Chapter 9: Heart Failure

INTRODUCTION

- *Heart failure* (HF) is a progressive syndrome that can result from any changes in cardiac structure or function that impair the ability of the ventricle to fill with or eject blood. HF may be caused by an abnormality in systolic function, diastolic function, or both. HF with reduced systolic function (ie, reduced left ventricular ejection fraction, LVEF) is referred to as HF with reduced ejection fraction (HFrEF). Preserved LV systolic function (ie, normal LVEF) with presumed diastolic dysfunction is termed HF with preserved ejection fraction (HFpEF).

PATHOPHYSIOLOGY

- Causes of systolic dysfunction (decreased contractility) include reduced muscle mass (eg, myocardial infarction [MI]), dilated cardiomyopathies, and ventricular hypertrophy. Ventricular hypertrophy can be caused by pressure overload (eg, systemic or pulmonary hypertension and aortic or pulmonic valve stenosis) or volume overload (eg, valvular regurgitation, shunts, high-output states).
- Causes of diastolic dysfunction (restriction in ventricular filling) include increased ventricular stiffness, ventricular hypertrophy, infiltrative myocardial diseases, myocardial ischemia and MI, mitral or tricuspid valve stenosis, and pericardial disease (eg, pericarditis and pericardial tamponade).
- The leading causes of HF are coronary artery disease and hypertension.
- Regardless of the index event, decreased cardiac output (CO) results in activation of compensatory responses to maintain circulation: (1) tachycardia and increased contractility through sympathetic nervous system activation, (2) the Frank–Starling mechanism, whereby increased preload (through sodium and water retention) increases stroke volume, (3) vasoconstriction, and (4) ventricular hypertrophy and remodeling. Although these compensatory mechanisms initially maintain cardiac function, they are responsible for the symptoms of HF and contribute to disease progression.
- In the *neurohormonal model* of HF, an initiating event (eg, acute MI) leads to decreased CO; the HF state then 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. These substances include angiotensin II, norepinephrine, aldosterone, natriuretic peptides, and arginine vasopressin (AVP).
- 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 changes in ventricular size (left ventricular hypertrophy), 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.
- Common precipitating factors that may cause a previously compensated HF patient to decompensate include myocardial ischemia and MI, pulmonary infections, nonadherence with diet or drug therapy, and inappropriate medication use. Drugs may precipitate or exacerbate HF through negative inotropic effects, direct cardiotoxicity, or increased sodium and water retention.

CLINICAL PRESENTATION

- Patient presentation may range from asymptomatic to cardiogenic shock.
- Primary symptoms are dyspnea (especially on exertion) and fatigue, which lead to exercise intolerance. Other pulmonary symptoms include

orthopnea, paroxysmal nocturnal dyspnea (PND), tachypnea, and cough.

- Fluid overload can result in pulmonary congestion and peripheral edema.
- Nonspecific symptoms may include fatigue, nocturia, hemoptysis, abdominal pain, anorexia, nausea, bloating, ascites, poor appetite or early satiety, and weight gain or loss.
- Physical examination may reveal pulmonary crackles, S_3 gallop, cool extremities, Cheyne–Stokes respiration, tachycardia, narrow pulse pressure, cardiomegaly, symptoms of pulmonary edema (extreme breathlessness and anxiety, sometimes with coughing and pink, frothy sputum), peripheral edema, jugular venous distention (JVD), hepatojugular reflux (HJR), hepatomegaly, and mental status changes.

DIAGNOSIS

- Consider the diagnosis of HF in patients with characteristic signs and symptoms. A complete history and physical examination with appropriate laboratory testing are essential in evaluating patients with suspected HF.
- Laboratory tests for identifying disorders that may cause or worsen HF include complete blood cell count; serum electrolytes (including calcium and magnesium); renal, hepatic, thyroid function tests, and iron studies; urinalysis; lipid profile; and A1C. Hyponatremia (serum sodium <130 mEq/L [mmol/L]) may indicate worsening volume overload and/or disease progression and is associated with reduced survival. Serum creatinine may be increased due to hypoperfusion; preexisting renal dysfunction can contribute to volume overload. B-type natriuretic peptide (BNP) is usually >100 pg/mL (29 pmol/L) and NT-proBNP >300 pg/mL (35 pmol/L).
- Ventricular hypertrophy can be demonstrated on chest radiograph or electrocardiogram (ECG). Chest radiograph may also show pleural effusions or pulmonary edema.
- Echocardiogram can identify abnormalities of the pericardium, myocardium, or heart valves and quantify LVEF to determine if systolic or diastolic dysfunction is present.
- The New York Heart Association Functional Classification System is intended primarily to classify symptoms according to the physician's subjective evaluation. Functional class (FC)-I patients have no limitation of physical activity, FC-II patients have slight limitation, FC-III patients have marked limitation, and FC-IV patients are unable to carry on physical activity without discomfort.
- The American College of Cardiology/American Heart Association (ACC/AHA) staging system provides a more comprehensive framework for evaluating, preventing, and treating HF (see further discussion below).

TREATMENT OF CHRONIC HEART FAILURE

- Goals of Treatment: Improve quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow disease progression, and prolong survival.

General Approach

- The first step is to determine the etiology or precipitating factors. Treatment of underlying disorders (eg, hyperthyroidism) may obviate the need for treating HF.
- *ACC/AHA Stage A:* These are patients at high risk for developing HF. Identify and modify risk factors to prevent development of structural heart disease and subsequent HF. Strategies include smoking cessation and control of hypertension, diabetes mellitus, and dyslipidemia. Although treatment must be individualized, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are recommended for HF prevention in patients with multiple vascular risk factors.
- *ACC/AHA Stage B:* These patients have structural heart disease but no HF signs or symptoms. Treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process. In addition to treatment measures outlined for stage A, patients with reduced LVEF (<40%) should receive an ACE inhibitor (or ARB) and an evidence-based β-blocker to prevent development of HF, regardless of whether they have had an

MI. Patients with a previous MI and reduced LVEF should also receive an ACE inhibitor or ARB, evidence-based β-blockers, and a statin.

