# Chronic Heart Failure

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## Learning Objectives

1. Given a patient case, assess the appropriateness of standard and adjunctive therapies for the management of heart failure (HF) including pharmacologic and nonpharmacologic therapies.
2. Given a patient case, construct a pharmacotherapy plan using evidence-based recommendations as outlined in the 2009 American Heart Association/American College of Cardiology and 2010 Heart Failure Society of America guidelines.
3. Apply clinical results from the literature, based on the differences between patients with HF caused by reduced ejection fraction (EF) and those with preserved EF, to achieve optimal outcomes.
4. Evaluate and modify drug therapy regimens in patients with HF with concomitant disease states including diabetes, atrial fibrillation, chronic kidney disease, and chronic obstructive pulmonary disease.
5. Develop a care plan that integrates the pharmacist's role in the medical management of patients with HF.

## Introduction

Despite considerable advances in its management, chronic heart failure (HF) continues to be a significant cause of morbidity and mortality. The standard of therapy for managing this disease has not appreciably changed in the past decade; however, new findings have further developed our understanding of how to use these therapies. Recent studies have advanced our understanding of the role of natriuretic peptides in the diagnosis and management of HF, as well as the role of other neurohormones in HF management. Registries have highlighted the significance of common comorbid diseases, and our understanding of how to manage such comorbidities in the setting of HF continues to emerge. In addition, the prevalence of HF with preserved ejection fraction (EF) has been recognized, and knowledge continues to evolve regarding its management. Finally, the pharmacist's role in managing HF continues to evolve as the profession becomes more integrally involved in multidisciplinary HF management.

About 5 million people in the United States are living with HF, and around 550,000 new diagnoses are made annually. The epidemic increase in HF incidence is caused by the exponential growth of the elderly population and the improved HF survival rate. Individuals receiving a diagnosis of HF have a 5-year mortality rate of about 50%, with the highest rates in older people, men, and African Americans. Hospitalization rates for HF, which continue to rise, are the primary cost driver of the disease. The 30-day and 1-year mortality rates after hospitalization for HF are 10.4% and 22%, respectively. The estimated direct and indirect costs of HF in the United States for 2010 are $39.2 billion, and this is believed to be greatly understated.

### Baseline Review Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Ramani GV, Uber PA, Mehra MR. Chronic heart failure: contemporary diagnosis and management. Mayo Clin Proc 2010;85:180–95.
- Miller AB, Piña IL. Understanding heart failure with preserved ejection fraction: clinical importance and future outlook. Congest Heart Fail 2009;15:186–92.
- Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. Arch Intern Med 2008;168:687–94.

### Abbreviations in This Chapter

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| ARA | Aldosterone receptor antagonist |
| ARB | Angiotensin receptor blocker |
| BNP | B-type natriuretic peptide |
| CKD | Chronic kidney disease |
| COPD | Chronic obstructive pulmonary disease |
| DM | Diabetes mellitus |
| EF | Ejection fraction |
| HF | Heart failure |
| HTN | Hypertension |
| ICD | Implantable cardioverter defibrillator |
| MI | Myocardial infarction |
| NYHA | New York Heart Association |
| PUFA | n-3 polyunsaturated fatty acid |
| SCr | Serum creatinine |

Unlike other cardiovascular diseases, HF is often the end stage of a variety of cardiac disease processes including hypertension (HTN) and ischemic heart disease. Hypertension is a common risk factor for developing HF; 75% of cases have antecedent HTN. Another common risk factor is ischemic heart disease. In patients with established coronary disease, diabetes mellitus (DM) is the strongest risk factor for HF and is strongly associated with increased risk of death from HF. Although there have been many randomized, controlled trials for various HF therapies, typically the demographics of patients in these studies vary substantially from those derived from registry data, which generally include patients from a mix of academic and community hospitals. Patients in clinical trials tend to be younger and are mainly men who have few comorbid diseases. In addition, patients with HF and preserved EF (i.e., EF greater than 40%) have largely been excluded from clinical trials, even though they account for more than 40% of patients with HF.

Although the neurohormonal model for HF has been established for decades, knowledge of the role of neurohormones in addition to angiotensin II, norepinephrine, and aldosterone in disease pathology continues to evolve. Recent studies have advanced our understanding of the role of B-type natriuretic peptide (BNP) and vasopressin in HF diagnosis and management.

## Heart Failure Caused by Reduced Ejection Fraction

The goals of managing HF are to slow disease progression, prolong survival, prevent hospitalizations, minimize symptoms, and maximize quality of life. Efforts should be made to treat patients with risk factors (e.g., HTN, DM, and myocardial infarction [MI]) because this provides the earliest opportunity to reduce the development of HF. It is also important to identify and treat any reversible, underlying cause (e.g., aortic stenosis).

### Standard Pharmacologic Therapy

Angiotensin-converting enzyme (ACE) inhibitors are the most widely studied drug class used in HF; they reduce mortality and hospitalizations, delay disease progression, and improve symptoms, clinical status, and quality of life. Therefore, ACE inhibitors are recommended in all stages of HF unless contraindicated. Angiotensin-converting enzyme inhibitors are generally preferred to angiotensin receptor blockers (ARBs) or direct-acting vasodilators because of a greater weight of evidence. In addition, one ARB, losartan, did not become generically available until recently, and its out-of-pocket cost makes this agent less desirable for many patients.

β-Blockers have consistently shown benefit in patients with structural heart disease regardless of symptoms. Like ACE inhibitors, β-blockers reduce the risk of death and/or hospitalization and improve the clinical status of patients. Both ACE inhibitors and β-blockers are critically important HF therapies, and every attempt should be made to initiate and achieve target dosages in all patients with HF. Whereas ACE inhibitors reduce mortality caused by progressive HF, β-blockers reduce mortality caused by both progressive HF and sudden cardiac death. Therapy with β-blockers should not be initiated in patients with fluid overload or low cardiac output states; however, they can be safely initiated before discharge in select patients. In addition, β-blockers should be continued in patients admitted to the hospital with acute HF if they were previously stable on a β-blocker and if considerable hypotension and cardiogenic shock are not present. Standard HF therapies are summarized in Table 1-1.

Most patients with HF are prescribed a loop diuretic for fluid control. A thiazide-like diuretic may be used in conjunction with the loop diuretic to further enhance sodium excretion and diuresis. Diuretics improve HF symptoms and exercise tolerance; however, their effects on mortality are unknown, and several retrospective analyses suggest they are harmful.

