, in turn, fuel the continued progression of remodeling. Ventricular hypertrophy and remodeling can occur in association with any condition that causes myocardial injury.[15] The onset of the remodeling process precedes the development of HF symptoms.

Cardiac remodeling is a complex process that affects the heart at the molecular and cellular levels.[11,15] Key elements in the process are shown in Fig. 36-5. Collectively, these events result in progressive changes in myocardial structure and function such as cardiac hypertrophy, myocyte loss, and alterations in the extracellular matrix. The progression of the remodeling process leads to reductions in myocardial systolic and/or diastolic function that, in turn, results in further myocardial injury, perpetuating the remodeling process and the decline in left ventricular performance. Angiotensin II, NE, ET, aldosterone, vasopressin, and numerous inflammatory cytokines, as well as substances under investigation, are active both systemically and locally in the heart. These substances play an important role in initiating the signal transduction cascade responsible for ventricular remodeling. Although these mediators produce harmful effects on the heart, their increased circulating and tissue concentrations are also toxic to other organs and serve as an important reminder that HF is a systemic as well as a cardiac disorder.[11,14,15]

FIGURE 36-5

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



Pressure overload (and probably hormonal activation) associated with HTN produces concentric hypertrophy (increase in the ventricular wall thickness without chamber enlargement), which is often found in HFpEF.[12] Conversely, eccentric left ventricular hypertrophy (myocyte lengthening with increased chamber size with minimal increase in wall thickness) characterizes the hypertrophy seen in patients with systolic dysfunction or previous MI. As the myocytes undergo change, so do various components of the extracellular matrix. For example, collagen degradation may lead to myocyte slippage, fibroblast proliferation, and increased fibrillar collagen synthesis, resulting in fibrosis and stiffening of the entire myocardium. Thus, a number of important ventricular changes that occur with remodeling include alterations in the geometry of the heart from an elliptical to a spherical shape, increases in ventricular mass (from myocyte hypertrophy), and changes in ventricular composition (especially the extracellular matrix) and volumes, all of which contribute to the impaired cardiac function. If the cardiac injury is acute (eg, MI), the ventricular remodeling process begins immediately. However, it is the progressive nature of this process that results in the continual worsening of the HF state, and thus is now the major focus for the identification of new therapeutic targets. In fact, HF pharmacotherapy associated with decreased mortality, and/or slowing the progression of the disease, produce these effects largely by slowing or reversing ventricular remodeling, a process often referred to as *reverse remodeling*.

Amyloid Cardiomyopathy

Amyloidosis is an multisystem disorder in which protein-based infiltrates deposit in tissues including the heart, kidneys, nerves, liver, lungs, and bowel leading to organ dysfunction and death. The vast majority of cardiac amyloidosis is caused by one of two proteins, light chains or transthyretin, resulting in distinct pathophysiology. While the two primary types of amyloidosis, immunoglobulin light chain (AL) and transthyretin (ATTR) are considered rare, ATTR amyloidosis is found in as many as 25% of adults older than 85 years on autopsy. Both forms of amyloidosis are underdiagnosed. Overall, 25% of patients with AL amyloidosis die within 6 months of diagnosis and 25% of patients with ATTR amyloidosis die within 24 months of diagnosis.

Cardiac amyloidosis occurs with the deposition of abnormal proteins into the extracellular space in the myocardium. Heart involvement may result in HF, more commonly HFpEF. Approximately 30 proteins are associated with amyloid cardiomyopathy; however, the most common is transthyretin. The DNA coding sequence for misfolded transthyretin can be inherited, causing the proteins to easily disassociate (hereditary type). ATTR cardiomyopathy

is under-recognized and may be present in up to 15% of older adults with HF. Most cases of cardiac amyloidosis are not inherited but rather related to the aging process. The non-hereditary type (wild-type) is mostly observed in patients older than 60 years. Progressive HF, complicated by arrhythmias and conduction disturbances, may be part of the natural history of the disorder.[16]

Recent advances in standard chemotherapy to treat AL amyloidosis have markedly improved patient outcomes such that auto-stem-cell transplant is now only rarely indicated. ATTR cardiomyopathy was treated only by cardiac transplantation. However, there are now three therapies approved for managing ATTR amyloidosis, depending on the clinical phenotype.[17–19]

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic disorder of the heart, occurring in one of every 200 to 500 persons. It is characterized by the presence of increased left ventricular (LV) wall thickness that is typically severe, asymmetric, and primarily affects the interventricular septum often resulting in obstruction of the left ventricular outflow tract. In up to 60% of adults with HCM, this disease is inherited in an autosomal dominant pattern, associated with mutations in genes encoding proteins of thick and thin myofilament contractile components of the cardiac sarcomere. HCM often remains clinically silent and is the most common cause of sudden death in athletes. Fortunately, pharmacologic, electrical, and surgical interventions have reduced mortality to 0.5% per year. Assessment of the risk of sudden cardiac death (SCD) is of paramount importance since sudden death is considered the main cause of death in younger patients with HCM. Genetic testing is increasingly being applied to patients who meet diagnostic criteria for HCM in order to identify the causative mutation for the disease and to determine the genetic predisposition of asymptomatic relatives. Typical symptoms of HCM include dyspnea, chest pain, palpitations, and syncope. Treatment is aimed at the improvement of symptoms, exercise capacity, and functional status. While pharmacological therapy is first-line, patients may experience symptoms refractory to medications, primarily related to left ventricular outflow obstruction, and surgical or other interventions may be needed.[20]

Neurohormonal Model of Heart Failure

2 3 The current paradigm used to describe HF pathogenesis is the *neurohormonal model*.[11] This model recognizes an initiating event (eg, MI, long-standing HTN) that leads to decreased CO and begins the "HF state." The problem then moves beyond the heart, and it becomes a systemic disease whose progression is mediated largely by neurohormones and autocrine/paracrine factors that drive myocyte injury, oxidative stress, inflammation, and extracellular matrix remodeling. While the former paradigms still guide us to some extent in the symptomatic management of the disease (eg, diuretics), it is this latter paradigm that helps us understand disease progression and, more importantly, the ways to slow disease progression. In the sections that follow, key neurohormones and autocrine/paracrine factors, collectively termed biomarkers, are described with respect to their role in HF and its progression. The benefits of current and investigational drug therapies can be better understood through a solid understanding of the neurohormones they regulate. Although the neurohormonal model provides a logical framework for our current understanding of HF progression and the role of various medications in attenuating this progression, it must be emphasized that this model does not completely explain HF progression.

Angiotensin II

Of the neurohormones and autocrine/paracrine factors that play an important role in HFrEF pathophysiology, angiotensin II is probably the best understood.[11,21] Angiotensin II has multiple actions that contribute to its detrimental effects. It is a potent vasoconstrictor mediated by binding to the angiotensin type 1 (AT1) receptor in the vasculature, and it also causes a release of AVP and ET-1. Angiotensin II facilitates the release of NE from adrenergic nerve terminals, heightening SNS activation. It promotes sodium retention through direct effects on the renal tubules and by stimulating aldosterone release. Its vasoconstriction of the efferent glomerular arteriole helps to maintain renal perfusion pressure in patients with severe HF or impaired renal function. Finally, angiotensin II and many of the neurohormones released in response to angiotensin II play central roles in stimulating ventricular hypertrophy, remodeling, myocyte apoptosis, oxidative stress, inflammation, and alterations in the myocardial extracellular matrix. Clinical trials showing that attenuating angiotensin II-mediated effects with ACE inhibitors or ARBs improve hemodynamics, symptoms, hospitalizations, and survival highlight the importance of angiotensin II in HF pathophysiology.[22]

Norepinephrine

NE plays a central role in tachycardia, vasoconstriction, and increased contractility and plasma renin activity in HFrEF.[14] Plasma NE concentrations are elevated in correlation with the degree of HF, and patients with the highest plasma NE concentrations have the poorest prognosis.[11] Excessive SNS

activation causes β_1-receptor downregulation with a subsequent loss of sensitivity to receptor stimulation. Excess catecholamines increase the risk of arrhythmias and can cause myocardial cell loss by stimulating both necrosis and apoptosis. Finally, NE contributes to ventricular hypertrophy and remodeling. The beneficial effects of β-blockers on outcomes in patients with HFrEF support the critical role of sympathetic nervous system activation and NE in the pathophysiology of the HF state.[8,22]

Aldosterone

Aldosterone-mediated sodium retention and its key role in volume overload and edema have long been recognized as important components of the HF syndrome.[11] Circulating aldosterone is increased in HF due to angiotensin II-stimulated synthesis, release of aldosterone from the adrenal cortex, and reduced heptatic clearance of aldosterone due to reduce hepatic perfusion. The direct effects of aldosterone on the heart may be even more important than sodium retention in HF pathophysiology. Aldosterone produces interstitial cardiac fibrosis through increased collagen deposition in the extracellular matrix of the heart. By increasing the stiffness of the myocardium, cardiac fibrosis may decrease systolic function and impair diastolic function. Extra-adrenal production of aldosterone in the heart, kidneys, and vascular smooth muscle also contributes to the progressive nature of HF through target organ fibrosis and vascular remodeling. Induction of a systemic proinflammatory state, increased oxidative stress, wasting of soft tissues and bone, secondary hyperparathyroidism, and mineral/micronutrient dyshomeostasis are other important pathologic actions of aldosterone that directly contribute to ventricular remodeling and HF progression.[11,21] Clinical trials with the aldosterone antagonists spironolactone[23] and eplerenone[24,25] showing significant reductions in morbidity and mortality in patients with HFrEF provide compelling evidence of the important role of aldosterone in HFrEF initiation and progression. Although not studied as extensively as in HFrEF, aldosterone antagonists also show benefit in select patients with HFpEF.[26,27]

Natriuretic Peptides

The natriuretic peptide family has three members, atrial natriuretic peptide, B-type natriuretic peptide (BNP), and C-type natriuretic peptide. Of these, BNP and its biologically related inactive peptide NT-proBNP are the most useful in the diagnosis and management of HF.[22,28] BNP and NT-proBNP are synthesized and released from the ventricle in response to pressure or volume overload. BNP or NT-proBNP plasma concentrations are elevated in patients with HF, increasing natriuresis and diuresis and attenuating activation of the RAAS and SNS. A recent clinical trial showing that neprilysin-mediated inhibition of natriuretic peptide breakdown improves outcomes in patients with HFrEF supports the importance of these peptides in HF pathophysiology.[29]

The development of easily performed commercial assays for BNP and NT-proBNP resulted in widespread interest in the role of these peptides as a biomarker for prognostic, diagnostic, and therapeutic use. In patients with chronic HFrEF, the degree of elevation in BNP concentrations is closely associated with poor outcomes.[28] Elevation of natriuretic peptide plasma concentrations now plays a key role in establishing the diagnosis of HF.[22] Clinicians should be aware that many cardiovascular and non-cardiovascular co-morbidities (eg, pulmonary embolism, pulmonary hypertension) as well as sex, race/ethnicity, and age may also affect natriuretic peptide levels.[22] In addition, obesity is associated with lower levels of BNP and NT-proBNP, and thus, diagnostic sensitivity in morbidly obese patients is reduced. The most well-established clinical application of BNP testing is in the urgent care setting where the BNP or NT-proBNP assay is useful when combined with clinical evaluation for differentiating dyspnea secondary to either HFrEF or HFpEF from other causes. In patients with either chronic or acute/hospitalized HF, measurements of BNP or NT-proBNP also have utility for risk stratification and prognosis.[28]

Studies evaluating the role of serial BNP measurement to guide drug therapy have not shown consistent improvement in long-term outcomes compared with standard medical therapy, particularly in patients with HFpEF.[28] Guidelines reflect this uncertainty and do not support the routine use of serial BNP measurement in chronic HF management.[28,30] Measurement of BNP should not preclude good clinical judgment and an individualized approach to each patient is imperative.

Other Factors

AVP is a pituitary peptide hormone that regulates renal water excretion and plasma osmolality.[11] Plasma concentrations of AVP are elevated in patients with HF, supporting its role in the pathophysiology of this disorder. The physiologic effects of AVP are mediated through the V_{1a}, V_{1b}, and V_2 receptors.

Stimulation of these receptors by increased circulating AVP results in several maladaptive responses including: (a) increased renal free water reabsorption in the face of plasma hypoosmolality resulting in volume overload and hyponatremia; (b) increased arterial vasoconstriction that contributes to reduced CO; and (c) stimulation of remodeling by cardiac hypertrophy and extracellular matrix collagen deposition. Although the AVP antagonists tolvaptan and conivaptan improve acute symptoms and increase serum sodium and urine output without affecting HR, BP, renal function, or other electrolytes, no improvements in morbidity and mortality were seen in clinical trials.[31]

The sodium-glucose-cotransporter-2 (SGLT2) is highly expressed in the renal proximal tubule and is responsible for reabsorbing more than 90% of filtered glucose that is coupled with Na^+ ions.[32] The SGLT2 inhibitors (eg, empagliflozin, dapagliflozin) lower blood glucose by increasing urinary glucose (and sodium) excretion resulting in diuresis and natriuresis. Clinical trials reported that these agents also reduce the risk of cardiovascular events in patients with HF, including hospitalizations, even in patients without diabetes, suggesting that mechanism(s) other than simply lowering blood glucose are important.[33] Although the exact beneficial mechanisms remain uncertain, these agents reduce inflammation, oxidative stress, and sympathetic nervous system activity as well as improve cardiac remodeling and myocardial energetics.[32,33] The impressive outcomes with these medications in patients with HF further support the notion of HF as a disorder driven by multiple systemic mechanisms.

Factors Precipitating/Exacerbating Heart Failure

Although significant advances have been made in treatment, symptom exacerbation, to the point that hospitalization is required, is a common and growing problem in patients with chronic HF. Hospitalization for HF exacerbation consumes large amounts of healthcare dollars and significantly impairs the patient's quality of life. Thus, there is great interest in identifying and then remedying factors that increase the risk of decompensation. Appropriate therapy can often maintain patients in a "compensated" state, indicating that they are relatively symptom-free. However, there are many aggravating or precipitating factors that may cause a previously compensated patient to develop worsened symptoms necessitating hospitalization. Often, these precipitating factors are reversible or treatable, thus thorough evaluation for their presence is imperative.

Cardiac events are a frequent cause of worsening HF.[34] Myocardial ischemia and infarction are potentially reversible causes that must be carefully considered since nearly 70% of patients with HF have coronary artery disease. Revascularization should be considered in eligible patients. Atrial fibrillation is a common comorbidity in patients with HF and is associated with increased morbidity and mortality.[35] Control of ventricular response, maintenance of sinus rhythm in appropriate patients, and prevention of thromboembolism are important elements in the treatment of patients with concomitant HF and atrial fibrillation. Uncontrolled HTN is also an important contributing factor and should be treated according to current guidelines.[36]

Noncardiac events are also associated with HF decompensation. Pulmonary infections frequently cause worsening HF. Many of these events would be preventable with the more widespread use of the pneumococcal and influenza vaccines. Pulmonary embolus, diabetes, chronic kidney disease, hypothyroidism, and hyperthyroidism should also be considered.

Nonadherence with prescribed HF medications or with dietary recommendations (eg, sodium intake and fluid restriction) is also a common cause of HF exacerbation.[34] Polypharmacy is common in patients with HF.[37] Thus, nonadherence is an important contributor to poor outcomes and socioeconomically disadvantaged patients appear to be disproportionately affected.