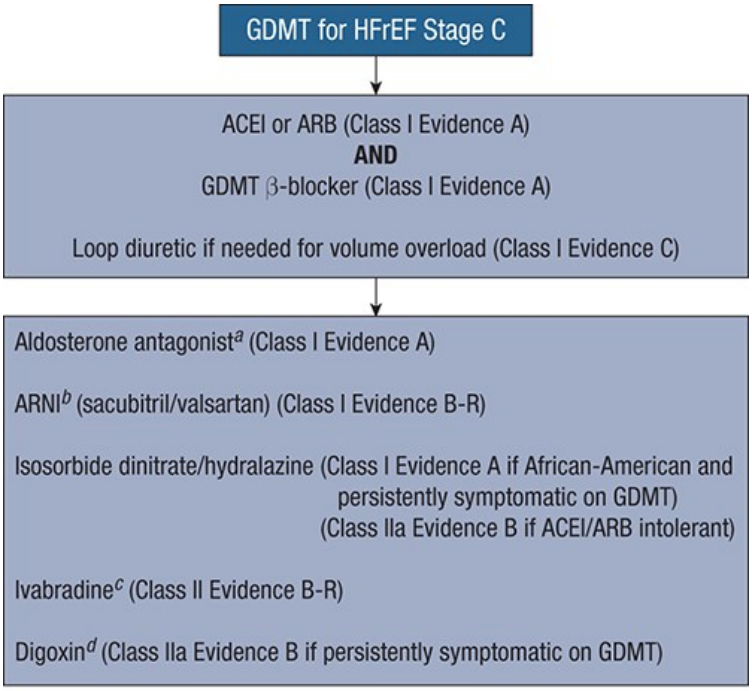
- *ACC/AHA Stage C:* These patients have structural heart disease and previous or current HF symptoms and include both HFrEF and HFpEF. In addition to treatments for stages A and B, patients with HFrEF in stage C should receive guideline-directed medical therapy (GDMT) that includes an ACE inhibitor, ARB, or angiotensin receptor–neprilysin inhibitor (ARNI; valsartan–sacubitril) together with an evidence-based β-blocker, and an aldosterone antagonist in eligible patients to reduce morbidity and mortality (**Fig. 9-1**). Loop diuretics, hydralazine–isosorbide dinitrate (ISDN), digoxin, and ivabradine are also used in select patients.

- *ACC/AHA Stage D HFrEF:* These patients have persistent HF symptoms despite maximally tolerated GDMT. They should be considered for specialized interventions, including mechanical circulatory support, continuous IV positive inotropic therapy, cardiac transplantation, or hospice care (when no additional treatments are appropriate).

FIGURE 9-1

Guideline-directed treatment algorithm for patients with ACC/AHA stage C heart failure with reduced ejection fraction. (Adapted from Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147–e239.)

(ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; bpm, beats per minute; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; K+, serum potassium.)



[a]NYHA class II-IV symptoms, estimated creatinine clearance >30 mL/min and K^+ <5.0 mEq/L
[b]NYHA class II-III symptoms tolerating an ACEI or ARB – switching to ARNI can further reduce morbidity/mortality
[c]NYHA class II-III symptoms in normal sinus rhythm and HR ≥70 bpm on maximally tolerated β-blocker dose
[d]Indication is to reduce hospitalizations
Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Nonpharmacologic Therapy of Chronic Heart Failure

- Interventions include cardiac rehabilitation and restriction of fluid intake and dietary sodium intake (<2–3 g of sodium/day) with daily weight measurements.
- In patients with hyponatremia (serum sodium <130 mEq/L [mmol/L]) or persistent volume retention despite high diuretic doses and sodium restriction, limit daily fluid intake to 2 L/day from all sources.
- Revascularization or anti-ischemic therapy in patients with coronary disease may reduce HF symptoms.
- Drugs that can aggravate HF should be discontinued if possible.

Pharmacologic Therapy for Stage C HFrEF

- In general, patients with stage C HFrEF should receive an ACE inhibitor, ARB, or ARNI along with an evidence-based β-blocker, plus an aldosterone antagonist in select patients (**Fig. 9-1**). Administer a diuretic if there is evidence of fluid retention. A hydralazine–nitrate combination, ivabradine, or digoxin may be considered in select patients. Drug dosing recommendations are provided in **Table 9-1**.

TABLE 9-1

Drug Dosing Recommendations for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)

Generic (Brand) Name	Initial Dose	Usual Range with Normal Renal Function
Loop Diuretics		
Furosemide (Lasix)	20–40 mg once or twice daily	20–160 mg once or twice daily
Bumetanide (Bumex)	0.5–1 mg once or twice daily	1–2 mg once or twice daily
Torsemide (Demadex)	10–20 mg once daily	10–80 mg once 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 (Prinivil, Zestril)	2.5–5 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
Trandolapril (Mavik)	1 mg once daily	4 mg once daily[a]
Perindopril (Aceon)	2 mg once daily	8–16 mg once daily
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]
β-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]
Carvedilol phosphate (Coreg CR)	10 mg once daily	80 mg once daily
Metoprolol succinate CR/XL (Toprol-XL)	12.5–25 mg once daily	200 mg once daily[a]
Aldosterone Antagonists		
Spironolactone (Aldactone)	12.5–25 mg once daily	25–50 mg once daily[a]
Eplerenone (Inspra)	25 mg once daily	50 mg once daily[a]
Other		
Hydralazine–Isosorbide Dinitrate (Bidil)	Hydralazine 37.5 mg 3 times daily	Hydralazine 75 mg 3 times daily[a]
	Isosorbide dinitrate 20 mg 3 times daily	Isosorbide dinitrate 40 mg 3 times daily[a]
Digoxin (Lanoxin)	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

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

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Data from Brater DC. Pharmacology of diuretics. Am J Med Sci. 2000;319:38-50; Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147–e239.