### Alternative/Adjunctive Pharmacologic Therapy for Select Patients

Angiotensin receptor blockers remain a reasonable alternative in patients intolerant of ACE inhibitor therapy. Although the combination of an ACE inhibitor and an ARB may be used in select patients, combination therapy with ACE inhibitors, ARBs, and aldosterone receptor antagonists (ARAs) is not recommended because of an increased risk of hyperkalemia.

**Table 1-1.** Standard and Alternative/Adjunctive HF Therapies by Category

| Select Agents and Target Dosages | Population | Outcome |
|---|---|---|
| Standard HF Therapies | | |
| ACE inhibitors<br>Captopril 50 mg three times daily<br>Enalapril 10 mg twice daily<br>Fosinopril 80 mg daily<br>Lisinopril 20–40 mg daily<br>Quinapril 20 mg twice daily<br>Perindopril 8–16 mg daily<br>Ramipril 10 mg daily<br>Trandolapril 4 mg daily | All patients with HF | Reduced mortality and reduced hospitalizations |
| ARBs<br>Candesartan 32 mg daily<br>Losartan 50–100 mg daily<br>Valsartan 160 mg twice daily | ACE inhibitor–intolerant patients (e.g., cough, angioedema – exert extreme caution if considered at all)<br>Persistently symptomatic despite standard therapy[a,b] | Same benefit as ACE inhibitors (in ACE inhibitor–intolerant patient)<br>Reduced combined CV death and HF hospitalization |
| β-Blockers (only one of three agents may be used):<br>Bisoprolol 10 mg daily<br>Carvedilol 25 mg twice daily (50 mg twice daily if > 85 kg)<br>Metoprolol succinate XL 200 mg daily | All patients with HF | Reduced mortality and reduced hospitalizations |
| Alternative/Adjunctive Therapies | | |
| ARAs<br>Spironolactone 25 mg/day<br>Eplerenone 50 mg/day | Moderately severe to severe HF (NYHA class III–IV) despite standard HF therapy[a]<br>HF symptoms or LV dysfunction immediately after MI<br>Serum creatinine < 2.5 mg/dL<br>Serum potassium < 5 mEq/L | Reduced mortality and reduced hospitalizations<br>Reduced mortality and reduced cardiovascular hospitalizations |
| Hydralazine 75 mg three times/day and isosorbide dinitrate 40 mg three times/day | Self-identified African Americans<br>Moderately severe to severe HF (NYHA class III–IV) despite standard HF therapy[a]<br>An alternative in patients with HF intolerant of ACE inhibitor and/or ARB | Reduced mortality and reduced hospitalizations |
| Digoxin (goal serum concentration 0.5–0.8 ng/mL) | Current or prior symptoms of HF | Reduced hospitalizations |

[a]Standard HF therapy = ACE inhibitor plus β-blocker.
[b]Addition of ARB to ACE inhibitor would not be considered standard therapy, but instead, alternative/adjunctive therapy.
ACE = angiotensin-converting enzyme; ARA = aldosterone receptor antagonist; ARB = angiotensin receptor blocker; CV = cardiovascular; HF = heart failure; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association; XL = extended release.

Although ACE inhibitors reduce hospitalization in a dose-related manner, the relationship between ARB dose and clinical outcome has not been extensively studied. The recent Effects of High-Dose versus Low-Dose Losartan on Clinical Outcomes in Patients with Heart Failure (HEAAL) trial randomized about 3800 patients who were intolerant of ACE inhibitor therapy to losartan 50 mg or 150 mg daily. The group of patients receiving the higher ARB dose had a significant reduction in the combined end point of death or HF hospitalization.

Digoxin improves symptoms, exercise tolerance, and quality of life regardless of underlying cardiac rhythm or cause of HF. However, no mortality benefit has been shown. Digoxin may be considered in patients with persistent symptoms despite standard therapy. Serum digoxin concentrations of 0.5–0.8 ng/mL are associated with the best outcomes.

The ARAs decrease mortality and hospitalization in HF patients with moderately severe to severe symptoms, as well as in patients who develop HF immediately after MI. The main risk associated with spironolactone and eplerenone use, especially in combination with either an ACE inhibitor or an ARB, is hyperkalemia. Several retrospective analyses have shown that the incidence of hyperkalemia requiring hospitalization is significantly greater than that observed in clinical trials and is likely caused by less stringent patient selection criteria. Hyperkalemia can be minimized by appropriate patient selection and monitoring (Box 1-1).

Combination therapy with hydralazine and isosorbide dinitrate may be considered in patients with contraindications to or intolerance of ACE inhibitors or ARBs. Literature suggesting a reduced benefit of ACE inhibitor therapy for African American patients led to the African-American Heart Failure Trial (A-HeFT). This trial was designed to assess the effect of adding combination hydralazine and isosorbide dinitrate to standard HF therapy (including ACE inhibitors and β-blockers) in African American patients with moderately severe to severe symptoms. The study showed that patients receiving hydralazine and isosorbide dinitrate therapy experienced a significant decrease in morbidity and mortality; however, they also had significantly more headaches (47.5% vs. 19.2%) and episodes of dizziness (29.3% vs. 12.3%) than the placebo group. These findings call into question the tolerability of this regimen. In addition, there were concerns regarding the addition of vasodilators to standard HF therapy because of hypotensive effects, particularly in patients with pretreatment low blood pressure. A retrospective analysis of the A-HeFT trial demonstrated that hydralazine and isosorbide dinitrate therapy is associated with a similar

**Box 1-1.** Strategies for Minimizing Hyperkalemia in Patients Treated with Aldosterone Receptor Antagonists

Impaired kidney function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine concentration exceeds 1.6 mg/dL. In elderly patients or others with low muscle mass in whom serum creatinine concentration does not accurately reflect glomerular filtration rate, a determination that glomerular filtration rate or creatinine clearance exceeds 30 mL/min is recommended.

Aldosterone antagonists should not be administered to patients with baseline serum potassium concentration in excess of 5.0 mEq/L.

An initial dosage of spironolactone 12.5 mg/day or eplerenone 25 mg/day is recommended, after which the dosage may be increased to spironolactone 25 mg or eplerenone 50 mg, if appropriate.

The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors (captopril 75 mg daily or more; enalapril or lisinopril 10 mg daily or more).

Nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors, should be avoided.

Potassium supplements should be discontinued or reduced.

Close monitoring of serum potassium concentration is required; potassium concentration and kidney function should be checked in 3 days and at 1 week after initiation of therapy and at least monthly for the first 3 months.

Diarrhea or other causes of dehydration should be addressed immediately.

ACE = angiotensin-converting enzyme.