Many medications can precipitate or exacerbate HF by one or more mechanisms: (a) negative inotropic effects; (b) direct cardiotoxicity; or (c) increased sodium and/or water retention (Table 36-4).[38] Agents with negative inotropic effects are primarily a concern in patients with HFrEF. Nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly recognized for their ability to exacerbate HF and increase the risk of hospitalization and mortality through volume retention, decreased renal function, and increased BP.[38] The ability of numerous antineoplastic agents to cause or worsen HF is increasingly recognized.[39,40]

TABLE 36-4

Selected Drugs That May Precipitate or Exacerbate Heart Failure

Negative inotropic effect Antiarrhythmics (disopyramide, dronedarone, flecainide, propafenone, sotalol) β-Blockers (eg, propranolol, metoprolol, carvedilol) Calcium channel blockers—nondihydropyridine type (verapamil, diltiazem) Itraconazole
Cardiotoxic Alkylating agents (eg, cyclophosphamide, ifosfamide, melphalan) Amphetamines (eg, cocaine, methamphetamine) Anthracyclines (eg, doxorubicin, daunorubicin, epirubicin, idarubicin) Antiarrhythmics (eg, disopyramide, dronedarone, flecainide, propafenone, sotalol) Antimetabolites (eg, fluorouracil, capecitabine, fludarabine, decitabine) Antimicrotubules (eg, docetaxel, paclitaxel) BCR-ABL inhibitors (eg, bosutinib, dastinib, imatinib, ponatinib) BRAF inhibitors (eg, dabrafenib) Carbamazepine Chimeric antigen receptor (CAR) T-cell therapy (eg, tisagenlecleucel, axicabtageneciloleucel) Daunomycin Ethanol Hormonal therapy (eg, aplalutamide, bicalutamide, darolutamide, nilutamide) Human epidermal growth factor receptor (HER/EGFR) inhibitors (eg, lapatinib, osimertinib) Human epidermal growth factor receptor 2 (HER2) inhibitors (eg, pertuzamab, trastuzumab) Immune checkpoint inhibitors (eg, nivolumab, ipilimumab, pembrolizumab) Immunomodulators (eg, lenalidomide, pomalidomide, thalidomide) MEK inhibitors (eg, binimetinib, cobimetinib, trametinib) Mitomycin Mitoxantrone Mitomycin Vascular endothelial growth factor (VEGF) inhibitors (eg, axitinib. bevacizumab, cabazantobinib, lenvatinib, pazopanib, sorafenib, sunitinib, vandetanib) Miscellaneous (eg, entrectinib, fedratinib, ripretinib, tretinoin)
Sodium and water retention Androgens and estrogens Cyclooxygenase-2 (COX-2) inhibitors Rosiglitazone and pioglitazone Glucocorticoids Nonsteroidal anti-inflammatory drugs (NSAIDs) Pioglitazone and rosiglitazone Salicylates (high dose) Sodium-containing drugs (eg, carbenicillin disodium, ticarcillin disodium)
Uncertain mechanism Dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, saxagliptin) TNF-α inhibitors (eg, adalimumab, infliximab, etanercept)

Many of the precipitating factors for HF are preventable, particularly through appropriate healthcare professional intervention. First and foremost,

multidisciplinary teams should work collaboratively to identify and address such factors. Given medications are often a precipitating factor, engaging a pharmacist in HF care is recommended to assist with identifying inadequate HF therapy, detecting medication nonadherence, and avoiding drug-drug interactions or other medication-related causes of HF.[41,42] A careful medication history is an important aspect of evaluating the cause(s) of HF exacerbation as many are amenable to pharmacist intervention. Attention to these factors can contribute to reducing the risk of adverse cardiovascular outcomes and improving the patient's quality of life.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Heart Failure

Symptoms

Common

- Dyspnea, particularly on exertion
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Exercise intolerance
- Fatigue
- Swollen ankles or other parts of the body
- Bendopnea

Less Common

- Cough
- Wheezing
- Nocturia
- Anorexia, poor appetite, early satiety
- Nausea
- Bloating
- Weight gain or loss
- Dizziness or syncope
- Depression
- Reduced cognitive function (especially in the elderly)

Signs

Specific for Heart Failure

- Jugular venous distention

- Cardiomegaly, lateral displacement of the apical impulse
- Hepatojugular reflux
- S_3 gallop
- Cheyne-Stokes respiration (advanced HF)

Less Specific for Heart Failure

- Peripheral edema (lower extremities, sacral, scrotal)
- Pulmonary rales
- Pulmonary edema
- Weight gain (>2 kg/week)
- Weight loss with muscle wasting/cachexia (advanced HF)
- Pleural effusion
- Tachycardia/irregular pulse
- Tachypnea
- Hepatomegaly/ascites
- Cool extremities
- Oliguria
- Narrow pulse pressure
- Cardiomegaly
- Peripheral edema
- Hepatomegaly
- Venous stasis changes

Laboratory tests

- BNP >35 pg/mL (ng/L; 10 pmol/L) for ambulatory patients or >100 pg/mL (ng/L; 29 pmol/L) for patients hospitalized or with decompensated HF
- NT-proBNP >125 pg/mL (ng/L; 15 pmol/L) for ambulatory patients or >300 pg/mL (ng/L; 35 pmol/L) for patients hospitalized or with decompensated HF
- An electrocardiogram may be normal or it could show numerous abnormalities including acute ST-T wave changes from myocardial ischemia, atrial fibrillation, bradycardia, left ventricular hypertrophy
- Serum creatinine: It may be increased due to hypoperfusion. Preexisting renal dysfunction can contribute to volume overload
- Complete blood count is useful to determine if HF is due to reduced oxygen-carrying capacity
- Chest x-ray: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions

- Echocardiogram: Used to assess LV size, valve function, pericardial effusion, wall motion abnormalities, and ejection fraction
- Hyponatremia: Serum sodium <130 mEq/L (mmol/L) is associated with reduced survival and may indicate worsening volume overload and/or disease progression

Data from Reference 1.

Signs and Symptoms

The primary manifestations of both HFrEF and HFpEF are dyspnea and fatigue, which lead to exercise intolerance, and fluid overload, which can result in peripheral edema and pulmonary congestion.[34,43] The presence of these signs and symptoms may vary considerably from patient to patient such that some patients have dyspnea but no signs of fluid retention, whereas others may have marked volume overload with few complaints of dyspnea or fatigue. However, many patients have both dyspnea and volume overload. Clinicians should remember that symptom severity often does not correlate with the degree of LV dysfunction. Patients with a low LVEF (less than 20%-25% [0.20-0.25]) may be asymptomatic, whereas those with preserved LVEF may have significant symptoms. Symptoms can vary considerably over time in a given patient, even in the absence of changes in ventricular function or medications.

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

Peripheral edema is a cardinal finding in HF. Edema usually occurs in dependent parts of the body and is often seen as ankle or pedal edema in ambulatory patients, although it may be manifested as sacral edema in bedridden patients. Adults typically have a 10-lb (4.5-kg) fluid weight gain before trace peripheral edema is evident; therefore, patients with acute decompensated HF may have no clinical evidence of systemic congestion except weight gain. Body weight is thus an excellent short-term endpoint for evaluating fluid status. Nonfluid weight gain and loss of muscle mass due to cardiac cachexia are potential confounders for long-term use of weight as a marker for fluid status. Hepatomegaly and ascites are other signs of systemic congestion.

Patients with HFrEF may exhibit signs and symptoms of low CO alone or in addition to volume overload. The primary complaint associated with hypoperfusion is fatigue. Objective indicators of low CO include worsening renal function, cool extremities, altered mental status, resting tachycardia, low systolic blood pressure, and narrow pulse pressure.

Diagnosis

No single test is available to confirm the diagnosis of HF—it is a clinical syndrome with current or prior signs and symptoms due to any cardiac structural and/or functional disorder corroborated by elevated plasma natriuretic peptide concentrations or objective evidence of pulmonary or systemic congestion from a cardiogenic cause.[1,43] Because HF can be caused or worsened by multiple cardiac and noncardiac disorders, some of which may be treatable or reversible, accurate diagnosis is essential for the development of therapeutic strategies. HF is often initially suspected in a patient based on symptoms. However, signs and symptoms lack sensitivity for diagnosing HF since they are frequently found with many other disorders. Even in patients with known HF, there is a poor correlation between the presence or severity of symptoms and the hemodynamic abnormality. With few exceptions, HFpEF cannot be distinguished from HFrEF on the basis of the history, physical examination, chest x-ray, and ECG alone.[9] Patients with HFpEF are often elderly, with multiple comorbidities.[9]

A complete history and physical examination targeted at identifying cardiac or noncardiac disorders or behaviors that may cause or hasten HF development or progression are essential in the initial patient evaluation. Careful medication history should also be obtained with a focus on the use of medications that can precipitate or exacerbate HF (Table 36-4).[38]

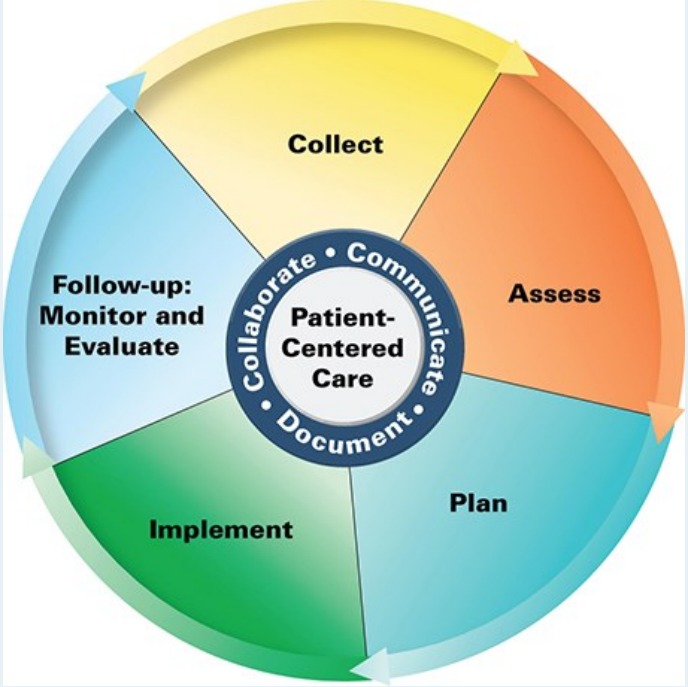
Particular attention should be paid to cardiovascular risk factors and to other disorders that can cause or exacerbate HF such as HTN, diabetes, atrial fibrillation, dyslipidemia, tobacco use, sleep-disordered breathing, iron deficiency, and thyroid disease. Since coronary artery disease is the cause of

HF in many patients, evaluation of the possibility of coronary disease is essential, especially in men. If coronary artery disease is detected, appropriate revascularization procedures may then be considered. The patient's volume status should be documented by assessing the body weight, JVD, and presence or absence of pulmonary congestion and peripheral edema. The biomarkers BNP or NT-proBNP are increased in most patients and their measurement is a key component of establishing the diagnosis of HF, particularly for differentiating dyspnea caused by HF from other causes.[1,30] The initial evaluation should include a complete blood count, serum electrolytes (including calcium and magnesium), assessment of renal and hepatic function, urinalysis, lipid profile, hemoglobin A1C, thyroid function tests, iron studies, chest x-ray, and 12-lead ECG.

Although the history, physical examination, and laboratory tests provide important insight into the underlying cause of HF, the echocardiogram is a standard test routinely used in the evaluation of the patient with HF. The echocardiogram is used to assess abnormalities in cardiac structure and function and should include evaluation of the pericardium, myocardium, and heart valves, and quantification of the LVEF to determine if systolic or diastolic dysfunction is present. Other imaging modalities may occasionally be used in conjunction with the echocardiogram including radionucleotide ventriculography, cardiac, computed tomography, and cardiac magnetic resonance.

PATIENT CARE PROCESS

Patient Care Process for Heart Failure



An illustration shows that patient-centered care includes collaboration, communication, and documentation. The actions associated with the care are collect, assess, plan, implement, and follow-up by monitoring and evaluating.

The processes of Collect and Assess are similar for patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) as are the processes of Implement and Follow-up: Monitor and Evaluate. In contrast, while the Plan process has many similarities between HFrEF and HFpEF, some important differences in the Plan are described below.

Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use) and dietary habits including intake of sodium-containing foods and fluid

- Current medications including over-the-counter (OTC), herbal products, dietary supplements
- Etiology of heart failure (Table 36-1)
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, left ventricular ejection fraction, echocardiogram, chest x-ray
  - Labs including complete blood count, comprehensive metabolic panel (eg, serum Na, K, BUN, creatinine), urinalysis, liver function tests, thyroid-stimulating hormone, iron studies (serum ferritin and transferrin saturation), brain natriuretic peptide (BNP) or NT-pro-BNP, electrocardiogram (ECG)
  - Physical examination (eg, signs/symptoms of volume overload [see the "Clinical Presentation" box])

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg, signs/symptoms of hypotension or poor perfusion)
- Presence of comorbidities (eg, coronary artery disease, hypertension, diabetes, atrial fibrillation)
- Presence of volume overload (eg, weight gain, rales, jugular vein distension, peripheral edema)
- Presence of exertional dyspnea, orthopnea, fatigue
- Emotional status (eg, presence of anxiety, depression)

Plan*

- HFrEF
  - Initiate and titrate guideline-directed medical therapy (GDMT) with ARNI/ACEI/ARB (ARNI preferred) + β-blocker + aldosterone antagonist + SGLT2 inhibitor (Fig. 36-6, Tables 36-7 and 36-9). Add diuretics if the patient is volume overloaded
  - Add additional drug therapy as indicated based on patient characteristics (eg, isosorbide dinitrate/hydralazine, ivabradine, digoxin, vericiguat [Figs. 36-6 and 36-7, Tables 36-7 and 36-9])
- HFpEF
  - Initiate and titrate GDMT with ARNI + aldosterone antagonist + SGLT2 inhibitor in select patients (Tables 36-7 to 36-9). Add diuretics if the patient is volume overloaded.
- Monitoring parameters including efficacy (eg, shortness of breath, lower extremity edema, pulmonary congestion) and safety (eg, worsening renal function, hypotension, bradycardia [if prescribed β-blocker, ivabradine, or digoxin], hyperkalemia); follow-up frequency and timing
- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information, medication administration)
- Self-monitoring for HF symptoms (eg, daily weights, sodium and fluid intake)
- Referrals to other providers when appropriate (eg, HF specialist for consideration of advanced therapies [HFrEF], electrophysiologist for placement of ICD [HFrEF, secondary prevention of sudden cardiac death in select patients with HFpEF] and/or CRT [HFrEF], dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan

- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, serum creatinine, electrolytes, vital signs, adherence assessment)

Follow-up: Monitor and Evaluate

- Resolution of HF signs and symptoms (eg, JVD, weight, shortness of breath)
- Evaluate the need for dose titration of GDMT and/or the initiation of additional therapies
- Presence of adverse effects (eg, serum creatinine, electrolytes, BP, HR)
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with the patient, caregivers, and other healthcare professionals.*

TREATMENT

Desired Outcomes

The goals of therapy in the management of chronic HF are to improve the patient's quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow progression of the disease, and prolong survival. Pharmacotherapy plays a key role in achieving these goals.[22,30] In addition, identification of risk factors for HF development and recognition of its progressive nature has led to increased emphasis on preventing the development of this disorder. In an attempt to standardize the definition of HF and provide clarity to clinicians and patients on optimal preventive and treatment approaches, an international group that included the Heart Failure Society of America developed a staging system to emphasize that HF is a continuum and that not only recognizes the evolution and progression of the disorder but also emphasizes risk factor modification and preventive treatment strategies (Table 36-5).[1]

TABLE 36-5

Stages of Heart Failure

Stages	Definition
Stage A **At-risk for heart failure**	Patients at risk for HF but without current or prior symptoms or signs of HF and without structural, biomarker, or genetic markers of heart disease ○ Patients with HTN, CVD, DM, obesity, known exposure to cardiotoxins, family history of cardiomyopathy
Stage B **Pre-heart failure**	Patients without current or prior symptoms or signs of HF but evidence of *one* of the following: ○ Structural heart disease: eg, LVH, chamber enlargement, wall motion abnormality, myocardial tissue abnormality, valvular heart disease ○ Abnormal cardiac function: eg, reduced LV or RV systolic function, evidence of increased filling pressures or abnormal diastolic dysfunction ○ Elevated natriuretic peptide levels or elevated cardiac troponin levels in the setting of exposure to cardiotoxins
Stage C **Heart failure**	Patients with current or prior symptoms and/or signs of HF caused by structural and/or cardiac abnormality ○ HF in remission *or* persistent HF
Stage D **Advanced heart failure**	Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT ○ Requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care

CVD, cardiovascular disease; DM, diabetes; GDMT, guideline-directed medical therapy; HF, heart failure; HTN, hypertension; LV, left ventricle; LVH, left ventricular hypertrophy; RV, right ventricle.

Data from Reference 1.

The four stages of this system differ from the NYHA functional classification that classifies symptoms according to the clinician's subjective evaluation and does not recognize preventive measures or the progression of the disorder (Table 36-6). For patients with symptomatic HF (Stage C or D), symptoms can change frequently over a short period of time due to changes in medications, diet, intercurrent illnesses, or other causes. For example, a patient with Stage C HF with NYHA class IV symptoms such as marked volume overload could improve to class I or II with appropriate GDMT, yet they will remain categorized as Stage C.

TABLE 36-6

New York Heart Association Functional Classification

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

The general principles used to guide the treatment of HFrEF are based on numerous large, randomized, double-blind, multicenter trials. No such randomized trials had been performed in patients with HFpEF. Consequently, the guidelines for the management of HFpEF are based primarily on clinical investigations in relatively small groups of patients, clinical experience, and concepts based on the knowledge and understanding of the pathophysiology of the disease process. Treatment of HFpEF has been directed primarily at alleviation of congestion with diuretics, managing precipitating factors and comorbid conditions (eg, ischemia, HTN, atrial fibrillation), and addressing underlying microvascular inflammation.[10] Previously, the typical therapies used for HFrEF have not shown a significant benefit for patients with HFpEF. However, more recent studies identified several agents that are also beneficial for HFpEF.

General Approach to Treatment

The complexity of the HF syndrome necessitates a comprehensive approach to management that includes accurate diagnosis, identification, and treatment of risk factors, elimination or minimization of precipitating factors, appropriate pharmacologic and nonpharmacologic therapy, and close monitoring and follow-up.

The first step in the management of chronic HF is to determine the classification of HF based upon LVEF and symptoms based upon NYHA functional class (see Tables 36-1 and 36-6) and/or any precipitating factors. Appropriate treatment of underlying disorders (eg, hyperthyroidism, valvular heart disease) may obviate the need for specific HF treatment. Revascularization or anti-ischemic therapy in patients with coronary disease may reduce HF symptoms. Drugs that aggravate HF (see Table 36-4) should be discontinued if possible.

Restriction of dietary sodium and fluid intake is an important lifestyle intervention for both HFrEF and HFpEF. Mild (<3 g/day) to moderate (<2 g/day) sodium restriction, in conjunction with daily measurement of weight, should be implemented to minimize volume retention and allow the use of lower and safer diuretic doses. Patients should avoid adding salt to prepared foods and eliminate foods high in sodium (eg, salt-cured meats, salted snack foods, pickles, soups, delicatessen meats, and processed foods). In patients with hyponatremia (serum Na <130 mEq/L [mmol/L]) or those with persistent volume retention despite high diuretic doses and sodium restriction, daily fluid intake should be limited to 2 L/day from all sources. However, both sodium and fluid restriction must be done with care in patients with HFpEF. Excessive restriction can lead to hypotension, a low-output state, and/or renal insufficiency. Daily weights may help assess volume status. Dietary and lifestyle factors that decrease the risk of development of CAD, HTN, diabetes, and obesity should be encouraged. Although guidelines indicate sodium restriction is reasonable to minimize congestion, proven benefits on clinical outcomes are lacking.

Other important general measures include patient and family counseling on the signs and symptoms of HF, detailed written instructions on the importance of appropriate medication use and compliance, activity level, diet, discharge medications, weight monitoring, continuity of care, and the

need for close monitoring and follow-up to reinforce compliance and minimize the risk of HF exacerbations and subsequent hospitalization.[22]

4 Treatment guidelines are organized around the four identified stages of HFrEF, and the recommendations are summarized in Fig. 36-6 and Fig. 36-7.[22,34] These figures address stages A-D with stage D discussed in greater detail in "Acute Decompensated Heart Failure," Chapter 37. While the guidelines primarily focus on HFrEF, discussions of HFpEF, acute decompensated HF, and management of patients with comorbid diseases often encountered in this population are included. Dosing recommendations for GDMT used to treat patients with HFrEF and HFpEF are provided in Table 36-7.