Diuretics

- Compensatory mechanisms in HF stimulate excessive sodium and water retention, often leading to systemic and pulmonary congestion. Consequently, diuretic therapy (in addition to sodium restriction) is recommended for all patients with clinical evidence of fluid retention. However, because they do not alter disease progression or prolong survival, diuretics are not required for patients without fluid retention.

- Thiazide diuretics (eg, **hydrochlorothiazide**) are relatively weak and are infrequently used alone in HF. However, thiazides or the thiazide-like diuretic **metolazone** can be used in combination with a loop diuretic to promote very effective diuresis. Thiazides may be preferred over loop diuretics in patients with only mild fluid retention and elevated BP because of their more persistent antihypertensive effects.

- Loop diuretics (**furosemide**, **bumetanide**, and **torsemide**) are usually necessary to restore and maintain euvolemia in HF. In addition to acting in the thick ascending limb of the loop of Henle, they induce a prostaglandin-mediated increase in renal blood flow that contributes to their natriuretic effect. Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary.

- Adverse effects of diuretics include hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, and renal dysfunction.

Angiotensin-Converting Enzyme Inhibitors

- ACE inhibitors decrease angiotensin II and aldosterone, attenuating many of their deleterious effects that drive HF initiation and progression. ACE inhibitors also inhibit the breakdown of bradykinin, which increases vasodilation and also leads to cough. ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in patients with HFrEF. Current guidelines recommend that all patients with HFrEF, regardless of whether or not symptoms are present, should receive an ACE inhibitor to reduce morbidity and mortality, unless there are contraindications.

- Clinical trials have documented favorable effects of ACE inhibitors on symptoms, HF progression, hospitalizations, and quality of life. ACE inhibitors improve survival by 20%–30% compared with placebo. The benefits are independent of HF etiology (ischemic vs nonischemic) and are greatest in patients with the most severe symptoms.

- Start therapy with low doses followed by gradual titration as tolerated to the target or maximally tolerated doses (**Table 9-1**). Dose titration is usually accomplished by doubling the dose every 2 weeks. Evaluate blood pressure (BP), renal function, and serum potassium at baseline and within 1–2 weeks after the start of therapy and after each dose increase. Although symptoms may improve within a few days of starting therapy, it may take weeks to months before the full benefits are apparent. Even if symptoms do not improve, continue long-term therapy to reduce mortality and hospitalizations.

- The most common adverse effects include hypotension, renal dysfunction, and hyperkalemia. A dry, nonproductive cough (occurring in 15%–20% of patients) is the most common reason for discontinuation. Because cough is a bradykinin-mediated effect, replacement with an ARB is reasonable; however, caution is required because crossreactivity has been reported. Angioedema occurs in approximately 1% of patients and is potentially life threatening; ACE inhibitors are contraindicated in patients with a history of angioedema. ACE inhibitors are contraindicated in pregnancy due to various congenital defects.

Angiotensin Receptor Blockers

- The ARBs block the angiotensin II receptor subtype AT_1, preventing the deleterious effects of angiotensin II on ventricular remodeling. Because they do not affect the ACE enzyme, ARBs do not affect bradykinin, which is linked to ACE inhibitor cough and angioedema.

- ARBs are now a guideline-recommended alternative in patients who are unable to tolerate an ACE inhibitor due to cough or angioedema. Although numerous ARBs are available, only **candesartan**, **valsartan**, and **losartan** are recommended in the guidelines because efficacy has been demonstrated in clinical trials. As with ACE inhibitors, initiate therapy with low doses and then titrate to target doses. Evaluate BP, renal function, and serum potassium within 1–2 weeks after starting therapy and after dosage increases, with these parameters used to guide subsequent dose changes.

- ARBs are not suitable alternatives in patients with hypotension, hyperkalemia, or renal insufficiency due to ACE inhibitors because they are just as likely to cause these adverse effects. Careful monitoring is required when an ARB is used with another inhibitor of the renin-angiotensin-aldosterone (RAAS) system (eg, ACE inhibitor or aldosterone antagonist) because this combination increases the risk of these adverse effects. Because ARBs do not affect bradykinin, they are not associated with cough and have a lower risk of angioedema than ACE inhibitors. Caution should be exercised when ARBs are used in patients with angioedema from ACE inhibitors because crossreactivity has been reported. Similar to ACE inhibitors, ARBs are contraindicated in pregnancy.

Angiotensin Receptor–Neprilysin Inhibitor

- **Valsartan/Sacubitril** is an ARNI approved to reduce the risk of cardiovascular death and hospitalization for HF in patients with NYHA class II–IV HF and reduced LVEF. Neprilysin is an enzyme that degrades bradykinin and other endogenous vasodilator and natriuretic peptides. By reducing neprilysin-mediated breakdown of these compounds, vasodilation, diuresis, and natriuresis are enhanced, and renin and aldosterone secretion is inhibited.
- In patients with HFrEF and NYHA class II–III symptoms tolerating an ACE inhibitor or ARB, current guidelines recommend replacing those drugs with the ARNI to further reduce morbidity and mortality. Discontinue ACE inhibitors 36 hours prior to initiating the ARNI; no waiting period is needed in patients receiving an ARB. Titrate the initial starting dose to the target dose after 2–4 weeks (see **Table 9-1**). Closely monitor BP, serum potassium, and renal function after the start of therapy and after each titration step.
- The most common adverse effects include hypotension, dizziness, hyperkalemia, worsening renal function, and cough. Angioedema is most common with sacubitril/valsartan than with enalapril (0.5% vs 0.2%, respectively). Sacubitril/valsartan is contraindicated in patients with a history of angioedema associated with an ACE inhibitor or ARB. It is also contraindicated in pregnancy and should not be used concurrently with ACE inhibitors or other ARBs.