Adapted with permission from Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:e1–e90.

decrease in mortality or hospitalization in patients with systolic blood pressure above or below the median.

**Nonpharmacologic Therapy**

Insertion of implantable cardioverter defibrillators (ICDs) is recommended in all patients with a left ventricular EF less than 35% who are symptomatic but expected to live beyond 1 year. More recently, biventricular pacing, also known as cardiac resynchronization therapy, has shown benefit and is indicated in patients with HF who have cardiac dyssynchrony manifested by prolonged QRS duration. Biventricular pacing involves pacing both the left and right ventricles to ensure consistent coordination of ventricular contraction.

## Heart Failure with Preserved Ejection Fraction

The proportion of individuals with HF and preserved EF has increased with time and now represents about 45% of patients with HF. The condition has several definitions in the health care literature, including EF greater than 40%, greater than 45%, and greater than 50%. However, it is most commonly described as EF greater than 40%. Although the survival rate among individuals with systolic dysfunction has improved with time, it remains unchanged in those with preserved EF. In fact, the most recent literature suggests similar 1-year mortality and 1-year hospitalization rates for patients with reduced and preserved EF. This result is not surprising given the scarce amount of literature dedicated to this disease state and the limitations of the studies conducted to date.

Patients with HF and preserved EF present similarly to those with reduced EF whose primary symptom is dyspnea. The neurohormonal cascade is also activated in patients with preserved EF. Although both HTN and ischemia are the primary etiologies of both types of HF, patients with reduced EF more commonly have ischemia as the underlying cause, and those with preserved EF more likely have HTN as the underlying cause.

**Therapy Goals**

Unlike in systolic dysfunction, no randomized, controlled trials have shown a delay in disease progression or reduction in mortality in patients with diastolic dysfunction. Thus, treatment goals in patients with HF and preserved EF include reducing symptoms, managing associated disease(s), and modifying underlying pathophysiology. Symptom management primarily addresses dyspnea, edema, and exercise intolerance from fluid retention. Diuretics are the mainstay of therapy for treating pulmonary and peripheral congestion. In addition to treating and preventing HTN and ischemia, comorbidities should be addressed (e.g., DM, atrial fibrillation, chronic kidney disease [CKD]).

Several therapies targeting the underlying neurohormonal activation associated with HF have been investigated. These include (1) using ACE inhibitors and ARBs to block angiotensin II; (2) using β-blockers to block norepinephrine; (3) using β-blockers, nondihydropyridine calcium channel blockers, and digoxin to slow the heart rate and improve diastolic filling time; and (4) using ARAs to prevent and reverse collagen deposition and fibrosis. Unfortunately, none of the studies in this subpopulation have produced meaningful results. Therefore, guidelines are all based on level C evidence, and all but diuretics receive a class IIb recommendation. The following discussion briefly summarizes the most robust data in this area.

**Pharmacologic Therapy**

Several trials have evaluated the impact of ACE inhibitors and ARBs on outcomes in patients with HF and preserved EF. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study evaluated perindopril versus placebo in patients with diastolic dysfunction defined as EF of about 40%. In addition, ARBs were compared with placebo in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity-Preserved (CHARM-Preserved) trial and in the Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial. Unfortunately, the primary composite end point was not significantly reduced in any of these trials. However, hospitalization for HF was significantly reduced in the PEP-CHF and CHARM-Preserved trials.

The statistical analysis of the CHARM-Preserved trial is noteworthy. The primary end point was reported to have occurred in 333 patients (22%) in the candesartan group and in 366 patients (24%) in the placebo group ($p=0.118$); however, the investigators also reported this result adjusted for covariates ($p=0.051$). In a prospective trial with sufficient power, randomization should achieve adequate balance between groups such that demographic differences between treatment groups do not require further adjustment in the primary end point. Thus, the covariate-adjusted results should be interpreted with caution.

The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial assessed the role of nebivolol in patients with HF and preserved EF. Although the composite end point of all-cause mortality or cardiovascular hospitalization was reduced, the study design limited the meaningfulness of these results. A trial assessing the effects of carvedilol in this patient population is under way. Another agent that slows heart rate and improves diastolic filling, verapamil, has been

studied in this subpopulation and demonstrated no significant improvement in a combined end point.

The Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure: The Ancillary Digitalis Investigation (DIG) trial assessed the role of digoxin in patients with HF and preserved EF. This small arm of the larger DIG trial found no benefit in primary or secondary end points. A post hoc analysis of the DIG trial compared the effects of digoxin maintained at low serum concentrations (0.5–0.8 ng/mL) with high serum concentrations (greater than 1 ng/mL) and placebo. The primary end point of all-cause mortality was significantly reduced in patients treated with digoxin at low concentrations.

More recently, the potential role of ARAs in preventing or reducing collagen deposition and fibrosis in patients with HF has become of interest. The Trial of Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure is under way, with the primary composite end point of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization. Table 1-2 summarizes the results of trials of patients with HF with preserved EF.

## Concomitant Diseases

As previously discussed, patients selected for clinical trials tend to have fewer comorbid diseases than patients with HF seen in actual clinical practice. These patients have high rates of the following comorbidities: HTN (about 75%); DM (45%); CKD, defined as serum creatinine (SCr) greater than 1.5 mg/dL (37%); and atrial fibrillation (30%). These comorbid diseases serve as precipitating factors for hospitalization and are associated with higher mortality. Prescribing standard HF therapies in the presence of these comorbidities often requires additional consideration of agent selection, dosing, titration, and/or monitoring.

### Hypertension

The lifetime risk of developing HF for patients with blood pressure greater than 160/90 mm Hg is twice that of patients with blood pressure less than 140/90 mm Hg. The American Heart Association has developed guidelines on HTN management in the prevention of coronary artery disease. Although the evidence supporting the recommendation is limited, in patients with reduced left ventricular function a goal blood pressure of less than 120/80 mm Hg is recommended. In addition, the guideline discourages allowing the diastolic blood pressure to fall to less than 60 mm Hg to ensure optimal filling of coronary arteries (especially in patients with coronary artery disease) and to prevent cardiac ischemia resulting in diastolic dysfunction.

For patients with left ventricular dysfunction, standard HF therapies that also reduce blood pressure are recommended. These therapies include ACE inhibitors (or ARBs), β-blockers, ARAs, thiazide or loop diuretics, and the combination of hydralazine and isosorbide dinitrate for African American patients. When considering β-blockers, carvedilol has both β- and α-blocking properties and may afford additional blood pressure control.