TABLE 36-7

Guideline Recommended Drug Therapies and Doses for HFrEF and HFpEF

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Loop Diuretics					
Furosemide	Lasix®	20-40 mg once or twice daily	20-160 mg once or twice daily	Cl_{cr} 20-50 mL/min (0.33-0.83 mL/s): 160 mg once or twice daily	Single doses exceeding those listed are unlikely to elicit additional response
				Cl_{cr} <20 mL/min (0.33 mL/s): 400 mg daily	
Bumetanide	Bumex®	0.5-1.0 mg once or twice daily	1-2 mg once or twice daily	Cl_c 20-50 mL/min (0.33-0.83 mL/s): 2 mg once or twice daily	Single doses exceeding those listed are unlikely to elicit additional response
				Cl_{cr} <20 mL/min (0.33 mL/s): 8-10 mg daily	
Torsemide	Demadex®	10-20 mg once daily	10-80 mg once daily	Cl_c 20-50 mL/min (0.33-0.83 mL/s): 40 mg once daily	Single doses exceeding those listed are unlikely to elicit additional response
				Cl_{cr} <20 mL/min (0.33 mL/s): 200 mg daily	
ACE Inhibitors					
Captopril	Capoten®	6.25 mg three times daily	50 mg three times daily[a]		
Enalapril	Vasotec®	2.5 mg twice daily	10-20 mg twice		

			daily[a]		
Lisinopril	Zestril®, Prinivil®	2.5-5.0 mg once daily	20-40 mg once daily[a]		
Quinapril	Accupril®	5 mg twice daily	20-40 mg twice daily		
Ramipril	Altace®	1.25-2.5 mg once daily	10 mg once daily[a]		
Fosinopril	Monopril®	5-10 mg once daily	40 mg once daily		Undergoes both hepatic and renal elimination
Trandolapril	Mavik®	1.0 mg once daily	4 mg once daily[a]		Undergoes both hepatic and renal elimination
Perindopril	Aceon®	2 mg once daily	8-16 mg once daily		Undergoes both hepatic and renal elimination
Angiotensin Receptor Blockers					
Candesartan	Atacand®	4-8 mg once daily	32 mg once daily[a]		
Valsartan	Diovan®	20-40 mg twice daily	160 mg twice daily[a]		
Losartan	Cozaar®	25-50 mg once daily	150 mg once daily[a]		
Angiotensin Receptor Blocker/Neprilysin Inhibitor					
Sacubitril/valsartan	Entresto®	49/51 mg sacubitril/valsartan twice daily	97/103 mg sacubitril/valsartan twice daily[a]		For patients taking a low dose of or not taking an ACE inhibitor or ARB or if eGFR is <30 mL/min/1.73 m^2, the starting dose is 24/26-mg sacubitril/valsartan twice daily
Beta-blockers					
Bisoprolol	Zebeta®	1.25 mg once daily	10 mg once daily[a]		
Carvedilol	Coreg®	3.125 mg twice daily	25 mg twice daily[a]	Target dose for patients weighing >85 kg is 50 mg twice daily	Should be taken with food
Carvedilol phosphate	Coreg CR®	10 mg once daily	80 mg once daily		Should be taken with food
Metoprolol succinate CR/XL	Toprol-XL®	12.5-25 mg once daily	200 mg once daily[a]		
Aldosterone Antagonists					

Spironolactone	Aldactone®	eGFR >50 mL/min/1.73 m^2: 12.5-25 mg once daily	25-50 mg once daily[a]	eGFR 30-49 mL/min/1.73 m^2: 12.5 mg once daily or every other day	The risk of hyperkalemia increases if serum creatinine is >1.6 mg/dL (141 µmol/L). Avoid if baseline potassium is >5 mEq/L (mmol/L)
Eplerenone	Inspra®	eGFR >50 mL/min/1.73 m^2: 25 mg once daily	50 mg once daily[a]	eGFR 30-49 mL/min/1.73 m^2: 25 mg every other day	The risk of hyperkalemia increases if serum creatinine is >1.6 mg/dL (141 µmol/L). Avoid if baseline potassium is >5 mEq/L (mmol/L)
SGLT2 Inhibitors					
Dapagliflozin	Farxiga®	10 mg daily	10 mg daily	eGFR ≥30 mL/min/1.73 m^2	
Empagliflozin	Jardiance®	10 mg daily	10 mg daily	eGFR ≥20 mL/min/1.73 m^2	
Others					
Hydralazine-Isosorbide Dinitrate	Bidil®	Hydralazine 37.5 mg three times daily	Hydralazine 75 mg three times daily[a]		Indicated in conjunction with standard heart failure therapy in patients with HFrEF to improve survival and reduce hospitalizations in Black patients. Also an alternative if intolerance to ACEI/ARB/ARNI (eg, angioedema)
Digoxin	Lanoxin®	Isosorbide dinitrate 20 mg three times daily	Isosorbide dinitrate 40 mg three times daily[a]	Reduce dose in elderly, patients with low lean body mass, and patients with impaired renal function	Indicated in conjunction with standard HF therapy in patients with HFrEF to improve symptoms and reduce hospitalizations. Target plasma concentration range is 0.5-0.9 ng/mL (µg/L; 0.6-1.2 nmol/L). Does not improve survival in patients with HFrEF
		0.125-0.25 mg once daily	0.125-0.25 mg once daily		
Ivabradine	Corlanor®	5 mg twice daily	5-7.5 mg twice daily	Avoid if resting heart rate <60 BPM before treatment	Indicated in conjunction with standard HF therapy in patients with HFrEF to reduce the risk of hospitalization in patients with HFrEF with a resting heart rate >70 BPM receiving maximally tolerated beta-blocker doses. Take with meals
Vericiguat	Verquvo®	2.5 mg once daily	10 mg once daily		Indicated in conjunction with standard HF therapy in patients with HFrEF to improve CV survival and reduce HF hospitalization. Take with food

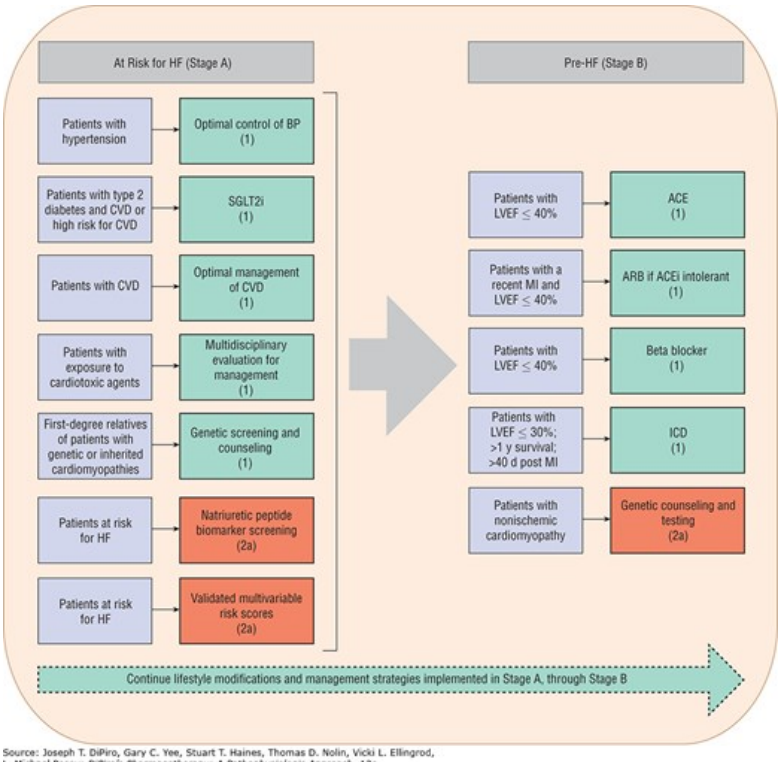
[a]Regimens proven in large clinical trials to reduce mortality.

BPM, beats per minute; Cl_{cr}, creatinine clearance; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction.

Data from References 22 and 44.

FIGURE 36-6

Recommendations (Class 1 and 2a) for Patients at Risk of HF (stage A) and those with Pre-HF (stage B). See ACC/AHA/HFSA for Class of Recommendation definitions provided under each recommendation (e.g., 1, 2a). ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; HF, heart failure; ICD, implantable cardioverter-defiibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SGLT2i, sodium glucose cotransporter 2 inhibitor. Data from Reference 22.



Less information guiding the treatment of HFpEF is available. This relative paucity of evidence is reflected in guidelines for the diagnosis and management of HFpEF; however, the most recent ACC/AHA/HFSA guidelines provided greater clarity.[22,30,45] In general, all three guidelines recommend treating comorbid conditions by controlling HR and BP, alleviating causes of myocardial ischemia, reducing volume, and restoring and maintaining sinus rhythm in patients with atrial fibrillation. Table 36-8 summarizes the therapeutic recommendations for HFpEF.

TABLE 36-8

Pharmacotherapy for Heart Failure with Preserved Ejection Fraction

Recommendations

- Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (a)
- In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (2a)
- In patients with HFpEF, management of AF can be useful to improve symptoms. (2a)
- In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (2b)
- In selected patients with HFpEF, the use of ARBs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (2b)
- In selected patients with HFpEF, ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (2b).

See ACC/AHA/HFSA for Class of Recommendation definitions provided under each recommendation (e.g., 1, 2a, 2b).

AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin II receptor-neprilysin inhibitor; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MRA mineralcorticoid receptor antagonist; SGLT2i, sodium glucose cotransporter 2 inhibitor

Data from Reference 22,30.

As the management of HF has become increasingly complex, disease management programs that include HF specialty clinics, home-based interventions, structured telephone support, and close patient follow-up are frequently used. Most are multidisciplinary and may include physicians, advanced practice nurses, dieticians, and pharmacists. In general, the programs focus on optimization of drug and non-drug therapy, patient and family education and counseling, exercise and dietary advice, intense follow-up by telephone or home visits, improving adherence to medications and lifestyle recommendations, encouragement of self-care, early recognition of and management of volume overload, and referral to palliative care when appropriate.[22] Such programs typically focus on patients with more severe HF who are at high risk for hospital admission. In general, multidisciplinary disease management programs improve quality of life and reduce HF and all-cause hospitalizations and costs, although these benefits are not consistently demonstrated in all studies.

Treatment of Stage A Heart Failure

Patients who are at risk for HF are classified as Stage A.[1] These patients have no HF signs and symptoms or structural or biomarker evidence of heart disease but are at risk for developing HF because of the presence of risk factors (Fig. 36-6). The emphasis in these patients is on risk factor identification and modification to prevent the development of structural heart disease and subsequent HF. Commonly encountered risk factors include HTN, dyslipidemia, diabetes, obesity, metabolic syndrome, smoking, exposure to cardiotoxins, and coronary artery disease, among others. Although each of these disorders individually increases risk, they frequently coexist in many patients and act synergistically to foster the development of both HFrEF and HFpEF.[3] Effective blood pressure control reduces the risk of developing HF by approximately 50%; thus, current HTN-treatment guidelines should be followed.[3,22,36] Obesity, diabetes, and metabolic syndrome also importantly contribute to the risk of developing HF.[3,46] Appropriate management of coronary disease and its associated risk factors are also important. Although treatment must be individualized, ACE inhibitors or ARBs and statins are recommended for HF prevention in select patients with atherosclerotic vascular disease or diabetes.[34] New to the guidelines addressing Stage A HF, sodium-glucose cotransporter type 2 (SGLT2) inhibitors should be strongly considered in patients with with type 2 diabetes and CVD or high risk for CVD as these agents reduce the risks of adverse cardiovascular events and hospitalization for HF.[46,47]

Treatment of Stage B Heart Failure

Patients in Stage B, or pre-HF, have structural heart disease, abnormal cardiac function (eg, systolic and/or diastolic dysfunction), or increased

natriuretic peptide plasma concentrations, but do not have current or prior HF symptoms.[1] This group includes patients with left ventricular hypertrophy, recent or remote MI, valvular disease, or LVEF <40% (0.4). Treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process. In addition to the treatment measures outlined in Stage A, all patients with an LVEF <40% (0.4) should receive an ACE inhibitor or ARB and a β-blocker, especially if there is a history of MI.[22] Management strategies implemented in patients at risk for HF (stage A) should be continued through stage B.[22]

Treatment of Stage C Heart Failure

Patients with structural heart disease and previous or current symptoms are classified in Stage C. Most patients with HFrEF in Stage C should be routinely treated with GDMT proven to improve morbidity and mortality (Fig. 36-7).[22] In select patients, hydralazine-isosorbide dinitrate (ISDN), loop diuretics, digoxin, ivabradine, and vericiguat may also be considered.[22] Nonpharmacologic therapy with devices such as an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) with a biventricular pacemaker is also indicated in certain patients with HFrEF in Stage C (see the "Nonpharmacologic Therapy" section).[22]

Treatment of Stage D Heart Failure

Patients with advanced HF are classified as Stage D.[1] These patients experience persistent symptoms despite receiving maximally tolerated GDMT. This stage is often also referred to as refractory or end-stage HF. These patients often undergo recurrent hospitalizations or cannot be discharged from the hospital without special interventions, have a poor quality of life, and are at high risk for morbidity and mortality. Patients with advanced HFrEF should be considered for referral to HF management programs so that specialized therapies including mechanical circulatory support, cardiac transplantation, and palliative care may be considered in addition to standard treatments outlined in Stages A to C.[34,48] Unfortunately, these same advanced therapies are not beneficial for patients with HFpEF. For all patients with advanced HFrEF or HFpEF, discussions with the patient and family members regarding prognosis, patient priorities for minimizing symptoms versus prolonging survival, options for additional treatments, and end-of-life and hospice care should be initiated.[22] The approach to the treatment of patients with Stage D HF is discussed in more detail in Chapter 37.

Nonpharmacologic Therapy

Sudden cardiac death, primarily due to ventricular tachycardia and fibrillation, is responsible for 40% to 50% of the mortality in patients with HFrEF. Implantation of an ICD prevents sudden cardiac death and is an effective primary prevention strategy to reduce the risk of mortality in selected patients with HFrEF.[49] Current guidelines recommend the use of an ICD for primary prevention in patients receiving GDMT with NYHA class II-III symptoms and an LVEF <35% (0.35) that are expected to live for at least 1 year.[49] In patients with NYHA class I symptoms and an LVEF <30% (0.30), an ICD is also recommended for primary prevention if life expectancy exceeds 1 year.[49]

Delayed electrical activation of the left ventricle, characterized on the ECG by a QRS duration that exceeds 120 ms, occurs in approximately one-third of patients with moderate-to-severe HFrEF. Since the left and right ventricles normally activate simultaneously, this delay results in asynchronous contraction of the ventricles and contributes to the hemodynamic abnormalities of HF. Implantation of a specialized biventricular pacemaker, cardiac resynchronization therapy (CRT), to restore synchronous activation of the ventricles improves ventricular function and hemodynamics and is associated with reverse remodeling and increased LVEF. The use of CRT improves exercise capacity, symptoms, quality of life, hospitalizations, and mortality in patients with HRrEF.[22] Guidelines recommend CRT in patients receiving GDMT that have NYHA class II-III or ambulatory class IV symptoms and with a QRS duration >150 ms and LVEF <35% (0.35).[22] CRT can also be considered in selected patients with a QRS duration between 120 and 149 ms. Combined CRT and ICD devices are used if the patient meets the indications for both devices.

Wireless hemodynamic monitoring of pulmonary artery pressures remotely as a supplemental measurement of fluid status in patients at high risk for HF-related hospitalization is now possible.[50] The CardioMEMS™ implantable pulmonary artery sensor reduces the risk of HF hospitalization in selected patients.[51] In contrast, the usefulness of noninvasive telemonitoring or remote monitoring of physiological parameters (eg, patient activity, impedance, HR) via implanted electrical devices (ICDs or CRT-Ds) to improve clinical outcomes remains uncertain.

In patients with stage D HFrEF receiving GDMT, the use of mechanical circulatory support with a left ventricular assist device (LVAD) can be considered in certain patients.[22] Although the criteria for use of these devices continue to rapidly evolve, they are frequently used to bridge patients to cardiac

transplant or as destination therapy in patients ineligible for transplant, and their use in these settings is associated with better survival and improved functional capacity.[22,52] Their use is covered in more detail in Chapter 37 (Acute Decompensated Heart Failure).