β-Blockers

- β-Blockers antagonize the detrimental effects of the sympathetic nervous systems in HF and slow disease progression. Clinical trial evidence demonstrated that certain β-blockers reduce HF mortality, all-cause hospitalizations, and hospitalizations for worsening HF, among other endpoints.
- The ACC/AHA guidelines recommend use of β-blockers in all stable patients with HFrEF in the absence of contraindications or a clear history of β-blocker intolerance. Patients should receive a β-blocker even if symptoms are mild or well controlled with ACE inhibitor and diuretic therapy. It is not essential that ACE inhibitor doses be optimized before a β-blocker is started because the addition of a β-blocker is likely to be of greater benefit than an increase in ACE inhibitor dose.
- β-Blockers are also recommended for asymptomatic persons with a reduced LVEF (stage B) to decrease the risk of progression to HF.
- **Carvedilol**, **metoprolol succinate (CR/XL)**, and **bisoprolol** are the only β-blockers shown to reduce mortality in large HF trials. Because bisoprolol is not available in the necessary starting dose of 1.25 mg, the choice is typically limited to either carvedilol or metoprolol succinate. Target doses are those associated with reductions in mortality in placebo-controlled clinical trials (**Table 9-1**).
- Initiate β-blockers in stable patients who have no or minimal evidence of fluid overload. Because of their negative inotropic effects, start β-blockers in very low doses with slow upward dose titration to avoid symptomatic worsening or acute decompensation. Doses should be doubled no more often than every 2 weeks, as tolerated, until the target or maximally tolerated dose is reached.
- Inform patients that β-blocker therapy is expected to positively influence disease progression and survival even if there is little symptomatic improvement. In addition, dose titration is a long, gradual process; response to therapy may be delayed; and HF symptoms may actually worsen during the initiation period.
- Adverse effects include bradycardia or heart block, hypotension, fatigue, impaired glycemic control in diabetic patients, bronchospasm in patients with asthma, and worsening HF. Absolute contraindications 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.

Aldosterone Antagonists

- **Spironolactone** and **eplerenone** block mineralocorticoid receptors, the target for aldosterone. In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion. However, diuretic effects with low doses are minimal, suggesting that their therapeutic benefits result from other actions. In the heart, aldosterone antagonists inhibit cardiac extracellular matrix and collagen deposition, thereby attenuating

cardiac fibrosis and ventricular remodeling. Aldosterone antagonists also attenuate the systemic proinflammatory state, atherogenesis, and oxidative stress caused by aldosterone.

- Current guidelines recommend adding a low-dose aldosterone antagonist to standard therapy to improve symptoms, reduce the risk of HF hospitalization, and increase survival in select patients provided that serum potassium and renal function can be carefully monitored. Based on clinical trial data in HFrEF, low-dose aldosterone antagonists may be appropriate for: (1) patients with mild to moderately severe HFrEF (NYHA class II–IV) who are receiving standard therapy, and (2) those with LV dysfunction and either acute HF or diabetes early after MI.
- Start with low doses (spironolactone 12.5 mg/day or eplerenone 25 mg/day) especially in older persons and those with diabetes or a creatinine clearance <50 mL/min/1.73m^2 (0.48 mL/sec/m^2 (**Table 9-1**).
- Avoid aldosterone antagonists in patients with renal impairment, elevated serum potassium (>5 mEq/L [mmol/L]), or history of severe hyperkalemia. Spironolactone also interacts with androgen and progesterone receptors, which may lead to gynecomastia, impotence, and menstrual irregularities in some patients.

Nitrates and Hydralazine

- **Isosorbide dinitrate (ISDN)** is a venodilator that reduces preload, whereas **hydralazine** is a direct arterial vasodilator that reduces systemic vascular resistance (SVR) and increases stroke volume and CO. The beneficial effects of combining a nitrate with hydralazine extend beyond their complementary hemodynamic actions and are likely related to attenuating the biochemical processes driving HF progression.
- Guidelines recommend addition of hydralazine/ISDN to self-described African Americans with HFrEF and NYHA class III–IV symptoms treated with ACE inhibitors (or ARBs) and β-blockers. The combination can also be useful in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or hypotension.
- Obstacles to successful therapy with the combination include the need for frequent dosing (ie, three times daily with the fixed-dose combination product), high frequency of adverse effects (eg, headache, dizziness, and GI distress), and increased cost for the fixed-dose combination product.

Ivabradine

- Ivabradine inhibits the I_f current in the sinoatrial node that is responsible for controlling HR, thereby slowing spontaneous depolarization of the sinus node and resulting in a dose-dependent slowing of the HR. It does not affect AV conduction, BP, or myocardial contractility. Elevated resting heart rate (HR) (>70–80 bpm) is an independent risk factor for adverse HFrEF outcomes, and β-blockers are frequently underdosed in clinical practice for a variety of reasons. Because of the clear benefits of β-blockers on mortality, clinicians should titrate to the maximum tolerated doses before considering use of ivabradine.
- Ivabradine is indicated to reduce the risk of hospitalization for worsening HF in patients with LVEF ≤35% who are in sinus rhythm with resting HR ≥70 bpm and are either on a maximally tolerated dose of a β-blocker or have a contraindication to β-blocker use.
- The usual starting dose is 5 mg twice daily with meals (**Table 9-1**). After 2 weeks of treatment, if the resting HR is between 50 and 60 bpm, the dose should be continued. If the HR is >60 bpm, the dose can be increased to the maximum of 7.5 mg twice daily. If at any point the HR is <50 bpm or the patient has symptomatic bradycardia, the dose should be reduced by 2.5 mg twice daily; if the patient is only receiving 2.5 mg twice daily, ivabradine should be discontinued.
- The most common adverse effects are bradycardia, atrial fibrillation, and visual disturbances.