### Atrial Fibrillation

Twenty percent of patients develop atrial fibrillation within 4 years of receiving a diagnosis of HF. The

**Table 1-2.** Clinical Trials Conducted in Patients with HF with Preserved EF

| Trial (therapy) | n | Population EF (%) | Outcome/Benefit |
|---|---|---|---|
| PEP-CHF (perindopril) | 852 | ≈ 40 | No change in composite end point<br>Reduced hospitalization for HF |
| CHARM-Preserved (candesartan) | 3023 | > 40 | No change in composite end point<br>Reduced hospitalization for HF |
| I-PRESERVE (irbesartan) | 4128 | > 45 | No change in composite end point |
| SENIORS trial (nebivolol) | 2128 | > 35[a] | Reduced all-cause mortality or cardiovascular hospitalization |
| DIG trial (digoxin) | 988 | > 45 | No change in primary or secondary end points (post hoc analysis—mortality benefit if serum digoxin concentration 0.5–0.8 ng/mL vs. > 1 ng/mL) |

[a]Interpretation of results was limited by including patients with an EF < 40%

CHARM-Preserved = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity-Preserved; DIG = Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure: The Ancillary Digitalis Investigation; EF = ejection fraction; HF = heart failure; I-PRESERVE = Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure.

prevalence of atrial fibrillation with concomitant HF increases with age and HF severity. Development of atrial fibrillation in HF is associated with increased mortality.

Managing atrial fibrillation in patients with HF is challenging. First, rapid ventricular response to atrial fibrillation results in loss of the atrial contribution to cardiac output, often contributing to fluid retention and leading to HF exacerbations and hospitalizations. Second, drug selection for ventricular rate control is difficult. The nondihydropyridine calcium channel blockers are contraindicated in HF with systolic dysfunction because of potent negative inotropic effects. Verapamil has greater negative inotropic effects than diltiazem. Negative inotropy occurs with aggressive dosing and titration of β-blockers; these agents should be used which caution in patients with HF. Digoxin is unlikely to be effective as a single agent, especially in patients with atrial fibrillation related to high sympathetic tone, which is present in most patients with HF. In addition, many antiarrhythmic agents have negative inotropic effects, and few agents are safe in this population. Serum digoxin concentrations above the goal range for additional rate control should not be recommended because of the risks of toxicity.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial provided important information regarding the treatment strategy of rate control versus rhythm control in patients with atrial fibrillation at high risk of stroke and death. Unfortunately, patients with HF were underrepresented in the AFFIRM trial, with less than 25% having impaired EF and only 25% having a history of HF. The Rhythm Control versus Rate Control in Heart Failure (AF-CHF) trial compared rate control with rhythm control in patients with EF less than 35% and HF symptoms. The primary outcome, time to cardiovascular death, was not significantly different between the two treatment groups. Nor were additional end points significantly different, including all-cause mortality, cardiovascular mortality, arrhythmia, HF, and stroke.

The AFFIRM investigators also emphasized that although the rate of ischemic stroke was low (about 1% per year in both groups), most strokes in both groups occurred in patients who had stopped taking warfarin or whose international normalized ratio was subtherapeutic at the time of the stroke. Therefore, the need for anticoagulation in both treatment strategies should be emphasized. Current performance measures for atrial fibrillation require assessment of thromboembolic risk factors, initiation of chronic anticoagulation therapy, and monthly measurement of international normalized ratio.

The AF-CHF trial showed that either rate control or rhythm control is appropriate in patients with atrial fibrillation and concomitant HF. If patients do not tolerate rate control because of frequent symptoms, including worsening HF, rhythm control should be considered with amiodarone or dofetilide, the only agents that do not adversely affect survival in patients with HF. When these drugs are initiated in patients with HF who have an ICD, the impact on defibrillation threshold may need to be reassessed to ensure adequate firing when a potentially fatal arrhythmia occurs. For dofetilide, drug interactions could prove fatal if the risk of torsades de pointes is further increased. Drugs can interact with dofetilide through two primary mechanisms: inhibition of cytochrome P450 3A4 and competition for kidney excretion. Although amiodarone is not associated with torsades de pointes, it does interact with several drugs commonly prescribed for cardiovascular disease. In addition to empirically reducing the dosage of warfarin (by 25% if amiodarone 100 mg/day is initiated, 30% for 200 mg/day, and 40% for 400 mg/day) and digoxin (by 50%), the dosage of simvastatin and similarly metabolized statins should be reduced to avoid an increased risk of myopathy.

A new antiarrhythmic agent, dronedarone, has recently received U.S. Food and Drug Administration label approval. Several important warnings should be considered regarding dronedarone, including that it is contraindicated in patients with New York Heart Association (NYHA) class IV HF or with NYHA class II–III HF and a recent decompensation requiring either hospitalization or referral to a specialized HF clinic.

More recently, use of radiofrequency ablation in patients refractory to or intolerant of rate or rhythm control has gained in popularity, and ongoing trials continue to assess the impact of ablation compared with antiarrhythmic therapy on long-term outcomes.

**Diabetes Mellitus**

Up to one-half of patients with HF have DM. Diabetes mellitus appears to be a strong and independent predictor of HF incidence and prognosis. For example, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program evaluated the role of candesartan, either as added to conventional therapy including an ACE inhibitor or as an alternative in patients intolerant of ACE inhibitors with low and preserved EF. This trial found a 1.5- to 2-fold higher mortality in patients with DM regardless of EF. This study provides evidence that the presence of DM may portend a poorer prognosis in patients with HF.

Unfortunately, many physicians are reluctant to use standard HF therapies in patients with DM for various reasons. For example, most β-blockers impair insulin sensitivity and potentiate insulin-induced hypoglycemia with delayed recovery of serum glucose concentrations. In addition, these agents may mask some manifestations of hypoglycemia, particularly tachycardia. Worsening hyperlipidemia, specifically hypertriglyceridemia, is an additional concern. Despite these limitations, guidelines emphasize that this

life-saving therapy should not be avoided in patients with HF and concomitant DM because the benefit far outweighs the risk. However, β-blockers should be used cautiously (but not avoided altogether) in patients with DM and recurrent hypoglycemic symptoms. Patients with DM should be counseled to monitor blood glucose control during β-blocker initiation and titration. Patients must be made aware that tachycardia and tremor may no longer be reliable symptoms of hypoglycemia. Close monitoring of cholesterol profiles is also warranted in these patients.