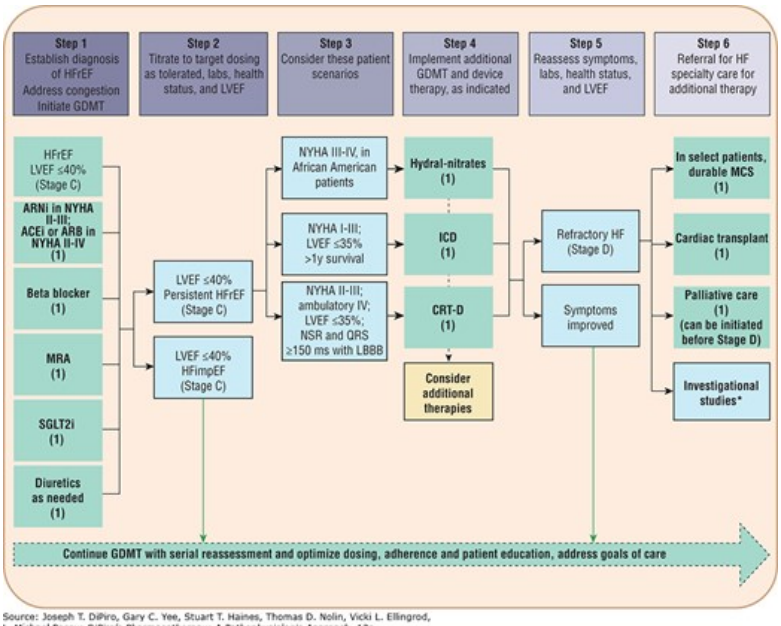
Pharmacologic Therapy

Pharmacologic Therapy for Stages B-D HFrEF

A treatment algorithm for the management of patients with Stages A or B HFrEF is shown in Fig. 36-6 and for Stages C and D HFrEF in Fig. 36-7. In general, patients with Stage B HFrEF should receive an ACE inhibitor or ARB and β-blocker and, in select patients, an SGLT2 inhibitor.[22] Patients with Stage C HFrEF should receive combined therapy with an ARNI (preferred) or ACE inhibitor or ARB, β-blocker, aldosterone antagonist, and SGLT2 inhibitor.[22] The optimal sequence for initiating these four medication classes remains uncertain. However, there is growing interest in simultaneous initiation of low doses of each drug class due to the incremental and early benefits of these different medications on morbidity and mortality.[53,54] Given the demonstrated benefits of optimal GDMT on crucial outcomes and that large numbers of patients receive inadequate GDMT, strategies to improve the initiation and dose titration of these life-saving treatments are clearly needed.[55,56]

FIGURE 36-7

Treatment of HFrEF Stages C and D. See ACC/AHA/HFSA for Class of Recommendation definitions. Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication. Medication doses should be increased to target as tolerated. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; MCS, mechanical circulatory support; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; and SGLT2i, sodium-glucose cotransporter 2 inhibitor. *Participation in investigational studies is appropriate for stage C, NYHA class II and III HF. *(Data from Reference 22.)*



A diuretic should be administered if there is evidence of fluid retention. Other therapies including the combination of hydralazine-nitrates, digoxin, ivabradine, or vericiguat can be considered in selected patients.[22] Drug dosing and monitoring are summarized in Tables 36-7 and 36-9.

TABLE 36-9

Drug Monitoring

Drug Class	Adverse Effect	Monitoring Parameters	Comments
Diuretics	Hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, renal dysfunction, thirst	BP, electrolytes, BUN, creatinine, glucose, uric acid, changes in weight, JVD	Dose should be adjusted based on volume status, renal function, electrolytes, and BP. Reassess these parameters 1-2 weeks after dose changes. Goal is lowest dose that maintains euvolemia.
ACE inhibitors	Angioedema, cough, hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis, history of angioedema, or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or increase in dose. Goal is target dose from clinical trials or highest tolerated.
ARBs	Hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or increase in dose. Use with caution in patients with a history of ACE inhibitor-associated angioedema. Goal is target dose from clinical trials or highest tolerated.
ARNI	Angioedema, hyperkalemia, hypotension, dizziness, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with a history of angioedema associated with ACE inhibitor or ARB therapy or in pregnancy. ACE inhibitors should be discontinued at least 36 hours before ARNI initiation. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or dose increase. Start with a low dose and double the dose every 2-4 weeks as tolerated based on BP, serum potassium, and renal function. Goal is target dose from clinical trials or highest tolerated.
β-Blockers	Bradycardia, heart block, bronchospasm, hypotension, worsening HF	BP, HR, ECG, signs and symptoms of worsening HF, blood glucose	Start with low dose and titrate upward no more often than every 2 weeks as tolerated based on BP, HR, and symptoms. Goal is target dose from clinical trials or highest tolerated. Patients may feel worse before they feel better.
Aldosterone antagonists	Gynecomastia/breast tenderness/menstrual irregularities (spironolactone), hyperkalemia, worsening renal function	BP, electrolytes, BUN, and creatinine	Assess BP, BUN, creatinine, and electrolytes at baseline. Check potassium 3 days and 1 week after initiation and then monthly for the first 3 months. Change to eplerenone if gynecomastia develops with spironolactone.
SGLT2 inhibitors	Mycotic genital infections, volume depletion, acute kidney injury, or impairment of renal function, necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis or pyelonephritis, diabetic ketoacidosis	Volume status (weight, BP, hematocrit, electrolytes), BUN, and creatinine, blood glucose and HbA1c if diabetic	Contraindicated for patients on dialysis (per package insert), lactating (no data), or with type 1 diabetes (risk of euglycemic acidosis). Monitor volume status, especially if receiving concomitant diuretics. Benefit for HFrEF is regardless of presence of diabetes.

Hydralazine	Hypotension, headache, rash, arthralgia, lupus, tachycardia	BP, HR	
Nitrates	Hypotension, headache, lightheadedness	BP, HR	
Digoxin	GI and CNS adverse effects, brady- and tachyarrhythmias	Electrolytes, BUN, creatinine, ECG, serum digoxin concentration	Target serum digoxin concentration 0.5-0.9 ng/mL (μg/L; 0.6-1.2 nmol/L)
Ivabradine	Bradycardia, hypertension, atrial fibrillation, luminous phenomena (phosphenes, transiently enhanced brightness in a portion of the visual field)	BP, HR, ECG	Start with 5 mg twice daily and after 2 weeks adjust dose to achieve a resting HR 50-60 BPM. Only use in patients in sinus rhythm.
Vericiguat	Hypotension, anemia	BP, Hgb, Hct	

Pharmacologic Therapy for HFpEF

With a few notable exceptions, the drugs used to treat HFpEF are the same as those used to treat HFrEF. However, the rationale for their use, the pathophysiologic process that is being addressed by the drug, and the dosing regimen may be different. For example, β-blockers are recommended for the treatment of both HFrEF and HFpEF. However, in HFpEF, β-blockers should only be prescribed to those patients who have a comorbid condition that have an indication for β-blocker therapy. In HFpEF, ACE inhibitors, ARBs, and β-blockers have not demonstrated efficacy in the absence of other comorbid conditions such as HTN or myocardial infarction. Diuretics also are used in the treatment of both HFrEF and HFpEF. However, the doses of diuretics used to treat HFpEF are, in general, much lower than those used to treat HFrEF. Some drugs, however, are used to treat HFpEF, but not HFrEF. Calcium channel blockers such as diltiazem, amlodipine, and verapamil have little utility in the treatment of HFrEF and are often contraindicated as described in Table 36-4. In contrast, each of these drugs may be useful in the treatment of HFpEF when used for the treatment of HTN.[57] Select therapies have now been shown to be beneficial in both HFrEF and select patients with HFpEF. Specifically, all patients with HFpEF benefit from SGLT2 inhibitors and select patients with HFpEF may benefit from an ARNI, ARB, and aldosterone antagonist.[57] Drug dosing and monitoring for these agents is similar in HFrEF and HFpEF and are summarized in Tables 36-7 and 36-9.

While dozens of trials demonstrated the benefit of pharmacotherapy in patients with HFrEF, only a few recent studies demonstrated benefit in patients with HFpEF. Early trials led to ARBs and spironolactone being recommended in HFpEF patients to reduce hospitalization.[27,58] While most studies targeting the renin-angiotensin-aldosterone system have been disappointing, the PARAGON-HF trial led to sacubitril/valsartan being the first therapy approved in the United States to reduce cardiovascular mortality and hospitalizations in patients diagnosed with HF regardless of LVEF, with the greatest benefit evident in patients with LVEF below normal.[59] Shortly afterward, two trials also demonstrated benefit with the SGLT2 inhibitors dapagliflozin and empagliflozin.[60,61] The results of these three pivotal HFpEF clinical trials are summarized in Table 36-10.

TABLE 36-10

Key Clinical Trials for HFpEF

Trial (No. of Patients)	Treatment	Inclusion Criteria	Primary Endpoint	Results
DELIVER (n=6,263)[61]	Dapagliflozin vs placebo daily for a median follow-up of 2.3 years, in addition to usual therapy	NYHA II-IV, EF >40% (0.40), NT-proBNP > 300 pg/ml (ng/L; 35 pmol/L) (>600 pg/ml [ng/L; 70 pmol/L] for patients with atrial fibrillation at baseline)	Composite of adjudicated CV death or worsening heart failure	The primary outcome occurred in 16.4% of the dapagliflozin group and 19.5% of the placebo group (HR 0.82, *P*<0.001). Of the two composite endpoints, there was only a reducttion in the risk of hospitalization for heart failure.
EMPEROR-Preserved (*n* = 5,988)[60]	Empagliflozin vs placebo daily for a median follow-up of 26.2 months, in addition to usual therapy	NYHA II-IV, EF >40% (0.40), NT-proBNP >300 pg/mL (ng/L; 35 pmol/L) (>900 pg/mL [ng/L; 106 pmol/L] for patients with atrial fibrillation at baseline)	Composite of adjudicated CV death or hospitalization for HF	The primary outcome occurred in 13.8% of the empagliflozin group and 17.1% of the placebo group (HR 0.79, *P* < 0.001). Of the two composite endpoints, there was only a significant reduction, in the risk of hospitalization for heart failure.
PARAGON-HF[59] (*n* = 4,822)	Sacubitril/valsartan vs valsartan	NYHA class II-IV with EF >45% (0.45)	Composite of CV death and total HF hospitalization	No significant difference was found in the primary endpoint between treatment groups (rate ratio 0.87; 95% CI 0.75-1.01, *P* = 0.06). A prespecified subgroup demonstrated benefit in patients with an EF in the lower part (45%-57% [0.45-0.57]) of the range.

NYHA, New York Heart Association; EF, ejection fraction; CV, cardiovascular; HF, heart failure; HR, hazard ratio; CI, confidence interval.

ACE Inhibitors

5 For decades, ACE inhibitors have been a key component of the pharmacotherapy of patients with HFrEF.[22] By blocking the conversion of angiotensin I to angiotensin II by ACE, the production of angiotensin II and, in turn, aldosterone is decreased. This decrease in angiotensin II and aldosterone attenuates many of the deleterious effects of these neurohormones that drive HF initiation and progression. ACE inhibitors also inhibit the breakdown of bradykinin, which increases vasodilation and also leads to cough. The evidence that ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in patients with HFrEF is unequivocal. As a result, prior and current guidelines recommend that all patients with HFrEF, regardless of whether or not symptoms are present, should receive ACE inhibitors to reduce morbidity and mortality, unless there are contraindications.[22,30,34] As described above, more recent evidence suggests that sacubitril/valsartan is preferred over ACE inhibitors (or ARBs) for HFrEF unless other circumstances (eg, affordability) are present in individual patients.

Numerous placebo-controlled clinical trials in both symptomatic and asymptomatic patients with reduced LVEF have documented the favorable effects of ACE inhibitor therapy on symptoms, HF progression, hospitalizations, and quality of life.[22] ACE inhibitors improve survival compared with placebo, and these benefits are maintained with continued therapy.[22] The benefits of ACE inhibitor therapy are independent of the etiology of HF (ischemic vs nonischemic) and are greatest in patients with the most severe symptoms. As efficacy has been demonstrated with numerous agents, the improved outcomes are a “class effect” of ACE inhibitors.

ACE inhibitor therapy should be started with low doses followed by gradual titration as tolerated to the target or maximally tolerated doses.[34,62] Dose titration is usually accomplished by doubling the dose every 2 weeks. Higher doses further reduce the risk of hospitalization, but not mortality,

compared to lower doses.[34] Blood pressure, renal function, and serum potassium should be evaluated at baseline and within 1 to 2 weeks after therapy is started and after each dose increase. Although symptoms may improve within a few days of initiating therapy, it may take weeks to months before the full benefits are apparent. Even if symptoms do not improve, long-term ACE inhibitor therapy should be continued to reduce the risk of mortality and hospitalization.

A number of ACE inhibitors are available; those commonly used in the treatment of patients with HF are summarized in Table 36-7. Although ACE inhibitors vary in their chemical structure (eg, sulfhydryl vs non–sulfhydryl-containing agents) and tissue affinity, all ACE inhibitors studied improve symptoms and mortality in patients with HFrEF.[22] However, it seems most prudent to use those agents documented to reduce morbidity and mortality because the dose required for these endpoints has been determined.[22]

Similar to sacubitril/valsartan and ARBs the primary adverse effects of ACE inhibitors are secondary to their major pharmacologic action of suppressing angiotensin II and increasing bradykinin. Hence, common adverse effects of ACE inhibitors are hypotension, renal dysfunction, and hyperkalemia.

A dry, nonproductive cough is the most common reason for discontinuation of ACE inhibitors, occurring in up to 15% to 20% of patients with a similar frequency with all the agents.[34] The cough usually occurs within the first few months of therapy, resolves within 1 to 2 weeks of drug discontinuation, and reappears with rechallenge. Because cough is a bradykinin-mediated effect, the replacement of ACE inhibitor therapy with sacubitril/valsartan (preferred) or an ARB is reasonable. Angioedema is a potentially life-threatening complication that is also due to bradykinin accumulation and occurs in approximately 1% of patients receiving an ACE inhibitor. It occurs more frequently in patients older than 65 years, Black patients, women, and patients with histories of drug rashes or seasonal allergies.[63] The use of ACE inhibitors is contraindicated in patients with a history of angioedema. Caution should be exercised if ARBs are used as an alternative therapy in patients with ACE inhibitor-induced angioedema, as cross-reactivity is reported.[34] ACE inhibitors are contraindicated in pregnancy due to the increased risk of fetal renal failure, intrauterine growth retardation, and other congenital defects.

Angiotensin II Receptor Blockers

5 The crucial role of the RAAS in the HF development and progression is well established as are the benefits of inhibiting this system with ACE inhibitors. However, angiotensin II can be formed in a number of tissues, including the heart, through non–ACE-dependent pathways (eg, chymase, cathepsin, and kallikrein).[11] By blocking the angiotensin II receptor subtype, AT1, ARBs attenuate the deleterious effects of angiotensin II on ventricular remodeling, regardless of the site of origin of the hormone. Since ARBs do not inhibit the ACE enzyme, these agents do not affect bradykinin, which is linked to ACE inhibitor cough and angioedema.

While ARBs are a guideline-recommended alternative in patients who are unable to tolerate an ACE inhibitor due to cough or angioedema, sacubitril/valsartan is preferred for patients with cough associated with an ACE inhibitor.[22] Numerous ARBs are available but only three agents, candesartan, valsartan, and losartan, are recommended in the treatment guidelines.[22] The efficacy of these agents is supported by the clinical trial data that document a target dose associated with improved survival and other important outcomes in patients with decreased EF.[34] The specific drugs and doses proven to be effective in clinical trials should be used (Table 36-7). The clinical use of ARBs is similar to that of sacubitril/valsartan and ACE inhibitors. Therapy should be initiated at low doses and then titrated to target doses (Table 36-7). Blood pressure, renal function, and serum potassium should be evaluated within 1 to 2 weeks after initiation of therapy and after increases in the dose, and these monitoring, parameters should be used to guide subsequent dose changes.

The role of ARBs in the treatment of HFpEF is less clear. The CHARM-Preserved trial was the first large prospective study to demonstrate some benefit (reduction in hospitalizations for HF) of an ARB in patients with HFpEF receiving standard background treatment, although no improvement in cardiovascular death was observed.[58] Adverse effects of candesartan in this study were frequent with candesartan-treated patients discontinuing therapy because of hypotension, increased serum creatinine, or hyperkalemia.

Similar to ARNI and ACE inhibitors, the major adverse effects of ARBs are related to the suppression of the RAAS. The incidence of and risk factors for developing hypotension, impaired renal function, and hyperkalemia with the ARBs are similar to those with ARNI and ACE inhibitors.[22] Thus, ARBs are not alternatives in patients who develop these complications from ACE inhibitors. Similar to ACE inhibitors, careful monitoring is required when an

ARB is used with an aldosterone antagonist as this combination increases the risk of these adverse effects. Since ARBs do not affect bradykinin, they are not associated with cough and have a lower risk of angioedema than ACE inhibitors.[63] However, because of reports of recurrences of angioedema after ARB use in patients with a history of ACE inhibitor-related angioedema, ARBs should be used with caution in any patient with a history of angioedema as cross-reactivity may occur.[63] Like ARNI and ACE inhibitors, ARBs are contraindicated in pregnancy.

Angiotensin II Receptor Blocker/Neprilysin Inhibitor (ARNI)

5 The first and only angiotensin receptor/neprilysin inhibitor approved for the treatment of patients with HFrEF is sacubitril/valsartan. It is a crystalline complex composed of the ARB valsartan and sacubitril, a neprilysin inhibitor prodrug. After ingestion, sacubitril dissociates from the complex and is cleaved into its active form LBQ657, which inhibits the action of neprilysin that degrades natriuretic peptides, bradykinin, and other endogenous vasodilator and natriuretic peptides.[64] By reducing the neprilysin-mediated breakdown of these compounds, vasodilation, diuresis, and natriuresis are enhanced and renin and aldosterone secretion is inhibited.

The PARADIGM-HF study compared sacubitril/valsartan to enalapril in patients with NYHA Class II-IV HFrEF.[29] There was a statistically significant reduction in the primary outcome of combined death from cardiovascular causes or first hospitalization for HF in patients receiving sacubitril/valsartan compared to enalapril. A similar reduction was seen in each component of the primary endpoint and death from any cause was also significantly reduced. Hypotension occurred more frequently in patients randomized to sacubitril/valsartan compared to enalapril. However, more patients receiving enalapril experienced cough and hyperkalemia greater than 6.0 mEq/L (mmol/L). Angioedema was rare in either treatment group.