Digoxin

- Although digoxin has positive inotropic effects, its benefits in HF are related to its neurohormonal effects. It attenuates the excessive sympathetic nervous system activation in HF and increases parasympathetic activity, thereby decreasing HR and enhancing diastolic filling. Observational studies of digoxin conducted in the context of contemporary HF therapy showed either neutral effects or reductions in hospitalizations and either neutral or detrimental effects of digoxin on mortality.

- Based on available data, digoxin is not considered a first-line agent in HF, but a trial may be considered in conjunction with GDMT including ACE inhibitors (or ARBs), β-blockers, and diuretics in patients with symptomatic HFrEF to improve symptoms and reduce hospitalizations. Digoxin may also be considered to help control ventricular rate in patients with HFrEF and supraventricular arrhythmias, although β-blockers are generally more effective rate control agents, especially during exercise.
- In the absence of digoxin toxicity or serious adverse effects, digoxin should be continued in most patients. Digoxin withdrawal may be considered for asymptomatic patients who have significant improvement in systolic function with optimal ACE inhibitor and β-blocker treatment.
- The target serum digoxin concentration for most patients is 0.5–0.9 ng/mL (0.6–1.2 nmol/L). Most patients with normal renal function can achieve this level with a dose of 0.125 mg/day. Patients with decreased renal function, low body weight, advanced age, or interacting drugs (eg, amiodarone) should receive 0.125 mg every other day.

Pharmacologic Therapy for HFpEF

- Treatment includes controlling HR and BP, alleviating causes of myocardial ischemia, reducing volume, and restoring and maintaining sinus rhythm in patients with atrial fibrillation. Many of the drugs are the same as those used to treat HFrEF (eg, diuretics, β-blockers), but the rationale and dosing may be different.
- A loop or a thiazide diuretic should be considered for patients with volume overload. Use a loop diuretic for more severe volume overload or inadequate response to a thiazide. Avoid lowering preload excessively, which may reduce stroke volume and CO. Start diuretics at low doses to avoid hypotension and fatigue.
- ACE inhibitors may be considered in all patients, especially patients with symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor.
- ARBs may be considered in all patients, especially those who are intolerant of ACE inhibitors.
- Aldosterone antagonists can reduce the risk of hospitalization in patients who do not have contraindications and are not at risk for hyperkalemia. They may be beneficial for patients with elevated BNP or NT-proBNP.
- β-Blockers should be considered in patients with one or more of the following conditions: (1) MI, (2) hypertension, and (3) atrial fibrillation requiring ventricular rate control.
- Nondihydropyridine calcium channel blockers (CCB; **diltiazem** or **verapamil**) should be considered for patients with atrial fibrillation warranting ventricular rate control who either are intolerant to or have not responded to a β-blocker. A nondihydropyridine or dihydropyridine (eg, **amlodipine**) CCB can be considered for symptom-limiting angina or hypertension.

TREATMENT OF ACUTE DECOMPENSATED HEART FAILURE (ADHF)

General Approach

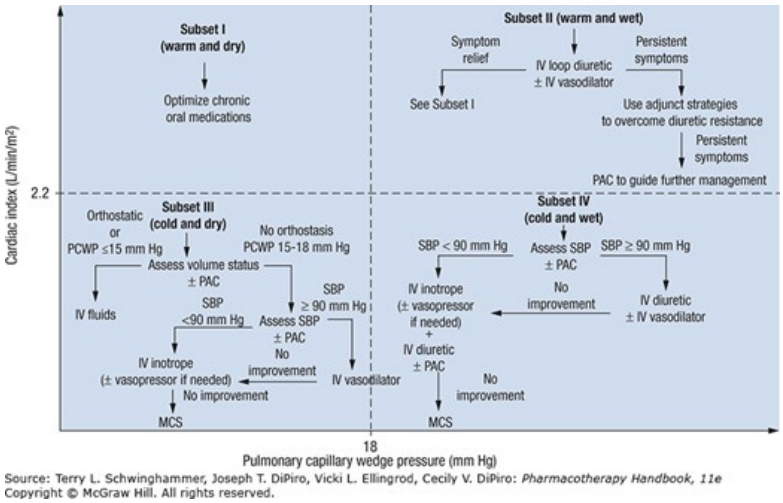
- *Acute decompensated heart failure* involves patients with new or worsening signs or symptoms (often resulting from volume overload and/or low CO) requiring medical intervention, such as emergency department visit or hospitalization.
- Goals of Treatment: The overall goals are to relieve symptoms, improve hemodynamic stability, and reduce short-term mortality so the patient can be discharged in a stable compensated state on oral drug therapy.
- Consider hospitalization based on clinical findings. Admission to an intensive care unit (ICU) may be required if the patient experiences hemodynamic instability requiring frequent monitoring of vital signs, invasive hemodynamic monitoring, or rapid titration of IV medications with close monitoring.
- Focus the history and physical exam on potential etiologies of ADHF; presence of precipitating factors (eg, arrhythmias, hypertension, myocardial ischemia or infarction, anemia, and thyroid disorders); onset, duration, and severity of symptoms; and a careful medication history.

- Symptoms of volume overload include dyspnea, orthopnea, PND, ascites, GI symptoms (poor appetite, nausea, early satiety), peripheral edema, and weight gain. Low output symptoms include altered mental status, fatigue, GI symptoms (similar to volume overload), and decreased urine output.
- Signs of volume overload include pulmonary crackles, elevated jugular venous pressure, HJR, S_3 gallop, and peripheral edema. Low output signs include tachycardia, hypotension (more commonly) or hypertension, narrow pulse pressure, cool extremities, pallor, and cachexia.
- Laboratory testing may include BNP or NT-proBNP, thyroid function tests, complete blood count, cardiac enzymes, and routine serum chemistries (eg, serum creatinine, liver function tests).
- Ascertain hemodynamic status to guide initial therapy. Patients may be categorized into one of four hemodynamic subsets based on volume status (euvolemic or "dry" vs volume overloaded or "wet") and CO (adequate CO or "warm" vs hypoperfusion or "cold") (**Fig. 9-2**).
- Reserve invasive hemodynamic monitoring for patients refractory to initial therapy, whose volume status is unclear, or who have significant hypotension or worsening renal function despite appropriate initial therapy.
- Address and correct reversible or treatable causes of decompensation.
- Assess medications being taken prior to admission and determine whether adjustment or discontinuation is required.
- If fluid retention is evident on physical exam, pursue aggressive diuresis, preferably with IV diuretics.
- In the absence of cardiogenic shock or symptomatic hypotension, strive to continue all GDMT for HF. β-blockers may be temporarily held or dose-reduced if recent changes are responsible for acute decompensation. Other GDMT (ACE inhibitors, ARBs, ARNI, and aldosterone antagonists) may also need to be temporarily withheld in the presence of renal dysfunction, with close monitoring of serum potassium. Most patients may continue to receive digoxin at doses targeting a trough serum concentration of 0.5–0.9 ng/mL (mcg/L; 0.6–1.2 nmol/L).