Patients with DM and HF also have an increased risk of hyperkalemia with the use of ACE inhibitors, ARBs, and ARAs. In one case-control study of patients with HF, those with DM had a 2.4-fold higher risk of hyperkalemia. Risk is also increased with CKD secondary to DM. The interplay between DM and CKD is discussed later in this chapter. Despite this risk, the beneficial effects of ACE inhibitors, ARBs, and ARAs far outweigh the increased risk of hyperkalemia in patients with HF. Therefore, rather than avoidance, close monitoring is warranted to ensure safety of these life-saving therapies.

Selecting antidiabetic agents for patients with HF is also complex. A general overview of standard therapies for DM in various HF stages is provided in Table 1-3. Although many practitioners voice concern about lactic acidosis with metformin use in patients with HF, a Cochrane review of lactic acidosis incidence in 206 comparative trials and cohort studies found only 6.3 cases/100,000 patient-years of metformin use compared with 7.8 cases/100,000 patient-years of non-metformin antidiabetic drug use. Lactic acidosis risk could be higher in patients with HF and CKD or hemodynamic stability. Therefore, metformin should definitely be avoided in patients with current or recent acute decompensated HF, CKD, fluctuating kidney function, or HF instability. The argument for using metformin despite the risk of lactic acidosis is based on the overwhelming amount of positive data regarding the benefits of this therapy. The Saskatchewan Health database found that either metformin alone or metformin in addition to a sulfonylurea reduced 1-year mortality compared with sulfonylurea alone. The National Heart Care Project database found that metformin alone or in combination with a thiazolidinedione reduced 1-year mortality and hospitalization for HF compared with a sulfonylurea or insulin.

Thiazolidinediones both increase the risk of developing new-onset HF and exacerbate existing HF. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) randomized individuals with DM and concomitant cardiovascular disease to either pioglitazone or conventional hypoglycemic therapy. The authors found significant increases in the risk of HF requiring hospitalization and in occurrence of HF not requiring hospitalization with thiazolidinediones. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial showed a higher incidence of new-onset HF with thiazolidinediones than with placebo in patients at high risk of developing type 2 DM. Overall, patients using these agents are at risk of developing American College of Cardiology/American Heart Association Stage C or symptomatic HF if they have Stage A and Stage B status (see Table 1-3).

**Chronic Kidney Disease**

Patients with HF often have impaired kidney function because of kidney hypoperfusion related to reduced cardiac output, intrinsic disease, and standard HF therapies. In addition, patients with CKD experience altered responses to standard HF therapies (e.g., impaired response to ACE inhibitors, ARBs, and

**Table 1-3.** Recommendations for Standard DM Therapies in Various HF Stages

| ACC/AHA HF Stage[a] | Standard Diabetes Therapies | Comments |
|---|---|---|
| A and B | First line: metformin | |
| | Second line: insulin and sulfonylurea | Mixed effects on CV risk factors; CV benefit to risk ratio equivalent |
| | Third line: thiazolidinediones | Close monitoring for new-onset HF |
| C and D | First line: insulin and sulfonylurea | |
| | Second line: metformin | Use only if stable HF and adequate and stable kidney function |
| | Contraindicated: thiazolidinediones | |

[a]Stage A = at high risk of HF but without structural heart disease or symptoms of HF (e.g., hypertension, DM, coronary artery disease); Stage B = structural heart disease but without signs or symptoms of HF; Stage C = structural heart disease with prior or current symptoms of HF; Stage D = refractory HF requiring specialized interventions.
ACC = American College of Cardiology; AHA = American Heart Association; CV = cardiovascular, DM = diabetes mellitus; HF = heart failure.

diuretics, increased risk of adverse effects with digoxin). Anemia associated with kidney disease and fistulas created for hemodialysis may worsen HF. Myocardial function may be depressed by uremic toxins or phosphate, thyroid, and parathyroid abnormalities. In general, patients with HF and CKD have poorer prognoses. Most patients with HF tolerate mild to moderate degrees of CKD without difficulty and without the need to adjust standard HF therapies. Once the SCr rises to greater than 3 mg/dL, the efficacy and safety of standard HF therapies are severely limited. Despite this limitation, standard HF therapies should not be denied in patients with severe CKD including patients requiring hemodialysis. Finally, BNP can be elevated in CKD, making BNP interpretation difficult. In such situations, it is imperative to take baseline BNP measurements when the patient's HF status is stable.

**Adjusted Dosing in DM and/or CKD**

Patients with DM often develop CKD. In combination, these two disease states alter the risk of adverse effects associated with, as well as the response to, standard HF therapies. Both disease entities place patients with HF at a higher risk of ACE inhibitor and ARB intolerance. Hyperkalemia occurs with higher incidence in patients with CKD, especially if DM is present. Kidney dysfunction associated with ACE inhibitor and ARB use may occur in 5% to 15% of patients with mild to moderate HF and in 15% to 30% of patients with severe HF. Diuretic dose reduction typically improves the CKD associated with these agents. An inappropriately high diuretic dose increases the risk of CKD and hypotension with ACE inhibitors and ARBs, whereas an inappropriately low diuretic dose may diminish ACE inhibitor and ARB response in patients with fluid overload. In patients with unstable HF, the hypotensive effects of ACE inhibitors and ARBs may attenuate the natriuretic response to diuretics.

An increased risk of hyperkalemia is associated with ARA initiation in patients with HF when DM or CKD is present. Although clinical trials of spironolactone and eplerenone excluded patients with an SCr greater than 2 mg/dL, very few patients with an SCr less than 1.5 mg/dL were enrolled. In addition, the risk of hyperkalemia increases progressively with an SCr greater than 1.6 mg/dL. In one study, patients with an estimated creatinine clearance less than 50 mL/minute had a 2-fold increased risk of hyperkalemia (10% vs. 5%). In those with an estimated clearance greater than 50 mL/minute the risk of hyperkalemia was equivalent to placebo (5% vs. 4%). In elderly patients or in those with low muscle mass, it is recommended that ARAs be initiated only when creatinine clearance is greater than 30 mL/minute. Additional caution is warranted in patients with chronic high-dose diuretic use and in patients with DM who require insulin.

In one dose-ranging trial, hyperkalemia occurred in 13% of patients receiving spironolactone 25 mg/day and in 20% of patients receiving 50 mg/day. Hyperkalemia risk is further increased with concomitant high-dose ACE inhibitor use. Nonsteroidal anti-inflammatory drugs should be avoided to reduce the risk of overt kidney failure and fluid accumulation in HF.