In the PARAGON-HF study, patients with HFpEF (LVEF of at least 45% [0.45] and NYHA class II-IV symptoms) were randomized to either sacubitril/valsartan or placebo (Table 36-10).[59] The primary endpoint, a composite of total hospitalizations for HF and death from cardiovascular causes, was not significantly different between the sacubitril/valsartan and placebo groups. A prespecified subgroup in patients with an LVEF in the lower part (45%-57% [0.45-0.57]) of the range suggested benefit. Based upon this subgroup analysis, the current guidelines for sacubitril/valsartan have been expanded to include those with HFpEF, particularly those with an LVEF on the lower end of this spectrum.[22]

In patients with HFrEF, ARNI is preferred over either ACE inhibitors or ARBs to improve survival, slow disease progression, reduce hospitalizations, and improve quality of life.[22] Patients receiving ACE inhibitors or ARBs can be switched to ARNI or ARNI can be used as initial treatment in patients with newly detected HFrEF without previous exposure to ACE inhibitors or ARBs.[22] ACE inhibitors should be discontinued 36 hours prior to initiating ARNI; no waiting period is needed in patients receiving an ARB. The rationale for avoiding overlap is due to an increased risk of angioedema given the neprilysin inhibitor, like an ACE inhibitor, prevents the breakdown of bradykinin. The initial starting dose for most patients being treated for HFrEF is 49/51 mg sacubitril/valsartan twice daily and titrated to the target dose of 97/103 mg sacubitril/valsartan twice daily after 2 to 4 weeks. A reduced dose of 24/26 mg sacubitril/valsartan is available for patients taking a low dose of either an ACE inhibitor or an ARB prior to initiation or those with severe renal dysfunction (eGFR <30 mL/min/1.73 m^2). Blood pressure, serum potassium, and renal function should be closely monitored after the start of therapy and after each titration step. The valsartan component of the combination product is 40% to 60% more bioavailable than conventional valsartan tablets. Thus, the 24-mg sacubitril/26-mg valsartan tablet is equivalent to 40 mg of valsartan.[65]

The primary adverse effects of ARNIs are secondary to their major pharmacologic action of suppressing angiotensin II, increasing bradykinin, and increasing BNP. The most common adverse effects of this agent are hypotension, renal dysfunction, and hyperkalemia. Given similar pharmacologic effects of ACE inhibitors and ARBs, specifically on angiotensin II (ACE inhibitors and ARBs) and bradykinin (primarily ACEIs), a similar side effect profile is generally observed. ARNIs, ACE inhibitors, and ARBs reduce BP in nearly all patients. Hypotension occurs most frequently soon after therapy is started, after an increase in dose, or in patients who are volume-depleted as may occur with diuretics. An often overlooked solution to hypotension is to space the administration times of vasoactive medications (eg, diuretics and β-blockers) throughout the day so that these medications are not all administered at or near the same time.

Functional renal insufficiency causes an increase in serum creatinine and blood urea nitrogen (BUN). As CO and renal blood flow decline, renal perfusion is maintained by the vasoconstrictor effect of angiotensin II on the efferent arteriole. Patients most dependent on this system for maintenance of renal perfusion (and therefore most likely to develop renal insufficiency with an ARNI, ACE inhibitor, or ARB) are those with severe HF, hypotension, hyponatremia, volume depletion, bilateral renal artery stenosis, and concomitant use of NSAIDs.[34,62] Increases in serum creatinine of

>0.5 mg/dL (44 µmol/L) if the baseline creatinine is <2 mg/dl (177) or >1 mg/dl (88 umol/L) if the baseline creatinine is >2 mg/dL (177 µmol/L) should prompt clinicians to dose reduce or discontinue therapy and evaluate potential causes for the abrupt decline in the renal function. Since renal dysfunction with these agents is secondary to alterations in renal hemodynamics, it is almost always reversible on discontinuation of the drug.

Hyperkalemia with ARNI, ACE inhibitors, or ARBs is most likely to occur in patients with renal insufficiency, in elderly patients, and in those taking concomitant potassium supplements, potassium-containing salt substitutes, or potassium-sparing diuretic therapy (including an aldosterone antagonist), especially if they have diabetes.[66] Patiromer or sodium zirconium cyclosilicate can be used to treat or prevent hyperkalemia in these patients.[66]

In contrast to ACE inhibitors, bradykinin side effects of cough and angioedema are rare with both ARNI and ARBs (the latter by virtue of combining sacubitril with the ARB, valsartan, rather than an ACE inhibitor). In fact, ACE inhibitor cough is a common reason to switch to sacubitril/valsartan or an ARB. While extremely rare, angioedema occurred more frequently with sacubitril/valsartan compared to enalapril (0.5% vs 0.2%, respectively).[29] The risk of angioedema is fourfold higher in Black patients.[66] Unlike ACE inhibitor cough, sacubitril/valsartan is contraindicated in patients with a history of angioedema associated with an ACE inhibitor or ARB. Sacubitril/valsartan is also contraindicated in pregnancy and should not be used concurrently with ACE inhibitors or other ARBs. As previously stated, ARNIs, ACE inhibitors, and ARBs are contraindicated in pregnancy.

β-Blockers

6 β-Blockers antagonize the detrimental effects of the SNS in HF and slow disease progression. Favorable effects of β-blockers in HF include antiarrhythmic effects, attenuation or reversal of ventricular remodeling, reduction in myocyte death from catecholamine-induced necrosis or apoptosis, improvement in left ventricular systolic function, reductions in HR and ventricular wall stress thereby reducing myocardial oxygen demand, and inhibition of plasma renin release.[34] There is overwhelming clinical trial evidence that β-blockers reduce morbidity and mortality in patients with HFrEF. As such, the ACC/AHA guidelines on the management of HF recommend that evidence-based β-blockers should be used in all stable patients with Stages B-D HFrEF (Figure 36-7) in the absence of contraindications or a clear history of β-blocker intolerance.[22] Patients should receive a β-blocker even if their symptoms are mild or well-controlled with other GDMT. Importantly, it is not essential that doses of other agents (eg, RAAS inhibitors) be optimized before a β-blocker is started because the addition of a β-blocker is likely to be of greater benefit than an increase in the dose of other medications.[30,34] β-Blockers are also recommended for patients with a reduced left ventricular EF (Stage B) to decrease the risk of progression to HF (Figure 36-6).[22,67]

Three β-blockers, in particular, reduced morbidity and mortality compared with placebo in randomized, controlled trials: carvedilol, metoprolol succinate (CR/XL), and bisoprolol. Each was studied in a large population with the primary endpoint of mortality, and in each case, the trial was stopped early because of significant survival benefit with the β-blocker. The US Carvedilol Heart Failure Study, the MERIT-HF trial with metoprolol succinate (Toprol-XL®), and the CIBIS II trial with bisoprolol each demonstrated a reduction in mortality; the latter two trials also showed a reduction in sudden death and death due to worsening HF compared with placebo.[68–70] Multiple post hoc subgroup analyses of the MERIT-HF and CIBIS II trials suggest that the benefits of β-blockade occur regardless of HF etiology or disease severity.

In contrast to earlier trials in which the majority of participants had either NYHA class II or class III HFrEF, the COPERNICUS trial examined the efficacy and safety of β-blockers in clinically stable patients with class IV HF who had symptoms at rest or with minimal exertion.[71] Like the other studies, COPERNICUS was stopped early after carvedilol demonstrated a significant reduction in mortality. Carvedilol was well tolerated in this population, with fewer participants receiving carvedilol compared with placebo requiring discontinuation of study medication.

In addition to improving survival, β-blockers improve multiple other endpoints. Clinical trials demonstrate reductions in all-cause hospitalization and hospitalizations for worsening HF with the β-blocker therapy.[70,72,73] Increases in LVEF of 5 to 10 units occur after several weeks to months of therapy. β-Blockers decrease ventricular mass, improve the sphericity of the ventricle, and reduce systolic and diastolic volumes (left ventricular end-systolic volume and LVEDV).[8,34] These effects are often collectively called reverse remodeling, referring to the fact that they return the heart toward a more normal size, shape, and function. β-Blockers are also associated with improvements in NYHA functional class, patient symptom scores or quality-of-life assessments, and exercise performance, as assessed by the 6-minute walk test.

6 The benefits of β-blockers in HFrEF are not a class effect; therefore, one of the three agents with proven survival benefits (carvedilol, metoprolol

succinate, or bisoprolol) should be used.[22] Metoprolol and bisoprolol selectively block the β1-receptor, while carvedilol blocks the β1-, β2-, and α1-receptors and also possesses antioxidant effects. The smallest commercially available tablet of bisoprolol is a scored 5-mg tablet. Since the recommended starting dose of 1.25 mg/day is not readily available, bisoprolol is the least commonly used of the three agents and, in fact, is not approved for use in HFrEF. Thus, therapy is generally limited to either carvedilol or metoprolol succinate, and there is no compelling evidence that one drug is superior to the other. While one trial found a lower mortality rate in patients treated with carvedilol 25 mg twice daily compared to immediate-release metoprolol 50 mg twice daily,[74] concerns regarding the formulation (immediate-release vs sustained-release) and dose (100 vs 200 mg/day) of metoprolol used limit the conclusions that can be drawn from the trial. The efficacy of the immediate-release formulation in reducing mortality in HF has not been proven. Metoprolol succinate provides more consistent plasma concentrations over a 24-hour period and appears to provide more favorable effects on HR variability, autonomic balance, and BP, suggesting that this formulation might be superior to immediate-release metoprolol. Data from HF registries suggest that metoprolol succinate and carvedilol are similarly effective.[75,76]

Pharmacologic differences between β-blockers may aid in the selection of a specific agent. Carvedilol is expected to have greater antihypertensive effects than the other agents because of its α-receptor blocking properties and may be preferred in patients with poorly controlled BP. Conversely, metoprolol or bisoprolol may be preferred in patients with low BP or dizziness and in patients with significant airway disease given their β-1 selectivity..

Most participants in β-blocker trials were on ACE inhibitors at baseline since the benefits of these agents were proven prior to β-blocker trials. The risk for decompensation during β-blocker initiation may be greater in the absence of preexisting ACE inhibitor, ARB, or ARNI therapy. Thus, ACE inhibitors, ARBs, or ARNIs are generally started first in most patients, especially if there is evidence of volume overload. Initiating a β-blocker first may be advantageous for patients with evidence of excessive SNS activity (eg, tachycardia) and may also be appropriate for patients whose renal function or potassium concentrations preclude starting an ACE inhibitor, ARB, or ARNI at that time.

Components that are critical for successful β-blocker therapy include appropriate patient selection, drug initiation and titration, and patient education. β-Blockers should be initiated in stable patients who have no or minimal evidence of fluid overload.[34] While β-blockers are typically started in the outpatient setting, initiation of a β-blocker prior to discharge in patients who are hospitalized for decompensated HF increases β-blocker usage compared with outpatient initiation without increasing the risk of serious adverse effects.[77,78] However, β-blockers should not be started in patients who are hospitalized in the intensive care unit or required intravenous inotropic support. In unstable patients, other HF therapy should be optimized, and then β-blocker therapy reevaluated once stability is achieved.

Initiation of a β-blocker at normal doses in patients with HF may lead to symptomatic worsening or acute decompensation owing to the drug's negative inotropic effect. For this reason, β-blockers are listed as drugs that may exacerbate or worsen HF (see Table 36-4). To minimize the likelihood of acute decompensation, β-blockers should be started in low doses with slow upward dose titration and close monitoring. β-Blocker doses should be doubled no more often than every 2 weeks, as tolerated, until the target or maximally tolerated dose is reached. Uptitration should be avoided if the patient experiences signs of worsening HF, including volume overload and poor perfusion. Fluid overload may be asymptomatic and manifest solely as an increase in body weight. Mild fluid overload may be managed by intensifying the diuretic therapy. Once the patient has been stabilized, dose titration may continue as tolerated until the target or highest tolerated dose is reached.[34] According to current guidelines, target doses are those associated with reductions in mortality in placebo-controlled clinical trials.[22] The starting and target doses achieved in clinical trials are described in Table 36-7. Data with both metoprolol and carvedilol suggest that HR may serve as a guide to the degree of β-blockade, with a greater magnitude of HR reduction associated with greater improvement in survival. Thus, lower β-blocker doses might be considered reasonable if the reduction in HR indicates a good response to β-blocker therapy.[79] Chapter 37, "Acute Decompensated Heart Failure," will discuss optimal management of β-blocker therapy during hospitalization, addressing appropriate scenarios for continuation and withdrawal of β-blocker therapy.

Good communication between the patient and the healthcare provider(s) is particularly important for successful therapy. It is important to educate patients that β-blocker therapy is expected to positively influence disease progression and survival even if there is little to no symptomatic improvement. Patients should understand that dose titration is a long, gradual process. Patients should also be aware that response to therapy may be delayed and that HF symptoms may actually worsen during the initiation period. In the event of worsening symptoms, patients who understand the potential benefits of long-term β-blocker therapy may be more likely to continue treatment.

As previously discussed, the primary utility of beta-blockers in HFpEF is treating comorbid conditions such as HTN, angina, and myocardial infarction. In patients with HFpEF, β-blockers may help to lower and maintain low pulmonary venous pressures by decreasing HR and increasing the duration of diastole. Tachycardia is poorly tolerated in patients with HFpEF for a variety of reasons. However, excessive bradycardia can result in a fall of CO

despite an increase in LV filling. Such considerations underscore the need for individualizing therapeutic interventions that affect HR. In general, it is not necessary to start at an extremely low dose and titrate the β-blocker in a slow, progressive fashion in HFpEF as it is in HFrEF. However, because patients tend to be older, have numerous comorbidities, and take many concomitant medications, it is prudent to start with a moderate dose of β-blockers in HFpEF. A meta-analysis examining the effects of β-blocker therapy on clinical outcomes in patients with HFpEF found lower all-cause mortality but no significant reduction for HF hospitalizations in observational studies.[80] In contrast, an individual patient-level meta-analysis found no benefit of β-blocker therapy in patients with HFpEF (EF >50% [0.5]) in normal sinus rhythm as compared to patients with reduced (EF <40% [0.4]) or mid-range EF (40%-49% [0.4-0.49]).[81]

Possible adverse effects with β-blocker use in HF include bradycardia or heart block, hypotension, fatigue, impaired glycemic control in diabetic patients, bronchospasm in patients with asthma, and worsening HF. Clinicians should monitor vital signs and carefully assess for signs and symptoms of worsening HF during β-blocker initiation and titration. Hypotension is more common with carvedilol due to its α1-receptor blocking properties. Bradycardia and hypotension generally are asymptomatic and require no intervention; however, β-blocker dose reduction is warranted in symptomatic patients. Fatigue usually resolves after several weeks of therapy, but sometimes requires dose reduction. In diabetic patients, β-blockers may worsen glucose tolerance and can mask the tachycardia and tremor (but not sweating) that accompany hypoglycemia. In addition, nonselective agents such as carvedilol may prolong insulin-induced hypoglycemia and slow recovery from a hypoglycemic episode. Despite this, there is evidence that carvedilol may improve insulin sensitivity and that β-blockers are well tolerated and significantly reduce morbidity and mortality in patients with diabetes and HFrEF. Thus, while β-blockers should be used cautiously in patients with recurrent hypoglycemia, concerns of masking symptoms of hypoglycemia or worsening glycemic control should not preclude β-blocker use in patients with diabetes. Patients with diabetes should be warned of these potential adverse effects and blood glucose should be monitored when initiating, adjusting, and discontinuing β-blocker therapy. Adjustment of hypoglycemic therapy may be necessary with concomitant β-blocker use in diabetics.

Absolute contraindications to β-blocker use include uncontrolled bronchospastic disease, symptomatic bradycardia, advanced heart block without a pacemaker, and acute decompensated HF. However, β-blockers may be tried with caution in patients with asymptomatic bradycardia, COPD, or well-controlled asthma. Particular caution is warranted in patients with marked bradycardia (HR <55 BPM) or hypotension (systolic BP <80 mm Hg).

Aldosterone Antagonists

7 Spironolactone and eplerenone are aldosterone antagonists that work by blocking the mineralocorticoid receptor, the target site for aldosterone, and, thus, they are also referred to as mineralocorticoid receptor antagonists. In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion. While the diuretic effects with low doses of aldosterone antagonists are minimal, the potassium-sparing effects can have significant consequences as discussed below. In the heart, aldosterone antagonists inhibit cardiac extracellular matrix and collagen deposition, thereby attenuating cardiac fibrosis and ventricular remodeling.[82] Aldosterone antagonists also attenuate the systemic pro-inflammatory state, atherogenesis, and oxidative stress caused by aldosterone. Thus, as with ACE inhibitors and β-blockers, the data on aldosterone antagonists also support the neurohormonal model of HF. In addition, there is evidence that aldosterone antagonists may attenuate aldosterone-induced calcium excretion and reductions in bone mineral density and protect against fractures in HF.[82]

Three randomized, placebo-controlled trials have evaluated low-dose aldosterone antagonism in patients with HFrEF or post-MI and left ventricular dysfunction. In each trial, the aldosterone antagonist was added to the standard therapy, which included an ACE inhibitor and diuretic. While the initial trial was conducted before the benefits of β-blockers were fully appreciated, participants in the latter two trials received β-blockers. All three trials excluded patients with significant renal dysfunction (eg, serum creatinine above 2.5 mg/dL [221 µmol/L]) and elevated serum potassium (eg, above 5 mEq/L [mmol/L]) at baseline.

The RALES trial was the first to examine the efficacy of aldosterone antagonism in HFrEF. Patients with current or recent NYHA class IV HFrEF were randomized to spironolactone 25 mg/day or placebo.[23] The study was stopped prematurely because of a significant reduction in the primary endpoint of total mortality with spironolactone. Spironolactone also significantly reduced hospitalizations for worsening HF and improved symptoms. The EPHESUS trial evaluated eplerenone in patients with left ventricular dysfunction after MI.[24] Treatment with eplerenone titrated to 50 mg/day was associated with significant reductions in mortality and hospitalizations from HF compared to placebo. The EMPHASIS-HF trial demonstrated significant improvements in clinical outcomes with eplerenone, titrated to 50 mg/day (mean dose of 39 mg/day), in patients with NYHA class II HF and an LVEF of 35% [0.35] or less.[25] Eplerenone treatment reduced the primary endpoint of cardiovascular death or HF hospitalization as well as all-cause and

cardiovascular mortality and hospitalization for HF.