FIGURE 9-2

General management algorithm for acute decompensated heart failure based on clinical presentation. Patients may be categorized into a hemodynamic subset based on signs and symptoms or invasive hemodynamic monitoring. Adjunct strategies for overcoming diuretic resistance include increasing the dose of loop diuretic; switching to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and in select patients, adding mechanical circulatory support.

(IV, intravenous; MCS, mechanical circulatory support; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; SBP, systolic BP.)



Nonpharmacologic Therapy for ADHF

- Place all patients with congestive symptoms on sodium restriction (<2 g daily) and consider fluid restriction for refractory symptoms.
- Consider noninvasive ventilation for patients in respiratory distress due to acute pulmonary edema, particularly those at risk for intubation.
- Provide pharmacologic thromboprophylaxis with unfractionated heparin or low-molecular-weight heparin for most patients with limited mobility; consider mechanical thromboprophylaxis with intermittent pneumatic compression devices in patients at high risk for bleeding.
- Most nonpharmacologic therapies for ADHF are reserved for patients failing pharmacologic therapy. Ultrafiltration and wireless invasive hemodynamic monitoring (W-IHM) may be used to manage congestive symptoms. Temporary mechanical circulatory support (MCS) with an intra-aortic balloon pump (IABP), ventricular assist device (VAD), or extracorporeal membrane oxygenation (ECMO) may be considered for hemodynamic stabilization until the underlying etiology of cardiac dysfunction resolves or has been corrected ("bridge to recovery") or until evaluation for definitive therapy (eg, durable MCS or cardiac transplantation) can be completed ("bridge to decision"). IV vasodilators and inotropes may be used with temporary MCS to maximize hemodynamic and clinical benefits or facilitate device removal. Systemic anticoagulant therapy is generally required to prevent device thrombosis, regardless of the method selected.
- Durable MCS with temporary device implantation is used for patients awaiting heart transplantation who are unlikely to survive until a suitable donor is identified ("bridge to transplantation"). Permanent device implantation is used in patients ineligible for heart transplantation due to advanced age or comorbid conditions ("destination therapy").
- Cardiac transplantation is the best option for patients with irreversible advanced HF. New surgical strategies such as ventricular aneurysm resection and myocardial cell transplantation offer additional options for patients ineligible for VAD implantation or heart transplantation.

Pharmacologic Therapy for ADHF

Loop Diuretics

- Current guidelines recommend IV loop diuretics (**furosemide**, **bumetanide**) as first-line therapy for ADHF patients with volume overload.
- Bolus administration reduces preload by functional venodilation within 5–15 minutes and later (>20 minutes) via sodium and water excretion, thereby improving pulmonary congestion. Although patients with HFrEF can tolerate significant reductions in preload without compromising stroke volume, excessive diuresis can decrease CO. Excessive reductions in venous return may also compromise CO in diastolic dysfunction, intravascular volume depletion, or patients in whom CO is significantly dependent on adequate filling pressure (ie, preload-dependent). Reflex increases in neurohormonal activation (ie, elevated renin, norepinephrine, and AVP) may result in arteriolar and coronary vasoconstriction, tachycardia, and increased myocardial oxygen consumption.
- Use low doses (equivalent to IV furosemide 20–40 mg) initially in ADHF patients who are naïve to loop diuretics. For patients taking loop diuretics prior to admission, a total daily dose of 1- to 2.5-times their home dose is recommended. Higher doses are associated with more rapid relief of congestive symptoms but may also increase the risk of transient worsening of renal function. Doses may be administered as either an IV bolus (ie, divided every 12 hours) or continuous IV infusion. Use diuretic therapy judiciously to obtain the desired improvement in congestive symptoms while avoiding a reduction in CO, symptomatic hypotension, or worsening renal function.
- Diuretic resistance may be improved by administering larger IV bolus doses, transitioning from IV bolus to continuous IV infusions, or adding a second diuretic with a different mechanism of action, such as a distal tubule blocker (eg, oral **metolazone**, oral **hydrochlorothiazide**, or IV **chlorothiazide**). Sequential nephron blockade with a loop and thiazide-type diuretic should generally be reserved for inpatients who can be monitored closely for development of severe electrolyte and intravascular volume depletion. In the outpatient setting, a very low dose of the thiazide-type diuretic or infrequent administration (eg, 1–3 times weekly) is recommended.

Vasopressin Antagonists

- Vasopressin receptor antagonists affect one or two AVP (antidiuretic hormone) receptors, V_{1A} or V_2. Stimulation of V_{1A} receptors (located in vascular smooth muscle cells and myocardium) results in vasoconstriction, myocyte hypertrophy, coronary vasoconstriction, and positive inotropic effects. V_2 receptors are located in renal tubules, where they regulate water reabsorption.