**Chronic Obstructive Pulmonary Disease**

Dyspnea is the key symptom in both HF and chronic obstructive pulmonary disease (COPD). It is often difficult to distinguish the two diseases and quantify the relative contribution of either to disability. In patients with HF and COPD, long-acting inhaled β-agonists should be avoided if possible, and short-acting rescue β-agonist use should be monitored closely. The latter is especially important during upward titration of β-blockers (including β1-selective agents) because β-selectivity may be diminished as target HF dosages are achieved. If the use of short-acting β-agonists is frequent, other COPD therapies (e.g., corticosteroids, anticholinergics) should be titrated to further optimize disease control. When used in diagnosing HF in patients with COPD, either in stable condition or during acute exacerbation, BNP thresholds are elevated compared with the cutoffs usually reported in patients without pulmonary disease. Therefore, as with CKD, it is important to have a baseline BNP concentration when the patient's HF status is stable.

Patients should be assessed for the presence of pulmonary HTN, a common comorbidity in patients with concomitant HF and COPD. Patients should also be assessed for obstructive sleep apnea, which is more common in obese patients. In patients with sleep apnea, initiating continuous positive airway pressure as indicated by sleep studies may further improve myocardial contractility. Nocturnal noninvasive ventilation, the provision of ventilatory assistance by a noninvasive interface mainly during sleep, has assumed an important role in the management of chronic hypoventilatory syndromes. The role of nocturnal noninvasive ventilation in patients with HF continues to be investigated.

The ACE inhibitors can cause a persistent nonproductive cough that can be confused with a respiratory infection. These agents may be discontinued inappropriately in patients with pulmonary causes of cough. Cough should be attributed to the ACE inhibitor only if respiratory disorders have been excluded and the cough disappears after cessation of ACE inhibitor and recurs with rechallenge. Because ACE inhibitor–induced cough is benign, many patients can be encouraged to tolerate it because of the beneficial effects of ACE inhibitors.

β-Blockers can aggravate bronchospastic symptoms in patients with asthma; however, many patients with asymptomatic or mild reactive airway disease

tolerate β-blockers well. Most patients with COPD do not have a bronchospastic component to their illness. Both metoprolol succinate and bisoprolol are agents of choice in patients with airway disease because of their β1-selectivity. As previously discussed, these agents may lose β1-selectivity when titrated to target HF doses. Although current guidelines urge caution regarding β-blocker use in patients with asthma, this life-saving therapy is recommended in patients with HF and COPD. In addition, the guidelines recommend avoiding β-blockers in patients with asthma and active bronchospasm.

## Role of the Pharmacist

### Pharmacist Intervention Trials

The impact of adding a pharmacist to the HF management team has been assessed in several studies. Patients randomly assigned to a team that included a pharmacist were more likely than the usual-care group to reach their target dose of ACE inhibitor. This translated to a lower mortality or rehospitalization rate.

In one study, adding a pharmacist to the team reduced readmission rates by 24% and mortality or readmission rates by 29% over the group lacking pharmacist intervention. Another study showed that pharmacist involvement in the care of patients with HF improved exercise capacity, pulmonary function, health-related quality of life, and self-adjustments. Although this study also indicated a trend toward fewer hospital admissions, the frequency of causality clinic visits increased. In contrast, another study indicated an improvement only in drug adherence, with no difference in clinical outcomes including rehospitalization, mortality, or quality of life. In a protocol-driven clinic, the joint efforts of a pharmacist and nurse resulted in an increase in the number of appropriate HF drugs and an upward titration toward target HF dosages as well as improved HF status and symptoms. In addition, adverse effects were minimized, and alcohol consumption and cigarette smoking were reduced. Two other studies assessed patient perceptions of the community pharmacist's involvement in the management of their HF. These studies indicated that pharmacists were an accessible and useful source of support for drug management. Furthermore, community pharmacist intervention can improve patient response to feedback, education, and goal setting.

As previously discussed, HF is a common complication of HTN. A recent pooled analysis of two randomized, controlled trials assessed the effect of pharmacist intervention on adverse drug events and drug errors in 800 HTN cases, stratified into complicated (defined as having HF or another cardiovascular complication) or uncomplicated groups. The risk of any event was 34% lower in the intervention group, including a lower risk of adverse drug events, preventable adverse drug events, potential adverse drug events, and drug errors. The investigators concluded that additional studies are needed to confirm these results. In another study, 12 randomized, controlled trials (n=2060) assessed the effect of pharmacist care activities on patients with HF. The studies were further categorized into those involving pharmacist-directed care (n=7, pharmacist identified as the key driver of the intervention) versus collaborative care (n=5, pharmacist identified as a member of the multidisciplinary team). Overall, pharmacist care was associated with significant reductions in the all-cause hospitalization and HF hospitalization rates. When the two categories of pharmacist care were compared, collaborative care led to greater reductions than pharmacist-directed care in HF hospitalization rates.

### Disease Management Programs

Heart failure disease management programs fall into three broad categories: HF clinics, care delivered in the home, and telemonitoring of patients who are at home. Studies of HF disease management provide convincing evidence that it is possible to significantly reduce rehospitalization rates and costs and improve functional status and quality of life for patients with HF.

Current guidelines recommend that patients recently hospitalized for HF and other patients at high risk be considered for referral to a comprehensive HF management program. High-risk patients include those with several of the comorbid diseases discussed earlier including CKD, DM, COPD, and several active comorbidities. In addition, patients with severe disease (as defined by low cardiac output, persistent NYHA class III or IV symptoms, and frequent hospitalization for any cause) should be referred to such programs. Finally, patients with psychosocial issues including a history of depression, cognitive impairment, or persistent nonadherence to therapeutic regimens also benefit from a disease management program.

Guidelines provide an overview of components that should be included in an HF management program. Patient counseling should include promotion of self-care such as self-adjustment of diuretic therapy and early recognition of symptoms of fluid overload. Behavioral strategies to increase adherence and close follow-up after hospitalization should be reviewed. Assistance with social and financial concerns is also an essential aspect of HF management programs. Finally, patients should be encouraged to get an influenza vaccination annually and a pneumococcal vaccination every 5 years. Pharmacists can play an important role in addressing these components.

### Reimbursement

Pharmacists play an important role in improving drug use quality by assisting health care teams with meeting nationally endorsed performance measures used by

the Centers for Medicare and Medicaid Services and the Joint Commission. Performance measures for HF include the following: evaluating left ventricular systolic function, prescribing an ACE inhibitor or ARB unless contraindicated, prescribing anticoagulation if atrial fibrillation is present, providing discharge instructions (diet, discharge drugs, follow-up appointment, weight monitoring, and what to do if symptoms worsen), and counseling on smoking cessation.