The TOPCAT trial examined the effect of spironolactone (mean dose 25 mg/day) in patients with HFpEF (EF >45% [0.45]).[27] There was no difference in the primary outcome composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF between the spironolactone and placebo groups; however, there was a significant reduction in the risk for hospitalization for HF. There appeared to be a difference in outcomes by region of enrollment. Post hoc analysis showed a greater reduction in the primary outcome with spironolactone among patients from the Americas, but not in those from Eastern Europe.[26] While the prespecified test for an interaction between region and study arm was not significant, differences in baseline characteristics by region and the lower event rate overall in patients from Eastern Europe confound the interpretation of the study results.

For optimal GDMT in patients with HFrEF and NYHA class II-IV symptoms, a low-dose aldosterone antagonist should be used to improve symptoms, reduce the risk of HF hospitalization, and increase survival provided that serum potassium and renal function can be carefully monitored.[22] Current guidelines recommend adding an aldosterone antagonist to decrease the risk for hospitalization for HF in patients with HFpEF, especially if LVEF is on the lower end of this spectrum.[30]

Aldosterone antagonist use in clinical trials was associated with significant increases in serum potassium and creatinine. Most trials demonstrated a higher rate of hyperkalemia (serum potassium ≥5.5 mEq/L [mmol/L] or ≥6.0 mEq/L [mmol/L]) with the aldosterone antagonist compared to placebo.[24,25,27] However, hyperkalemia occurs more commonly in clinical practice than in clinical trials.[83] Risk factors for hyperkalemia include impaired renal function, high potassium concentrations, failure to decrease or stop potassium supplements when starting aldosterone antagonists, diabetes, inadequate laboratory monitoring, high potassium intake, and concomitant use of both ACE inhibitors and ARBs or NSAIDs.[84] The ACC/AHA recommended strategies to minimize the risk for hyperkalemia with aldosterone antagonists in HF and are summarized in Table 36-11.[34] Chief among these recommendations is to avoid aldosterone antagonists in patients with renal dysfunction or elevated serum potassium. Serum creatinine may overestimate renal function in the elderly and in patients with decreased muscle mass, in whom creatinine clearance should serve as a guide for the appropriateness of aldosterone antagonist therapy. The risk for hyperkalemia is dose-dependent, and the morbidity and mortality reductions with aldosterone antagonists in clinical trials occurred at low doses (ie, spironolactone 25 mg/day and eplerenone 50 mg/day). Therefore, the doses of aldosterone antagonists should be limited to those associated with beneficial effects in order to decrease the risk for hyperkalemia. Initiation of every other-day dosing is appropriate for patients with marginal renal function or who are otherwise at high risk for hyperkalemia. Notably, both ARNI and SGLT2 inhibitors may reduce the risk of hyperkalemia with aldosterone antagonists.[85] Spironolactone also interacts with androgen and progesterone receptors, which may lead to gynecomastia, impotence, and menstrual irregularities in some patients. Such adverse effects are less frequent with eplerenone owing to its low affinity for the progesterone and androgen receptors.

TABLE 36-11

Recommended Strategies for Reducing the Risk for Hyperkalemia with Aldosterone Antagonists

- Avoid starting aldosterone antagonists in patients with any of the following:
  - Serum creatinine concentration >2.0 mg/dL (177 µmol/L) in women or >2.5 mg/dL (221 µmol/L) in men or a creatinine clearance <30 mL/min/1.73 m^2 (0.29 mL/s/m^2)
  - Recent worsening of renal function
  - Serum potassium concentration >5.0 mEq/L (mmol/L)
  - History of severe hyperkalemia
- Start with low doses (12.5 mg/day for spironolactone and 25 mg/day for eplerenone) especially in the elderly and in those with diabetes or a creatinine clearance <50 mL/min/1.73 m^2 (0.48 mL/s/m^2).
- Decrease or discontinue potassium supplements when starting an aldosterone antagonist.
- Avoid concomitant use of NSAIDs or COX-2 inhibitors.
- Avoid concomitant use of high-dose ACE inhibitors or ARBs.
- Avoid triple therapy with an ACE inhibitor, ARB, and aldosterone antagonist.
- Monitor serum potassium concentrations and renal function within 3 days and 1 week after the initiation or dose titration of an aldosterone antagonist or any other medication that could affect potassium homeostasis. Thereafter, potassium concentrations and renal function should be monitored monthly for the first 3 months, and then every 3 months.
- If potassium exceeds 5.5 mEq/L (mmol/L) at any point during therapy, discontinue any potassium supplementation or, in the absence of potassium supplements, reduce or stop aldosterone antagonist therapy.
- Counsel patients to:
  - limit intake of high potassium-containing foods and salt substitutes.
  - avoid the use of over-the-counter NSAIDs.
  - temporarily discontinue aldosterone antagonist therapy if diarrhea develops or diuretic therapy is interrupted.

Data from Reference 34.

Sodium-Glucose Cotransporter Type 2 (SGLT2) Inhibitors

Initially developed for diabetes given their glucose-lowering potential by blocking renal tubular glucose reabsorption, SGLT2 inhibitors are also benefical in HF. These agents inhibit glucose and sodium reabsorption in the proximal renal tubule which promotes urinary glucose excretion and causes a modest diuresis.[86] Under normoglycemic conditions, the kidneys contribute to blood glucose homeostasis by nearly complete reabsorption of filtered glucose. The majority (>90%) of glucose reabsorption occurs early in the proximal tubule via SGLT2, while the remainder is reabsorbed by SGLT1 in the late proximal tubule. Although the mechanism of benefit from these agents in HF remains uncertain, treatment with SGLT2 inhibitors leads to osmotic diuresis and natriuresis, reduction in arterial pressure and stiffness, and a shift to ketone-based myocardial metabolism. Additional benefit may be related to the reduction of preload and afterload, thereby reducing cardiac stress and injury and ultimately leading to reduced myocardial hypertrophy, fibrosis, and remodeling.[32,86]

Cardiovascular outcome trials in patients with type 2 diabetes demonstrated that SGLT2 inhibitors improved both CV and renal outcomes as well as a reduction in hospitalizations for HF. Thus, outcome trials in patients with HF with and without diabetes were designed. In the DAPA-HF and EMPEROR-Reduced trials, patients with HFrEF and NYHA class II-IV symptoms, both dapagliflozin and empagliflozin reduced the risk of worsening HF and cardiovascular death compared to placebo. In addition, both agents demonstrated a significant reduction in each of the individual components of the composite endpoint.[87,88] Importantly, these benefits were observed both in patients with and without diabetes. As a result, both agents are now foundational components of optimal GDMT for patients with HFrEF (with or without diabetes) and are recommended by current guidelines for use in this population.[22] In the EMPEROR-Preserved trial, empagliflozin (fixed dose of 10 mg daily) also reduced the primary outcome of cardiovascular death or HF hospitalization in patients with HFpEF.[60]

Dosing, monitoring, and related recommendations for SGLT2 inhibitors are detailed in Tables 36-7 and 36-9. The DAPA-HF trial did not enroll patients with an eGFR <30 mL/min/1.73 m^2 and the limit of eGFR for inclusion in the EMPEROR-Reduced trial was 20 mL/min/1.73 m^2. These agents are indicated in patients with renal function above or very near these eGFR thresholds. Renal function (eGFR) may initially decrease with SGLT2 inhibitor initiation but improve over time. Patient counseling is imperative with the use of SGLT2 inhibitors, especially in the HF population. It is unclear if SGLT2 inhibitors will contribute to volume depletion and the potential need for diuretic dose adjustment. And thus, patients should be counseled to weigh daily and contact their healthcare provider should their weight start to decline and to avoid abrupt changes in position as orthostasis may occur in the setting of over diuresis. Patients should be monitored for acute kidney injury and renal function impairment; temporary discontinuation of diuretic may be required in settings of reduced oral intake or fluid losses. Patients should also be advised to monitor for and report mycotic genital infections and urinary tract infections. Urosepsis and pyelonephritis are also potential risks with SGLT2 inhibitors. Necrotizing fasciitis of the perineum, also known as Fournier's gangrene, is a rare but serious and potentially life-threatening adverse effect that may occur in either females or males. Patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area should also be assessed for fever or malaise. Patients with diabetes may be at increased risk for ketoacidosis and temporary discontinuation before scheduled surgery is recommended to avoid this potential risk. Patients who present with signs and symptoms of metabolic acidosis should be assessed for ketoacidosis, regardless of blood glucose level.

Diuretics

9 The compensatory mechanisms in HF stimulate excessive sodium and water retention, often leading to pulmonary and systemic congestion.[44,89] Diuretic therapy, in addition to sodium restriction, is recommended in all patients with clinical evidence of fluid retention. Once fluid overload has been resolved, many patients require chronic diuretic therapy to maintain euvolemia. Among the drugs used to manage HF, diuretics are the most rapid in producing symptomatic benefits. However, diuretics do not prolong survival or alter disease progression, and therefore are not considered mandatory therapy. Thus, patients who do not have fluid retention would not require diuretic therapy.

The primary goals of diuretic therapy are to reduce symptoms associated with fluid retention, improve exercise tolerance and quality of life, and reduce hospitalizations from HF. Diuretics accomplish this by decreasing pulmonary and peripheral edema through the reduction of preload. Although preload is a determinant of CO, the Frank-Starling curve (see Fig. 36-4) shows that patients with congestive symptoms have reached the flat portion of the curve. A reduction in preload improves symptoms but has little effect on the patient's SV or CO until the steep portion of the curve is reached. However, diuretic therapy must be used judiciously because over-diuresis can lead to a reduction in CO, renal perfusion, and symptoms of volume depletion.

Diuretic therapy is usually initiated in low doses in the outpatient setting, with dosage adjustments based on symptom assessment and daily body weight. Change in body weight is a sensitive marker of fluid retention or loss, and it is recommended that patients monitor their status by taking daily morning body weights. Patients who gain 1 lb/day (~0.5 kg/day) for several consecutive days or 3 to 5 lb (1.4-2.3 kg) in a week should contact their healthcare provider for instructions (which often will be to increase the diuretic dose temporarily). Such action often will allow patients to prevent a decompensation that requires hospitalization. Patients may be directed to self-adjust their diuretic dose based on changes in HF symptoms and daily body weight. Hypotension or worsening renal function (eg, increases in serum creatinine) may be indicative of volume depletion and necessitates a reduction in the diuretic dose. Assessing volume status is particularly important before ACE inhibitor/ARB/ARNI initiation or dose titration as over-diuresis may predispose patients to hypotension and other adverse effects with these agents.

In patients with HFpEF, diuretic treatment should be initiated at low doses in order to avoid hypotension and fatigue. Hypotension can be a significant problem in the treatment of HFpEF because patients have a steep LV diastolic pressure-volume curve such that a small change in volume causes a large change in filling pressure and CO. Hence, diuretic dosing should be tailored to individual patient needs.

Loop Diuretics

Loop diuretics are usually necessary to restore and maintain euvolemia in HF. They act by inhibiting a Na–K–2Cl transporter in the thick ascending limb of the loop of Henle, where 20% to 25% of filtered sodium normally is reabsorbed. Loop diuretics also induce a prostaglandin-mediated increase in renal blood flow, which contributes to their natriuretic effect. Coadministration of NSAIDs, including cyclooxygenase-2 inhibitors, blocks this prostaglandin-mediated effect and can diminish diuretic efficacy. Excessive dietary sodium intake may also reduce the efficacy of loop diuretics. Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary to obtain adequate delivery of the drug to the site of action.

There are three loop diuretics available that are routinely used: furosemide, bumetanide, and torsemide.[44,89] They share many similarities in their pharmacodynamics, with their differences being largely pharmacokinetic in nature. Relevant information on the loop diuretics is listed in Tables 36-7 and 36-9. Following oral administration, the peak effect with all the agents occurs in 30 to 90 minutes, with a duration of 4 to 8 hours (longer for torsemide). Following IV administration, the diuretic effect begins within minutes. All three drugs are highly (>95%) bound to plasma proteins, and reach the tubular lumen by active transport via the organic acid transport pathway. The magnitude of the effect is determined by the peak concentration achieved in the nephron, and there is a threshold concentration that must be achieved before any diuresis occurs. Competitors for the organic acid transport pathway (probenecid or organic by-products of uremia) can inhibit the delivery of loop diuretics to their site of action and decrease effectiveness.

The greatest difference between the agents is bioavailability. The bioavailability of bumetanide and torsemide is essentially complete (80%-100%), whereas furosemide bioavailability exhibits marked intra- and inter-patient variability.[44,89] Furosemide bioavailability ranges from 10% to 100%, with an average of 50%. Thus, if bioequivalent IV and oral doses are desired, oral furosemide doses should be approximately double that of the IV dose, whereas IV and oral doses are the same for torsemide and bumetanide. Coadministration of furosemide and bumetanide with food can decrease bioavailability significantly, whereas food has no effect on the bioavailability of torsemide. The intra-abdominal congestion that can occur in HF also may slow the rate (and thus decrease the peak concentration) of furosemide, which can reduce its efficacy. Thus, furosemide is most problematic with respect to the rate and extent of absorption and the factors that influence it, whereas torsemide has the least variable bioavailability.

These differences in bioavailability and variability may have clinical implications. For example, several studies suggest that torsemide is absorbed reliably and may be associated with better outcomes than the more variably absorbed furosemide.[44] Torsemide may modulate neurohormonal levels resulting in attenuation of cardiac remodeling. Torsemide is preferred in patients with persistent fluid retention despite high doses of other loop diuretics. While the costs of torsemide exceed those of furosemide, pharmacoeconomic analyses suggest that the costs of care are similar or less with torsemide.

Heart failure is one of the disease states in which the maximal response to loop diuretics is reduced. This is believed to result from a decrease in the rate of diuretic absorption and/or increased proximal or distal tubule reabsorption of sodium, possibly due to increased activity of the Na–K–2Cl transporter.[44,89] As a consequence, loop diuretics exhibit a ceiling effect in HF, meaning that once the ceiling dose is reached, no additional diuretic response is achieved by increasing the dose. Thus, when this dose is reached, additional diuresis can be achieved by giving the drug more often (twice daily or occasionally three times daily) or by giving combination diuretic therapy. Multiple daily dosing achieves a more sustained diuresis throughout the day. When dosed two or three times daily, the first dose is usually given first thing in the morning and the final dose in the late afternoon/early evening. The appropriate chronic dose of a loop diuretic is that which maintains the patient at a stable dry weight without symptoms of dyspnea. Loop diuretic dose ranges and recommended ceiling doses are listed in Table 36-7.

Diuretics cause a variety of metabolic abnormalities, with severity related to the potency of the diuretic.[44,89] The reader is referred to Chapter 37, "Acute Decompensated Heart Failure" for a detailed discussion on the adverse effects of diuretic therapy. Hypokalemia is the most common metabolic disturbance with thiazide and loop diuretics, which in HF patients may be exacerbated by hyperaldosteronism. Hypokalemia increases the risk for ventricular arrhythmias in HF and is especially worrisome in patients receiving digoxin. It is often accompanied by hypomagnesemia. Since adequate magnesium is necessary for the entry of potassium into the cell, co-supplementation with both magnesium and potassium may be necessary to correct the hypokalemia. Concomitant ARNI, ACE inhibitor/ARB and/or aldosterone antagonist therapy may help minimize diuretic-induced hypokalemia because these drugs tend to increase serum potassium concentration through their inhibitory effect on aldosterone secretion. Nonetheless, the serum potassium concentration should be monitored closely in patients with HF and supplemented appropriately when needed.

Thiazide Diuretics

Thiazide diuretics such as hydrochlorothiazide block sodium reabsorption in the distal convoluted tubule (~5%-8% of filtered sodium). The thiazides, therefore, are relatively weak diuretics and infrequently used alone in HF. However, thiazides or the thiazide-like diuretic, metolazone, can be used in combination with loop diuretics to promote an effective diuresis. In addition, thiazide diuretics may be preferred in patients with only mild fluid retention and elevated BP because of their more persistent antihypertensive effects compared with loop diuretics. Given patients with HFpEF often have ongoing uncontrolled HTN, thiazide diuretics may be used to manage this disorder.

Other Treatments for Heart Failure in Select Patients

Nitrates and Hydralazine

Nitrates and hydralazine were originally combined in the treatment of HFrEF because of their complementary hemodynamic actions. Nitrates, by serving as nitric oxide donors, activate guanylate cyclase to increase cyclic guanosine monophosphate (cGMP) in vascular smooth muscle resulting in venodilation and decreased preload. Hydralazine is a direct-acting arterial vasodilator causing a decrease in SVR and resultant increases in SV and CO (Fig. 36-1). However, the beneficial effects of hydralazine and nitrates extend beyond their hemodynamic actions and are likely related to attenuating the biochemical processes driving HF progression.

Based on the results of initial clinical trials showing ISDN and hydralazine were more effective in African Americans, the African-American Heart Failure Trial (A-HeFT) enrolled self-identified African Americans with NYHA class III or IV HFrEF receiving standard HF therapy and compared outcomes in patients randomized to the fixed-dose combination of hydralazine/Isosorbide dinitrate (BiDil®) or placebo.[90] The trial was terminated early because of a significant reduction in all-cause mortality in patients receiving hydralazine/isosorbide compared with placebo. Based on these results, BiDil® was approved by the FDA to treat HFrEF in African Americans.

Guidelines recommend the addition of hydralazine/ISDN to African American patients with HFrEF with persistent symptoms despite ARNI, β-blocker, aldosterone antagonist, and SGLT2 inhibitor therapy.[22] Hydralazine/ISDN can also be useful in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or possibly hypotension.

Despite its efficacy, the use of hydralazine/ISDN is limited by the need for three times daily dosing and frequent adverse effects including dizziness, headache, and GI distress. Because of cost, some clinicians use generic hydralazine and ISDN as separate agents, rather than BiDil®. Although the generic and brand name products are not bioequivalent as determined in healthy volunteer studies, it is unknown if these pharmacokinetic differences impact clinical outcomes.