✔ **Tolvaptan** selectively binds to and inhibits the V_2 receptor. It is an oral agent indicated for hypervolemic and euvolemic hyponatremia in patients with syndrome of inappropriate antidiuretic hormone (SIADH), cirrhosis, or HF. Tolvaptan is typically initiated at 15 mg orally daily and then titrated to 30 or 60 mg daily as needed to resolve hyponatremia. It is a substrate of cytochrome P450-3A4 and is contraindicated with potent inhibitors of this enzyme. The most common side effects are dry mouth, thirst, urinary frequency, constipation, and hyperglycemia.

✔ **Conivaptan** nonselectively inhibits both the V_{1A} and V_2 receptors. It is an IV agent indicated for hypervolemic and euvolemic hyponatremia due to a variety of causes but is not indicated for patients with HF.

- Monitor patients closely to avoid an excessively rapid rise in serum sodium that could cause hypotension or hypovolemia requiring drug discontinuation. Therapy may be restarted at a lower dose if hyponatremia recurs or persists and adverse effects resolve.
- The role of vasopressin receptor antagonists in the long-term management of HF is unclear. In a clinical trial of hospitalized patients with HF, tolvaptan improved hyponatremia, diuresis, and signs/symptoms of congestion. However, the study failed to demonstrate improved long-term outcomes, including morbidity and mortality. Another randomized trial in patients with ADHF found worsening renal function in significantly more patients receiving tolvaptan than placebo. Overall, these two trials do not support routine use of tolvaptan in ADHF, and it should be reserved for managing severe hyponatremia.

Vasodilators

- Venodilators reduce preload by increasing venous capacitance, improving symptoms of pulmonary congestion in patients with high ventricular filling pressures. Arterial vasodilators counteract the peripheral vasoconstriction and impaired CO that can result from activation of the sympathetic nervous system, RAAS, and other neurohormonal mediators in HF. Arterial vasodilators reduce impedance, decreasing afterload and causing reflex improvement in LV performance and increased CO. Mixed vasodilators act on both arterial resistance and venous capacitance vessels, reducing congestive symptoms while increasing CO.
- IV vasodilators should be considered before positive inotropic therapy in patients with low CO and elevated SVR (or elevated BP in those without a pulmonary artery catheter). However, hypotension may preclude their use in patients with preexisting low BP or SVR.
- **IV nitroglycerin** is often preferred for preload reduction in ADHF, especially in patients with pulmonary congestion. It reduces preload and pulmonary capillary wedge pressure (PCWP) via functional venodilation and mild arterial vasodilation. In higher doses, nitroglycerin displays potent coronary vasodilating properties and beneficial effects on myocardial oxygen demand and supply, making it the vasodilator of choice for patients with severe HF and ischemic heart disease.

  ✔ Initiate nitroglycerin at 5–10 mcg/min (0.1 mcg/kg/min) and increase every 5–10 minutes as necessary and tolerated. Maintenance doses usually range from 35 to 200 mcg/min (0.5–3 mcg/kg/min). Hypotension and excessive decrease in PCWP are important dose-limiting side effects. Tolerance to the hemodynamic effects may develop over 12–72 hours of continuous administration.

- **Sodium nitroprusside** is a mixed arteriovenous vasodilator that increases cardiac index (CI) to a similar degree as dobutamine and milrinone despite having no direct inotropic activity. However, nitroprusside generally produces greater decreases in PCWP, SVR, and BP.

  ✔ Hypotension is an important dose-limiting adverse effect of nitroprusside, and its use should be primarily reserved for patients with elevated SVR. Close monitoring is required because even modest HR increases can have adverse consequences in patients with underlying ischemic heart disease or resting tachycardia.

  ✔ Nitroprusside is effective in the short-term management of severe HF in a variety of settings (eg, acute MI, valvular regurgitation, after coronary bypass surgery, and ADHF). It does not usually worsen, and may improve, the balance between myocardial oxygen demand and supply. However, an excessive decrease in systemic arterial pressure can decrease coronary perfusion and worsen ischemia.

  ✔ Nitroprusside has a rapid onset and a duration of action <10 minutes, necessitating continuous IV infusions. Initiate therapy with a low dose (0.1–0.2 mcg/kg/min) to avoid excessive hypotension, and increase by small increments (0.1–0.2 mcg/kg/min) every 5–10 minutes as tolerated. Usual effective doses range from 0.5 to 3 mcg/kg/min. Taper nitroprusside slowly when transitioning to oral medications to avoid the rebound phenomenon of reflex neurohormonal activation after abrupt withdrawal. Nitroprusside-induced cyanide and thiocyanate

toxicity are unlikely when doses <3 mcg/kg/min are administered for less than 3 days, except in patients with significant renal impairment (ie, serum creatinine >3 mg/dL [265 µmol/L]).

Inotropes

- Prompt correction of low CO in patients with "cold" subsets (III and IV) is required to restore peripheral tissue perfusion and preserve end-organ function. Although IV inotropes can improve hypoperfusion by enhancing cardiac contractility, potential adverse outcomes limit their use to select patients with refractory ADHF. Inotropes should be considered only as a temporizing measure to maintain end-organ perfusion in patients with cardiogenic shock or severely depressed CO and low systolic BP (ie, ineligible for IV vasodilators) until definitive therapy can be initiated, as a "bridge" for patients with advanced HF who are eligible for MCS or cardiac transplantation, or for palliation of symptoms in patients with advanced HF who are ineligible for MCS or cardiac transplantation.

- Dobutamine and milrinone produce similar hemodynamic effects, but dobutamine usually causes more pronounced increases in HR, and milrinone is associated with greater relaxation in arterial smooth muscle.

- **Dobutamine** is a β_1- and β_2-receptor agonist with some α_1-agonist effects; its positive inotropic effects are due to effects on β_1-receptors. Stimulation of cardiac β_1-receptors does not generally produce a significant increase in HR. Modest peripheral β_2-receptor-mediated vasodilation tends to offset minor α_1-receptor-mediated vasoconstriction; the net vascular effect is usually vasodilation.