Pharmacists can assist in improving quality measures including providing the drug expertise pertaining to order set development/maintenance, screening targeted patients, providing concurrent interventions with health care professionals to ensure appropriate prescribing and administration, and appropriately documenting contraindications. In addition, pharmacists can assist with discharge drug counseling and documentation to achieve desired outcomes, analysis and modification of drug use systems to ensure safety, and general disease state management. For example, the pharmacist can assist with ensuring that an ACE inhibitor/ARB and β-blocker are initiated in outpatients with HF. In 2008, the Centers for Medicare and Medicaid Services acknowledged pharmacists' documentation of the rationale for not prescribing these standard HF therapies in individual patients with contraindications.

As previously discussed, a pharmacist can also actively participate in appropriate initiation and monitoring of warfarin in patients with HF atrial fibrillation. The reporting and meeting of core performance measures is increasingly connected with reimbursement. The importance of pharmacist involvement in optimizing drug quality to meet these core measures cannot be overemphasized.

## Monitoring

### Monitoring Response to Therapy

B-type natriuretic peptide is a protein secreted by cardiac ventricles. Although elevated plasma BNP concentrations can occur in pulmonary embolism, acute MI, and ischemia, they also are associated with reduced left ventricular EF and hypertrophy. Two forms of natriuretic peptide can be measured in patients with HF: BNP and N-terminal proBNP. Both types increase with age, more so in women or in those with CKD; therefore, the test is less specific in these populations. Both measurements should be used cautiously in those with morbid obesity because these patients have lower-than-expected concentrations.

The diagnostic value of BNP plasma concentrations in HF is considered a class IIa recommendation in the American Heart Association/American College of Cardiology guidelines. A BNP concentration less than 50 pg/mL has a 96% negative predictive value, whereas an N-terminal proBNP concentration less than 300 pg/mL has a 98% negative predictive value. B-type natriuretic peptide concentrations should not be used alone; all relevant clinical data should be used in the diagnosis of HF.

Continuous plasma BNP concentration monitoring has been suggested for treatment optimization. The Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) trial showed a reduction in the risk of HF-related death or hospitalization in optimally treated patients who were managed to a goal BNP concentration of less than 100 pg/mL. However, the Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) did not show improvement in rates of hospitalization-free survival in elderly patients (75 years or older) who received target drug doses based on BNP concentrations. More data are required to define the role of this therapeutic monitoring strategy, which is not currently recommended in the guidelines.

In a recent trial, patients were randomized to intensive management with BNP concentrations or multidisciplinary care. Intensive management included visits with an HF specialist if the patient was high risk (i.e., BNP greater than 2200 pg/mL). More patients in the intensive management group received triple therapy of ACE inhibitor/ARB, β-blocker, and spironolactone. Intensive management also decreased hospitalizations as well as the combined end point of death or HF hospitalization. This study indicates a prognostic benefit to more intense treatment of patients with a high BNP concentration at discharge. However, the practical and economic limitations of this strategy are considerable.

### Patient Self-Care

Thorough patient and caregiver education is of paramount importance because most HF care is done at home. Patients must have the education and counseling to be active and effective participants in their care. Regarding daily weight monitoring, patients should be instructed to contact their provider if they experience a 1-kg to 1.5-kg (2–3-lb) weight gain within 2–3 days. Select patients may be provided a plan for flexible diuretic dosing based on weight changes. It is also helpful to discuss specific diet recommendations including a low-sodium diet. It is particularly helpful to show patients how to read food labels for sodium content per serving, and to give examples of high- and low-sodium foods. Box 1-2 reviews standard counseling points to review with each patient with HF.

### Parameters for Hospitalization and Discharge

One challenging aspect of the medical management of a patient with HF is recognizing when hospitalization is required. In addition to hospitalizing patients with evidence of decompensated HF, the Heart Failure Society of America guidelines recommend hospitalizing patients who are experiencing dyspnea at rest,

hemodynamically significant arrhythmias (including new-onset atrial fibrillation), and acute coronary syndromes. Hospitalization should be considered early to prevent severe exacerbations. Patients who have experienced weight gain of 5 kg or more (even if they are not experiencing dyspnea) or those with signs or symptoms of pulmonary or systemic congestion (even if they have not gained weight) should undergo careful assessment for hospitalization. Additional situations in which to consider hospitalization include major electrolyte disturbances, repeated ICD firings, pneumonia, pulmonary embolus, stroke, and diabetic ketoacidosis.

Patients recently hospitalized for HF should have a follow-up clinic visit, generally within 7–10 days of discharge. Before discharge, practitioners should ensure the patient has a scale at home for use in daily weight monitoring. Patients with advanced HF or recurrent HF admissions should have a follow-up within 3 days of discharge. This may be accomplished through a telephone call or home health visit.

**Box 1-2.** Counseling Points for Patients with HF

- Indication and common or important adverse events for each drug
- Risk factor modification (smoking, HTN control, DM control)
- Exercise recommendations
- Signs/symptoms of worsening HF and appropriate intervention if signs/symptoms develop
- Fluid and sodium restrictions
- Weigh self and record weight daily, and perform appropriate intervention if weight gain occurs

DM = diabetes mellitus; HF = heart failure; HTN = hypertension.

## Additional Therapeutic Considerations

### Alternative Medicines and Supplements

Complementary and alternative drug therapy is considered by many patients. Pharmacists need to be aware of these agents and the evidence related to them. Both coenzyme Q10 and hawthorn improve left ventricular EF. Supplementation with thiamine in patients with HF receiving diuretics also has been associated with improved EF. L-Arginine may have beneficial effects on kidney function in patients with HF. Levocarnitine, vitamin C, D-ribose, and vitamin E have been evaluated but demonstrate no significant benefit in HF management. Of importance, many of these studies are small and should be considered hypothesis generating in most cases.

One trial randomized about 7000 patients with symptomatic HF to n-3 polyunsaturated fatty acids (PUFAs) 1 g/day or placebo. After a median follow-up of 3.9 years, the composite end point of time to death or cardiovascular hospitalization was reduced in patients receiving PUFAs. The difference in mortality was not significant. The number needed to treat to avoid death or hospitalization was 44. All patients received optimal drug management during the trial. These results imply that PUFAs may be an agent to consider in HF management. Additional studies are needed to assess the benefit of PUFAs in HF.

Patients with HF are susceptible to developing iron deficiency caused by depleted iron stores or defective iron absorption. Symptoms of iron deficiency include fatigue, dyspnea, and exercise intolerance; therefore, repletion in patients with HF may improve functional capacity and quality of life. Symptomatic improvement has been shown in patients who received intravenous iron for 24 weeks. The NYHA functional class improved significantly as well.