In contrast to the beneficial effects of hydralazine/ISDN in patients with HFrEF, in patients with HFpEF nitrates reduce exercise capacity and do not improve quality of life or plasma NT-proBNP concentrations.[91] Adverse events, including worsening HF and presyncope/syncope, were more frequent with nitrate treatment. These findings suggest that in the absence of another indication for nitrate therapy (eg, angina), nitrates provide no benefits to patients with HFpEF.

Ivabradine

Ivabradine reduces HR and is used in the treatment of HFrEF.[92] Ivabradine selectively inhibits the I_f current responsible for controlling the depolarization rate of the sinus node.[92] By blocking this current, ivabradine slows the spontaneous depolarization of the sinus node resulting in a dose-dependent slowing of the HR. Ivabradine does not affect AV conduction, blood pressure, or myocardial contractility.[92]

Elevated resting HR (>70-80 BPM) is emerging as an important independent risk factor for adverse outcomes in patients with HFrEF and is associated with increased hospital admissions, disease progression, and mortality.[93] New approaches to address increased HR in these patients are needed because, for a variety of reasons, β-blockers are frequently underdosed in clinical practice and the benefits of β-blockers are associated with the degree of HR reduction and the dose administered.[93,94] In the SHIFT trial, ivabradine reduced the risk of hospitalization for worsening HF in patients with HFrEF in sinus rhythm.[95] As a result, guidelines recommend the use of ivabradine after GDMT is optimized in patients with HFrEF in sinus rhythm who have a resting HR >70 BPM and are receiving maximally tolerated β-blocker doses.[22]

The starting dose of ivabradine in most patients is 5 mg twice daily with meals. After 2 weeks of treatment, the resting HR should be evaluated, and if between 50 and 60 BPM, the dose should be continued. If the heart rate is >60 BPM, the dose can be increased to a maximum of 7.5 mg twice daily. If at any point, the HR is <50 BPM or if the patient has symptomatic bradycardia, the dose should be reduced by 2.5 mg twice daily. In this case, if the patient is receiving only 2.5 mg twice daily, then ivabradine should be discontinued. Because of the clear benefits of β-blockers on mortality and that many patients treated with β-blockers are under-dosed, clinicians should remember to titrate to the maximum tolerated doses before determining the need for ivabradine. The most common adverse effects associated with ivabradine were bradycardia, atrial fibrillation, and visual disturbances.

Digoxin

11 The benefits of digoxin in HF are related to its neurohormonal modulating activity.[96] These benefits occur at low plasma concentrations and little inotropic effect is produced. Digoxin attenuates the excessive SNS activation present in HF patients. Chronic HF is also marked by autonomic dysfunction, most notably suppression of the parasympathetic (vagal) system. Digoxin increases parasympathetic activity in HF patients and leads to a decrease in HR, thus enhancing diastolic filling. The vagal effects also result in slowed conduction and prolongation of AV node refractoriness, thus slowing the ventricular response in patients with atrial fibrillation. This leads to a decrease in HR, which enhances diastolic filling. Because atrial fibrillation is a common complication of HF, the combined neurohormonal and negative chronotropic effects of digoxin may be beneficial for such patients.

The Digitalis Investigation Group (DIG) trial examined the effects of digoxin on survival and hospitalization in patients with HF symptoms, an LVEF of <45% (0.45), and in sinus rhythm.[97] No significant differences in all-cause mortality were found between patients receiving digoxin and placebo. Digoxin reduced hospitalizations for worsening HF compared with placebo. Among patients with an LVEF greater than 45% (0.45) (HFpEF) who were enrolled in an ancillary DIG trial, there was no apparent benefit of digoxin on hospitalizations or mortality.[98] Therefore, digoxin is recommended in HFrEF after GDMT is optimized.[22] An analysis of the trial database found that lower serum digoxin concentrations (SDCs) were associated with decreased mortality, whereas higher concentrations were not.[99] Specifically, compared with placebo, SDCs of 0.5 to 0.9 ng/mL (μg/L; 0.6-1.2 nmol/L) were associated with lower mortality, all-cause hospitalizations, and HF hospitalizations. Based on these data, for most patients, the target SDC should be 0.5 to 0.9 ng/mL (μg/L; 0.6-1.2 nmol/L).[34] In most patients with normal renal function, this serum concentration range can be achieved with a daily dose of 0.125 mg. Patients with decreased renal function or low body weight, the elderly, or those receiving interacting drugs (eg, amiodarone) should receive 0.125 mg daily or every other day. Routinely measuring SDCs is not necessary unless digoxin toxicity is suspected or there are other conditions that may significantly affect SDC such as worsening renal function or the initiation of an interacting drug. Digoxin combined with a β-blocker or amiodarone is superior to either agent alone for controlling ventricular response in patients with concomitant atrial fibrillation and HF.[34] Target SDCs are the same regardless of whether the patient is in sinus rhythm or atrial fibrillation. Several equations and nomograms have been proposed to estimate digoxin maintenance doses based on estimated renal function for a particular patient and population pharmacokinetic parameters. These methods are extensively reviewed elsewhere.[100]

The DIG trial was conducted prior to the proven benefits and widespread use of β-blockers in HF. Observational studies have reexamined digoxin in the context of contemporary HF therapy and shown variable results.[101–103] In patients with HFrEF receiving more contemporary GDMT, digoxin withdrawal is associated with an increased risk of hospital readmissions for HF and the combined endpoint of HF readmission and mortality.[104] Based on the totality of data, digoxin is not considered a first-line agent in HF but a trial may be considered in conjunction with GDMT in patients with symptomatic HFrEF to improve symptoms and reduce hospitalizations.[22] Digoxin may also be considered to help control ventricular response rate in patients with HFrEF and supraventricular arrhythmias.

There is no established role for digoxin in HFpEF when patients are in normal sinus rhythm. Digoxin may be of benefit in patients with concomitant HFpEF and atrial fibrillation.[105]

Digoxin pharmacokinetics are well described.[100] There is a long “distribution phase” after administration of oral or IV digoxin, resulting in a lag time before a maximum pharmacologic response is observed. Blood samples for measurement of SDCs should be collected at least 6 hours and preferably 12 hours or more after the last dose. The drug efflux transporter P-glycoprotein (P-gp) plays an important role in the bioavailability, renal and nonrenal clearance, and drug interactions with digoxin. Clinically important pharmacokinetic/pharmacodynamic drug interactions exist with a range of mechanisms including reduced bioavailability through various processes (eg, antacids, cholestyramine, kaolin-pectin, metoclopramide), altered gut bacteria (eg, clarithromycin, tetracycline), reduced clearance through P-glycoprotein inhibition (eg, cyclosporine, ranolazine, ritonavir) and hypokalemia/hypomagnesemia increasing risk of digoxin toxicity (eg, thiazide or loop diuretics). Select interactions occur through multiple mechanisms such as increased bioavailability and reduced renal and nonrenal clearance through P-glycoprotein inhibition resulting in 50% to 100% or greater increases in serum digoxin concentrations (eg, amiodarone, verapamil, quinidine, ketoconazole, macrolide antibiotics) requiring up to a 50% reduction in dose. One standard GDMT, spironolactone, may alter the clearance of digoxin, and thus close monitoring of serum concentrations is warranted. In addition, spironolactone may interfere with some digoxin assays, thus, increasing apparent digoxin concentrations.

Digoxin can produce a variety of cardiac and noncardiac adverse effects, but it is usually well tolerated by most patients.[96] Noncardiac adverse effects frequently involve the GI (nausea/vomiting) or CNS (halos, photophobia, problems with color perception including red-green or yellow-green vision)

systems but also may be nonspecific (eg, fatigue, weakness, confusion). Cardiac manifestations include numerous different arrhythmias caused by the drug's multiple electrophysiologic effects including both various tachy- and bradyarrhythmias ranging from sinus bradycardia to third-degree heart block and premature ventricular contractions to ventricular arrhythmias. Rhythm disturbances are of particular concern because patients with chronic HF are already at increased risk for sudden cardiac death, presumably due to ventricular arrhythmias. Patients at increased risk of toxicity include those with impaired renal function, decreased lean body mass, the elderly, and those taking interacting drugs. Hypokalemia, hypomagnesemia, and hypercalcemia will predispose patients to cardiac manifestations of digoxin toxicity. Thus, concomitant therapy with diuretics may lead to electrolyte abnormalities and increase the likelihood of cardiac arrhythmias. Similarly, hypothyroidism, myocardial ischemia, and acidosis will also increase the risk of cardiac adverse effects. Although digoxin toxicity is commonly associated with plasma concentrations greater than 2 ng/mL (μg/L; 2.6 nmol/L), toxicity may occur at lower concentrations, and clinicians should remember that digoxin toxicity is based on the presence of symptoms rather than a specific plasma concentration.[100] Usual treatment of digoxin toxicity includes drug withdrawal or dose reduction and treatment of cardiac arrhythmias and electrolyte abnormalities. In patients with life-threatening digoxin toxicity, purified digoxin-specific Fab antibody fragments should be administered.

Vericiguat

11 One of the detrimental consequences of HF is endothelial dysfunction and reactive oxygen species generation.[106] Vericiguat is a novel pharmacotherapy that modulates endothelial dysfunction.[107] Under normal conditions, the vascular endothelium generates nitric oxide (NO) which stimulates soluble guanylate cyclase (sGC) mediated cyclic guanosine monophosphate (cGMP) production. The endocardial endothelium is also sensitive to NO and relies upon increasing intracellular cGMP to regulate contractility and diastolic function. In HF, this process becomes dysregulated, leading to insufficiency of NO, sGC and cGMP, resulting in impaired diastolic relaxation and microvascular dysfunction. While administration of nitrates, in combination with hydralazine, reduce mortality in HFrEF, this benefit has only been demonstrated in self-identified African American patients.[90] Vericiguat is an sGC stimulator that binds to sGC and enhances the effect of NO to increase cGMP activity.[107]

In the VICTORIA trial, patients with HFrEF (LVEF <45% [0.45]), recent ADHF requiring hospitalization or outpatient intravenous diuretics, and elevated BNP levels were randomized to vericiguat or placebo.[108] Patients receiving vericiguat demonstrated a significant, but modest, reduction in the primary endpoint of cardiovascular death or HF hospitalization. Vericiguat was well tolerated with no differences in symptomatic hypotension or syncope between groups. While renal function and electrolytes were unaffected, there was a concerning and as yet unexplained greater incidence of anemia found in patients receiving vericiguat. The place in therapy for verciguat is unclear given the limited benefit but it may lie in the lack of significant hemodynamic, renal, and electrolyte effects in the setting of a high-risk population that often does not tolerate GDMT. Similar to digoxin, it is[22] Vericiguat is not indicated in HFpEF given the lack of benefit and potential lack of safety (hypotension, syncope) demonstrated in the VITALITY-HFpEF Trial.[109]

Calcium Channel Blockers

Calcium channel blockers have a limited role in HFrEF. While dihydropyridine type agents (eg, amlodipine, felodipine) are safe to use in patients with HFrEF, these agents have a neutral effect on morbidity or mortality. Hence, they can be safely used to manage HTN or angina in patients with HFrEF but they should only be considered after other doses of GDMT with blood pressure–lowering effects are optimized. In contrast, the nondihydropyridine calcium channel blockers, verapamil and diltiazem, are contraindicated in HFrEF due to their negative inotropic effects. As such, nondihydropyridines are listed as medications that can exacerbate HF in Table 36-4.

Calcium channel blockers can provide symptom-targeted treatment in patients with HFpEF by decreasing HR and increasing exercise tolerance. They can also provide disease-targeted therapy by treating HTN and coronary artery disease. However, the beneficial effect of these agents on exercise tolerance is not always paralleled by improved LV diastolic function or increased relaxation rate. Of the calcium channel blockers, the nondihydropyridines are the most effective because they lower heart rate in addition to lowering BP. Nondihydropyridines are also frequently used to treat the comorbidities of HTN and atrial fibrillation in patients with HFpEF. Sustained-release nifedipine, because of its strong vasodilator properties, tends to cause hypotension, reflex tachycardia, and peripheral edema. These characteristics make it less useful in HFpEF. Amlodipine may be effective because it reduces BP. Initial daily doses are verapamil 120 to 240 mg, diltiazem 90 to 120 mg, and amlodipine 2.5 mg.

Heart block is a contraindication for nondihydropyridines. The most common adverse effects are bradycardia and heart block (for the nondihydropyridines). Peripheral edema and headache also are common. Nondihydropyridines exacerbate the bradycardic effects of β-blockers, and

verapamil raises digoxin serum concentrations by 70%. Generic formulations, but not necessarily generic equivalents to the original brand names, are available for some of the calcium channel blockers.

Tafamidis

Tafamidis stabilizes the TTR tetramer by binding to the thyroxine-binding sites and thereby slowing its disassociation into monomers and halting the amyloid deposition process. The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) included 441 patients with either hereditary (24%) or wild type (76%) ATTR cardiomyopathy.[17] The trial results showed the superiority of tafamidis meglumine to placebo in reducing all-cause mortality and reducing the rate of hospitalizations due to cardiovascular complications. No differences in the primary outcome were observed between hereditary and wild-type ATTR patients. Approved in the United States in 2019, tafamidis is dosed once daily as either a single 61 mg capsule or four 20 mg capsules (80 mg total) of tafamidis meglumine. Recent guidelines recommended tafamadis in select patients with ATTR cardiac amyloidosis to reduce cardiovascular morbidity and mortality.[22]

Special Populations

HF is often accompanied by other cardiovascular and non-cardiovascular disorders whose natural history or therapy may affect morbidity, mortality, and treatment approach.[3,33] Optimal management of these concomitant disorders in the context of the patient's HF is an important consideration in the overall care of the patient.

Although HTN has been replaced by ischemic heart disease as the most common cause of HF, up to 90% of patients with HF have a current or a previous history of HTN.[3] HTN directly contributes to the development of both HFrEF and HFpEF as well as indirectly by increasing the risk of coronary artery disease. Effective treatment of HTN markedly reduces the risk of developing HF.[3] Pharmacotherapy of HTN in patients with HFrEF should initially involve GDMT with blood pressure reducing effects (eg, ARNI, β-blockers, aldosterone antagonists). If control of HTN is not achieved after optimizing treatment with these agents, the addition of ISDN/hydralazine or a dihydropyridine calcium channel blocker such as amlodipine may be considered. In patients with HFpEF, both verapamil and diltiazem can be safely used in conjunction with other therapies known to benefit select patients with HFpEF, specifically ARNI or ARBs. In patients with either HFrEF or HFpEF, target levels of BP should be less than 130/80 mm Hg, consistent with current guidelines (see Chapter 30, "Hypertension").[30,36]

Coronary artery disease is the most common cause of HFrEF and a less common cause of HFpEF. Appropriate management of coronary disease and its risk factors is thus an important strategy for the prevention and treatment of HF (see Chapter 32, "Stable Ischemic Heart Disease"). Coronary revascularization should be strongly considered in patients with both HF and angina.[34] Pharmacotherapy of angina in patients with HF should utilize drugs that can effectively treat both disorders. In HFrEF, nitrates and β-blockers are effective antianginals and are the preferred agents for patients with both disorders since they may improve clinical outcomes. In HFrEF, both amlodipine and felodipine are safe to use in this setting while nondihydropyrindines should be avoided. In HFpEF, given nitrates, β-blockers and verapamil have neutral effects on HF outcomes, they can also be safely used. Optimization of treatments for secondary prevention of coronary and atherosclerotic vascular disease should also be considered.[3]

Atrial fibrillation is the most frequently encountered arrhythmia and it is commonly found in both HFrEF and HFpEF, with the prevalence increasing in parallel to the severity of HF and an association with worse long-term prognosis.[34,35] Moreover, HF exacerbations and atrial fibrillation are closely linked causes of hospitalization and it is often difficult to determine which disorder caused the other. Thus, optimal management according to established guidelines is required with careful attention paid to control of ventricular response, symptoms, and anticoagulation for stroke prevention (see Chapter 40, "Arrhythmias").[35,110]

Digoxin is frequently used to slow ventricular response in patients with HF and atrial fibrillation. However, it is more effective at rest than with exercise and it does not affect the progression of HF. In addition, the potential for digoxin to increase mortality in patients with atrial fibrillation is a growing concern.[111] β-Blockers are more effective than digoxin and have the added benefits of improving morbidity and mortality in patients with HFrEF. Combination therapy with digoxin and a β-blocker may be more effective for rate control than either agent used alone. Calcium channel blockers with negative inotropic effects such as verapamil or diltiazem should be avoided in patients with HFrEF but are effective in patients with HFpEF.

There appear to be no differences in outcomes between the rhythm- (restoration and maintenance of sinus rhythm) and rate-control approaches to

atrial fibrillation in patients with HF.[35,105] In general, amiodarone and dofetilide are the preferred agents if rhythm control is needed in HFrEF.[105] Class I antiarrhythmics and dronedarone should be avoided in HFrEF. Because of the limited efficacy and potential for serious adverse effects with antiarrhythmic drugs, there is a growing interest in the use of catheter ablation for restoring sinus rhythm in HF.[110,112] Several recent studies have shown an improvement in clinical outcomes after AF ablation in HF patients highlighting the emerging role of the invasive approach in this subset of patients.[22,112]

Several noncardiovascular diseases warrant special consideration in HF including diabetes, COPD, depression, gout, chronic kidney disease (CKD), and iron deficiency.[33]

Type 2 diabetes is a common comorbid condition in patients with HF with each disorder independently enhancing the risk of the other.[113] Patients with diabetes are at two- to fourfold increased risk of developing HF compared to those without diabetes through increased risk of coronary artery disease and multiple other mechanisms.[113] Adequate glycemic control is critical to reducing the risk of HF development and progression.[113] For most patients with diabetes and HF, a more lenient HbA1c goal of 7% to 8% (53-64 mmol/mol) is suggested and should be individualized based on numerous patient characteristics.[113] Metformin remains a first-line therapy in patients at risk for or with established HF unless contraindications are present.[113] As previously discussed, SGLT2 inhibitors are now standard GDMT for HFrEF.[22] If additional glucose-lowering is needed, a glucagon-like peptide-1 (GLP-1) receptor agonist demonstrating CV benefits (dulaglutide, liraglutide, or semaglutide) should be considered.[113] The dipeptidyl peptidase-4 (DPP-4) inhibitors should be avoided due to the increased risk of HF. The thiazolidinediones and sulfonylureas should be avoided. Insulin therapy may be necessary for some patients to achieve glycemic control. Readers are referred to Chapter 94 ("Diabetes Mellitus") for more in-depth treatment recommendations.