  ✔ CI is increased because of inotropic stimulation, arterial vasodilation, and a variable increase in HR. It causes relatively little change in mean arterial pressure (MAP) compared with the more consistent increases observed with dopamine. Dobutamine should be considered over milrinone when a significant decrease in MAP might further compromise hemodynamic function.

  ✔ Vasodilation usually reduces PCWP, making dobutamine particularly useful in the presence of low CI and an elevated LV filling pressure; however, these effects may be detrimental in the presence of reduced filling pressure.

  ✔ Initial doses of 2.5–5 mcg/kg/min may be increased progressively to 20 mcg/kg/min based on clinical and hemodynamic responses. The dose should be tapered rather than abruptly discontinued.

  ✔ Dobutamine's major adverse effects are tachycardia and ventricular arrhythmias. Potentially detrimental increases in oxygen consumption have also been observed.

- **Milrinone** inhibits phosphodiesterase III and produces positive inotropic and arterial and venous vasodilating effects (an inodilator). It has supplanted use of amrinone, which has a higher rate of thrombocytopenia.

  ✔ During IV administration, milrinone increases stroke volume and CO with minimal change in HR. However, the vasodilating effects may predominate, leading to decreased BP and a reflex tachycardia. Milrinone also lowers pulmonary PCWP by venodilation and is particularly useful in patients with a low CI and elevated LV filling pressure. However, this decrease in preload can be hazardous for patients without excessive filling pressure, thus blunting the improvement in CO. Use milrinone cautiously in severely hypotensive HF patients because it does not increase, and may even decrease, arterial BP.

  ✔ Most patients are started on a continuous IV infusion of 0.1–0.3 mcg/kg/min, titrated to a maximum of 0.75 mcg/kg/min. A loading dose of 50 mcg/kg over 10 minutes can be given if rapid hemodynamic changes are required, but its use is uncommon due to an increased risk of hypotension.

  ✔ The most notable adverse events are arrhythmia, hypotension, and thrombocytopenia. Measure the platelet count before and during therapy.

- **Norepinephrine** and **dopamine** have combined inotropic and vasopressor activity. Although therapies that increase SVR are generally avoided in ADHF, they may be required in select patients where marked hypotension precludes use of traditional inotropes (eg, septic shock, refractory cardiogenic shock). These agents are sometimes combined with traditional inotropes so each drug can be adjusted independently to achieve the desired hemodynamic response, although little data exist to support that practice.

✔ Norepinephrine stimulates α_1- and β_1-adrenergic receptors. Stimulation of β_1-receptors in myocardial tissue increases HR, contractility, and therefore CO, but peripheral α_1-receptor-induced vasoconstriction is the predominant clinical hemodynamic effect. Lack of affinity for β_2-receptors may be responsible for the limited impact of norepinephrine on CO.

✔ Dopamine is an endogenous precursor of norepinephrine that stimulates α_1, β_1, β_2, and D_1 (vascular dopaminergic) receptors. Positive inotropic effects mediated primarily by β_1-receptors are prominent with doses of 2–5 mcg/kg/min. The CI is increased with minimal changes in SVR. At doses between 5 and 10 mcg/kg/min, chronotropic and α_1-mediated vasoconstriction become more prominent and MAP usually increases as a result of increases in both CI and SVR.

✔ Studies of low-dose dopamine (2–5 mcg/kg/min) given with IV loop diuretics to enhance diuresis demonstrated no improvements in urine output, renal protection, or symptom relief, but increased rates of tachycardia. Thus, low-dose dopamine may not provide any advantages over traditional inotropes in this setting.

EVALUATION OF THERAPEUTIC OUTCOMES

Chronic Heart Failure

- Ask patients about the presence and severity of symptoms and how symptoms affect daily activities.
- Evaluate efficacy of diuretic treatment by disappearance of the signs and symptoms of excess fluid retention. Focus the physical examination on body weight, extent of JVD, presence of HJR, and presence and severity of pulmonary congestion (crackles, dyspnea on exertion, orthopnea, and PND) and peripheral edema.
- Other outcomes are improvement in exercise tolerance and fatigue, decreased nocturia, and decreased HR.
- Monitor BP to ensure that symptomatic hypotension does not develop as a result of drug therapy.
- Body weight is a sensitive marker of fluid loss or retention, and patients should weigh themselves daily and report changes of 3–5 lb (1.4–2.3 kg) to their healthcare provider so adjustments can be made in diuretic doses.
- Symptoms may worsen initially on β-blocker therapy, and it may take weeks to months before patients notice symptomatic improvement.
- Routine monitoring of serum electrolytes (especially potassium and magnesium) and renal function (BUN, serum creatinine, eGFR) is mandatory in patients with HF.

Acute Decompensated Heart Failure

- Assess the efficacy of drug therapy with daily monitoring of weight, strict fluid intake and output measurements, and HF signs/symptoms. Monitor frequently for electrolyte depletion, symptomatic hypotension, and renal dysfunction. Assess vital signs frequently throughout the day.
- Patients should not be discharged until optimal volume status is achieved, they have been successfully transitioned from IV to oral diuretics, and IV inotropes and vasodilators have been discontinued for at least 24 hours.
- Optimize GDMT in hemodynamically stable patients without contraindications, including reinitiation of therapies withheld earlier in the admission. Low-dose β-blockers may be safely initiated at discharge without increasing the risk of readmission. Transitioning eligible patients to the ARNI sacubitril/valsartan may also be considered.
- Schedule a follow-up appointment at 7–10 days postdischarge and a nurse visit or phone call at 3 days for select patients. Also schedule pertinent follow-up labs (eg, potassium, serum creatinine, INR, serum digoxin concentration).
- All patients should be considered for referral to a formal disease management program.

See Chapter 35, Chronic Heart Failure, authored by Robert B. Parker, Jean M. Nappi, and Larisa H. Cavallari, and Chapter 36, Acute Decompensated

Heart Failure, authored by Brent N. Reed and Jo E. Rodgers, for more detailed discussions of these topics.