Given COPD (see Chapter 45, "Chronic Obstructive Pulmonary Disease") co-presents in many patients with HF, concern about the safe use of β-blockers exists.[33] Overall, the benefit of β-blockers in HFrEF outweighs the risk of worsening pulmonary disease with the exception of those with acute bronchospasm. Use of β1-selective agents (eg, bisoprolol, metoprolol succinate) over nonselective agents are preferred and patients should be counseled to monitor for and report worsening pulmonary symptoms.[33] Limited retrospective data suggest preference may be given to the use of ARBs over ACE inhibitors.[33]

While there have been several studies assessing the role of interventions addressing depression in HF patients, it remains unclear if antidepressants have any benefit. Still, antidepressants should still be considered in patients voicing depressive symptoms (see Chapter 88, "Depressive Disorders"). The selective serotonin receptor inhibitors have been safe in HF, and thus, these agents are preferred over serotonin-norepinephrine receptor inhibitors and TCAs.[33]

Gout (see Chapter 113, "Gout and Hyperuricemia") is common in HF patients receiving diuretic therapy. Colchicine is safe and effective in patients with HF experiencing an acute gout flare.[33] Close monitoring for gastrointestinal symptoms and myelosuppression is warranted in the setting of renal dysfunction or concomitant use of CYP3A4 or P-glycoprotein inhibitors. If patients do not tolerate or fail colchicine, corticosteroids are an alternative; however, dose and duration should be limited. NSAIDs are contraindicated in patients with HF as is febuxostat. Allopurinol is the preferred urate-lowering therapy.

Present in over 50% of patients with HFrEF, the effect of CKD on serum potassium and creatinine can substantially impact GDMT use, particularly ACE inhibitors, ARBs, ARNI, and aldosterone antagonists.[33] These agents, along with the SGLT2 inhibitors, are also renoprotective and should be used if at all possible in patients with HFrEF and CKD. Potassium binders may be necessary if hyperkalemia develops. Erythrocyte stimulating agents should not be used to correct anemia in patients with HF alone but may be considered in those with concomitant CKD, low hemoglobin concentrations (ie, <10 g/dL [100 g/L; 6.21 mmol/L]), and adequate or repleted iron stores.

Iron deficiency, defined as ferritin <100 ng/mL (mcg/L) or 100 to 299 ng/mL (mcg/L) with a transferrin saturation (TSAT) <20% [0.2]), is present in approximately 50% of patients with chronic HFrEF and 80% of individuals admitted to the hospital for ADHF.[114] Thus, iron studies should be routinely assessed in patients with symptomatic HFrEF, regardless of the presence or absence of anemia. If iron deficiency is present, the total iron deficit should be calculated using the Ganzoni equation and intravenous repletion should occur with iron product selection taking into consideration cost and feasibility (eg, inpatient versus outpatient) to improve symptoms, functional status and reduce HF hospitalizations.[30,33,115]

EVALUATION OF THERAPEUTIC OUTCOMES

Although mortality is an important endpoint, it does not give a complete measure of the overall impact of HF because many patients are repeatedly hospitalized for HF exacerbations and continue to survive, albeit with a significantly reduced quality of life. Thus, some of the more important therapeutic outcomes in HF management, such as prolonged survival or prevention or slowing of the progression of HF, are difficult to quantify in an individual patient. However, after appropriate diagnostic evaluation to determine the etiology of HF, ongoing clinical assessment of patients typically focuses on the evaluation of three general areas: (a) functional capacity, (b) volume status, and (c) laboratory monitoring.

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

Assessment of volume status is a vital component of the ongoing care of patients with HF. This evaluation provides the clinician with important information about the adequacy of diuretic therapy. Since the cardinal signs and symptoms of HF are caused by excess fluid retention, the efficacy of diuretic treatment is readily evaluated by the disappearance of these signs and symptoms. The physical examination is the primary method for the evaluation of fluid retention, and specific attention should be focused on the patient's body weight, the extent of JVD, the presence of hepatojugular reflux, presence, and the severity of pulmonary congestion, and peripheral edema. Specifically, in a patient with pulmonary congestion, monitoring is indicated for resolution of rales and pulmonary edema and improvement or the resolution of DOE, orthopnea, and PND. For patients with systemic congestion, a decrease or disappearance of peripheral edema, JVD, and hepatojugular reflux is sought. Other therapeutic outcomes include an improvement in exercise tolerance and fatigue, decreased nocturia, and a decrease in HR. Clinicians also will want to monitor BP and ensure that the patient does not develop symptomatic hypotension as a result of drug therapy. Body weight is a sensitive short-term marker of fluid loss or retention, and patients should be counseled to weigh themselves daily, reporting changes of 3 to 5 lb (1.4-2.3 kg) to their healthcare provider so that adjustments can be made in diuretic doses. Patients and healthcare providers should be aware that HF progression may be slowed even though symptoms have not been resolved.

Routine monitoring of serum electrolytes and renal function is required in patients with HF. Assessment of serum potassium and magnesium is especially important because hypokalemia and hypomagnesemia are common adverse effects of diuretic therapy and are associated with an increased risk of arrhythmias and digox in toxicity (hypokalemia). The risk of hyperkalemia is also high as expected with the use of ACE inhibitors, ARBs, ARNI, and aldosterone antagonists and is associated with adverse outcomes.[83,116] A serum potassium ≥4 mEq/L (mmol/L) should be maintained with some evidence suggesting it should be ≥4.5 mEq/L (mmol/L).[117] Assessment of renal function (BUN and serum creatinine) is also an important endpoint for monitoring diuretic and RAAS inhibitor therapy. Common causes of worsening renal function in patients with HF include over-diuresis, adverse effects of RAAS inhibition, and hypoperfusion.

Excellent overviews on approaches to initiating and titrating evidence-based therapies, care coordination, monitoring parameters, therapeutic endpoints, improving adherence, care of common comorbidities that impact treatment, and solutions to frequently encountered problems when evaluating and treating patients with HF are available.[22,62]

ABBREVIATIONS

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ARB	angiotensin receptor blocker

ARNI	angiotensin-receptor blocker/neprilysin inhibitor
AVP	arginine vasopressin
BNP	B-type natriuretic peptide
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
CKD	chronic kidney disease
CO	cardiac output
COX-2	cyclooxygenase-2
CRT	cardiac resynchronization therapy
ESC	European Society of Cardiology
ET	endothelin
GDMT	guideline-directed medical therapy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
HR	heart rate
HTN	hypertension
IABP	intra-aortic balloon pump
ICD	implantable cardioverter-defibrillator
JVD	jugular venous distension
LVAD	left ventricular assist device
LVEDV	left ventricular end-diastolic volume
LVEDP	left ventricular end-diastolic pressure

LVEF	left ventricular ejection fraction
MI	myocardial infarction
NE	norepinephrine
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
PCWP	pulmonary capillary wedge pressure
P-gp	P-glycoprotein
RAAS	renin–angiotensin–aldosterone system
SDC	serum digoxin concentration
SNS	sympathetic nervous system
SVR	systemic vascular resistance
TNF-α	tumor necrosis factor-α
TZD	thiazolidinedione

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SELF-ASSESSMENT QUESTIONS

The next two questions refer to the following case:

A White patient with HFrEF (LVEF 30% [0.3]) has mild fatigue and dyspnea on exertion. Serum electrolytes, creatinine clearance, and other labs are within normal limits and the serum digoxin concentration collected 18 hours after the previous dose is 0.8 ng/mL (µg/L; 1 nmol/L). The blood pressure is 125/75 mm Hg and heart rate is 60 bpm. The patient's cardiovascular drug regimen is unchanged over the previous 3 months and includes:

Lisinopril 10 mg orally daily

Carvedilol 25 mg orally twice daily

Furosemide 40 mg orally twice daily

Digoxin 0.125 mg orally daily

Spironolactone 25 mg orally daily

Atorvastatin 40 mg orally at bedtime

1. Which of the following is the most appropriate change to the patient's pharmacotherapy?

A. Initiate amlodipine

B. Increase the digoxin dose to 0.25 mg/day

C. Initiate ivabradine

D. Change lisinopril to sacubitril/valsartan

2. Which of the following should be added to reduce the risk of death and hospitalization in this patient?

A. Hydralazine/isosorbide dinitrate

B. Dapagliflozin

C. Diltiazem

D. Metformin

3. Sacubitril/valsartan is contraindicated in patients with which of the following?

A. Hypokalemia

B. Concomitant therapy with bumetanide

C. Angioedema with ramipril

D. Blood pressure >130/80 mm Hg

4. Which of the following medications may exacerbate HFrEF?

A. Naproxen

B. Amlodipine

C. Rosuvastatin

D. Empagliflozin

5. Which of the following medication can increase wheezing and shortness of breath in a patient with HFrEF and COPD?

A. Carvedilol

B. Spironolactone

C. Bumetanide

D. Dapagliflozin

6. Which of the following adverse effects associated with ramipril can be managed by switching to valsartan?

A. Cough

B. Hypotension

C. Hyperkalemia

D. Fetal toxicity

7. Patients receiving empagliflozin for HFrEF should be counseled about which of the following?

A. The risk of pulmonary toxicity when used with carvedilol

B. Signs and symptoms of urinary tract infections

C. The risk of seizures when used with ACE inhibitors

D. Signs and symptoms of volume overload

8. The risk of hyperkalemia is increased when spironolactone is used concurrently with which of the following medications?

A. Ivabradine

B. Furosemide

C. Ibuprofen

D. Metolazone

9. Which of the following should be used to monitor loop diuretic therapy in patients with heart failure?

A. Daily weights, serum potassium, serum creatinine

B. Thyroid-stimulating hormone (TSH) and free T4

C. Fasting blood sugar and hemoglobin A1C

D. Fasting lipid profile

10. Which of the following best describes the use of sacubitril/valsartan in patients with heart failure?

A. It is contraindicated in patients with type 2 diabetes

B. ACE inhibitors should be discontinued at least 36 hours before starting sacubitril/valsartan

C. Hypokalemia is a common adverse effect

D. It causes less hypotension than an ACE inhibitor or ARB

11. Hypokalemia is a potential complication of which of the following medications?

A. Carvedilol

B. Eplerenone

C. Losartan

D. Torsemide

12. What is the most appropriate therapy for a patient with HFrEF that develops lisinopril-induced angioedema?

A. Change to ramipril

B. Change to sacubitril/valsartan

C. Change to hydralazine/isosorbide dinitrate

D. Change to amlodipine

13. A patient with Stage C HFrEF is taking sacubitril/valsartan 49/51 mg orally twice daily, dapagliflozin 10 mg orally daily, furosemide 40 mg orally twice daily, digoxin 0.125 mg orally daily, and metoprolol succinate 25 mg orally daily. The patient presents with increasing shortness of breath, fatigue, ankle swelling, and an 8-pound (3.6 kg) weight gain over the past 2 weeks. Labs are significant for serum potassium of 5.2 mEq/L (mmol/L), serum creatinine 1.0 mg/dL (88 µmol/L), and serum digoxin concentration 0.8 ng/mL (mcg/L; 1 nmol/L) collected 18 hours after the last dose. Vital signs are BP 125/75 mm Hg and heart rate 75 BPM. Which is the most appropriate immediate intervention?

    A. Increase the furosemide dose to 80 mg twice orally daily

    B. Increase the metoprolol dose to 50 mg orally daily

    C. Initiate spironolactone 12.5 mg orally daily

    D. Increase the digoxin dose to 0.25 mg orally daily

14. A patient with HFrEF (LVEF 30-35% [0.3-0.35]) is in normal sinus rhythm and is receiving sacubitril/valsartan 97/103 mg orally twice daily, dapagliflozin 10 mg orally daily, carvedilol 50 mg orally twice daily, digoxin 0.125 mg orally daily, spironolactone 25 mg orally daily, and furosemide 40 mg orally twice daily. Vital signs are BP 110/75 mm Hg and pulse 85 bpm. All labs are within normal limits. Which would be the most appropriate medication to add to reduce hospitalization?

    A. Potassium chloride

    B. Ivabradine

    C. Diltiazem

    D. Vericiguat

15. A patient with HFpEF (LVEF 50-55% [0.5-0.55]) also has diabetes, hypertension, hyperlipidemia, asthma, and atrial fibrillation. Current vital signs are: HR 85 bpm and BP 128/85 mm Hg. Current labs include serum creatinine 1.0 mg/dL (88 µmol/L), serum potassium 4.3 mEq/L (mmol/L), and HgbA1c 6.8% (51 mmol/mol). Current medications include hydrochlorothiazide 25 mg orally daily, lisinopril 10 mg orally daily, atorvastatin 20 mg orally daily, aspirin 81 mg orally daily, metformin 1000 mg orally twice daily, fluticasone 250/50 inhale 1 puff twice daily, and albuterol PRN. Which of the following medications will most likely improve health outcomes in this patient with HFpEF?

    A. Metoprolol succinate

    B. Ivabradine

    C. Empagliflozin

    D. Amlodipine

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** In this patient who remains symptomatic, changing enalapril to sacubitril/valsartan will reduce the risk of mortality and may improve symptoms. See the "Pharmacologic Therapy for Stages B–D HFrEF" section and Fig. 36-7.

2. **B.** In patients with HFrEF with or without diabetes that meet the eGFR criteria, an SGLT2 inhibitor (either dapagliflozin or empagliflozin) is indicated to reduce the risk of major cardiovascular events including mortality and hospitalizations. See the "Pharmacologic Therapy for Stages B–D HFrEF" section and Fig. 36-7.

3. **C.** Entresto® (sacubitril/valsartan) is contraindicated in patients with a history of angioedema with an ACE inhibitor or ARB. See the "Pharmacologic Therapy for Stages B–D HFrEF" section and Table 36-9.

4. **A.** Naproxen is an NSAID and can worsen heart failure by causing fluid retention, worsening renal function, and increasing blood pressure. See Table 36-4.

5. **A.** Carvedilol, a non-selective beta-blockers, can increase the risk of wheezing and shortness of breath in patients with COPD. A selective beta-blocker (eg, metoprolol succinate) should be considered in these patients. The other agents are not associated with pulmonary adverse effects. See the "Pharmacologic Therapy for Stages B–D HFrEF" section and "Special Populations" section.

6. **A.** ACE inhibitors inhibit bradykinin breakdown and can cause cough in up to 15% to 20% of patients. Valsartan, as well as other ARBs, do not affect bradykinin and are not associated with cough. See the "Pharmacologic Therapy for Stages B–D HFrEF" section.

7. **B.** By increasing urinary glucose excretion, the SGLT2 inhibitors increase the risk of urinary tract infections as well as genital mycotic infections. Patients should be counseled on the signs and symptoms of these infections and the importance of seeking prompt medical attention should they occur. See the "Pharmacologic Therapy for Stages B–D HFrEF" section and Table 36-9.

8. **C.** The risk of hyperkalemia is increased when the aldosterone antagonist spironolactone (or eplerenone) is used with ibuprofen or any other NSAID. See Table 36-11.

9. **A.** Daily weights are useful to monitor the volume status of patients with either HFrEF or HFpEF that are receiving loop diuretics. As these agents can also cause hypokalemia and worsen renal function with excessive volume depletion, serum potassium and creatinine should also be monitored. See the "Pharmacologic Therapy for Stages B–D HFrEF" section and Table 36-9.

10. **B.** ACE inhibitors should be discontinued at least 36 hours before administering sacubitril/valsartan because of the risk of angioedema. See the "Pharmacologic Therapy for Stages B–D HFrEF" section and Table 36-9.

11. **D.** Torsemide, as well as the other loop diuretics furosemide and bumetanide, are associated with an increased risk of hypokalemia. Serum potassium concentrations should be monitored at baseline and 1-2 weeks after initiation or dose change. See the "Pharmacologic Therapy for Stages B–D HFrEF" and Table 36-9.

12. **C.** Hydralazine/isosorbide dinitrate would be most appropriate in this situation. The combination may reduce mortality and is not associated with angioedema. Both ramipril and sacubitril/valsartan are contraindicated in patients with a history of ACE inhibitor-induced angioedema. See the "Pharmacologic Therapy for Stages B–D HFrEF" section and Table 36-9.

13. **A.** This patient is demonstrating signs/symptoms of volume overload (eg, weight gain, increasing SOB, and lower extremity edema) so an increase in the furosemide dose is indicated. Because the patient is experiencing worsening heart failure symptoms, the metoprolol dose should not be increased now. Spironolactone would not be used because of hyperkalemia. The serum digoxin concentration is within the therapeutic range (0.5-0.9 ng/mL [mcg/L; 0.6-1.2 nmol/L]) so the digoxin dose should not be increased. See Table 36-9 and the "Clinical Presentation" box.

14. **B.** This patient is receiving optimal GDMT with maximum dose sacubitril/valsartan, dapagliflozin, carvedilol, and spironolactone. Despite the maximum dose of carvedilol (50 mg twice daily), the patient's resting heart rate remains above 70 BPM. In patients receiving maximally tolerated doses of beta-blockers, the addition of ivabradine targeting a resting heart rate of < 60 BPM, reduces the risk of hospitalization in patients with HFrEF. See the "Other Treatments for Heart Failure in Select Patients" and Table 36-7 and Table 36-9.

15. **C.** Empagliflozin should be added. Recent evidence from the EMPEROR-Preserved trial showed that empagliflozin reduced the risk of death and hospitalization for heart failure in patients with HF and LVEF > 40% (0.40). See the "Pharmacologic Therapy for HFpEF" section and Tables 36-8 and 36-10.