### Vasopressin Antagonists

Tolvaptan, an oral, selective, V2-vasopressin receptor antagonist that has shown benefits in correcting low serum sodium concentrations, is indicated for hypervolemic or euvolemic hyponatremia. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial failed to show a significant improvement with tolvaptan treatment compared with placebo in clinical end points such as all-cause mortality or HF rehospitalization.

Of importance, all tolvaptan studies initiated the drug in the hospital setting, where both the diuretic effects and the serum sodium concentration effects could be monitored daily. Although tolvaptan is orally available, it should be initiated in the inpatient setting to avoid excessive fluid loss and rapid shifts in serum sodium concentration, which may lead to osmotic demyelination.

## Conclusion

Recent studies continue to clarify how to best optimize use of standard HF therapies. Although adjunctive therapy also plays an important role in treating select patients, close monitoring and follow-up are required. Nonpharmacologic therapies remain an important component of HF management. Recent literature has provided important information regarding the distinct similarities and differences between HF because of reduced EF and HF with preserved EF. However, clinical trials have shown the limited benefit of several therapies in patients with HF with preserved EF. Therefore, the best method for managing this condition is unclear.

Comorbidities also contribute to complications in patients with HF and often make the optimal use of

standard HF therapies challenging. Given the obstacles to achieving optimal therapies in HF, it is easy to understand how the pharmacist's role in the multidisciplinary management of these patients has become more evident in recent trials. New concepts in monitoring HF, including patient self-monitoring, have also begun to play a greater role in HF management. As new therapeutic options arise, the complexities associated with their use must be considered.

## Annotated Bibliography


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   Angiotensin receptor blockers are effective in the treatment of HF, although they remain second line to ACE inhibitors. The relationship between dose and clinical outcomes was investigated in this trial, which randomized 3846 patients with symptomatic HF, left ventricular EF less than 40%, and intolerance to ACE inhibitors to either losartan 150 mg or 50 mg daily. Intolerance to ACE inhibitors was caused by cough in 86% of cases. During a median follow-up of 4.7 years, the rates of death or HF hospitalization were 43% in the high-dose group and 46% in the low-dose group (p=0.027). This difference was driven mainly by a reduction in the risk of HF hospitalization. Hyperkalemia, hypotension, and kidney dysfunction occurred more often in the high-dose group, although rates of discontinuation were similar and low in both groups. Patients without a history of hypotension showed greater benefit with high-dose losartan. Results of this trial highlight the benefit of incremental inhibition of the renin-angiotensin system and suggest that similar benefit is achievable by dose increase as opposed to adding a drug in a different class. Further studies are required to directly address this question.

2. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart failure events. N Engl J Med 2009;361:1329–38.

   Patients with HF are at increased risk of sudden death. Placement of an ICD reduces the risk of sudden death and improves survival in patients with HF and a left ventricular EF less than 35%. In addition, patients with HF experience worsening symptoms and frequent hospitalizations associated with ventricular dyssynchrony. Cardiac resynchronization therapy with biventricular pacing is effective in synchronizing ventricular contractions and reducing the hospitalization rate in patients with NYHA class III/IV with a left ventricular EF of 35% or less and a QRS of 120 milliseconds or more. The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy randomized 1820 adult patients with either ischemic cardiomyopathy (NYHA class I or II) or nonischemic cardiomyopathy (NYHA class II only) to receive either cardiac resynchronization therapy with an ICD or only an ICD. Patients also had to be in sinus rhythm, have a left ventricular EF of 30% or less, and have a prolonged QRS duration of 130 milliseconds or more. All patients were clinically eligible for ICD therapy. The primary end point of all-cause mortality or nonfatal HF events (whichever came first) was significantly decreased in the combination group with a relative risk reduction of 34% (p<0.001). The benefit did not differ significantly between patients with ischemic or nonischemic cardiomyopathy. The superiority of the combination was driven mainly by the 41% reduction in the risk of HF events. Cardiac resynchronization therapy was also associated with a reduction in left ventricular volume and an increase in left ventricular EF. This trial affected clinical practice in two important ways. First, the trial found (a priori) no difference in benefit between patients with ischemic and nonischemic cardiomyopathy. Previous studies had supported the use of ICDs only in patients with ischemic etiology of HF; therefore, ICD use in patients with nonischemic etiology became a standard of care. Second, this study showed the benefit of cardiac resynchronization therapy in addition to ICD in patients with a QRS of 130 milliseconds or more, which has become a standard of care in such patients.

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   Although many patients with HF have systolic dysfunction, an equal number have HF because of diastolic dysfunction or preserved EF (greater than 40% to 45%). Unlike in systolic dysfunction populations, this population has undergone study in few randomized, controlled trials, and no trial has shown a benefit in morbidity or mortality. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial was a randomized, double-blind, placebo-controlled trial assessing 850 patients older than 70 years (mean age = 76 ± 5 years) with diastolic dysfunction (defined as EF of about 40%) randomized to perindopril (titrated to 4 mg/day) or placebo. The minimal follow-up was 1 year (median follow-up = 2.1 years). Unfortunately, study enrollment and event rates were low, and statistical power for the primary end point was reduced to 35%. In addition, about 27% of patients withdrew from both treatment groups after 1 year to start open-label ACE inhibitor therapy. The primary end point of composite all-cause mortality or unplanned HF hospitalization was not significantly reduced (hazard ratio [HR] = 0.919; p=0.545). At 1 year, the primary end point trended toward benefit (HR = 0.692; p=0.055), and HF hospitalization was significantly reduced (HR = 0.628; p=0.033). In addition, functional class and 6-minute walk distance improved considerably. Because of insufficient power with this study, the long-term effect of ACE inhibitors on outcomes in patients with HF with

preserved EF remains unclear. Nonetheless, the beneficial effects on HF hospitalization, functional class, and 6-minute walk distance are promising.

4. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved ejection fraction: the CHARM-Preserved trial. Lancet 2003;362:777–81.

   The CHARM program consisted of three trials. One, the CHARM-Preserved trial, studied patients with diastolic dysfunction or preserved EF. The CHARM-Preserved trial randomized 3023 patients with EF greater than 40% to candesartan (titrated to 32 mg/day) or placebo. The primary outcome was cardiovascular death or admission to a hospital for HF. Median follow-up was 36.6 months. Although the primary end point was not significantly reduced (HR = 0.89; p=0.118), hospitalization for HF was significantly reduced (p=0.017). More recently, the I-PRESERVE trial enrolled patients with HF and preserved EF (greater than 45%), randomizing them to irbesartan or placebo. The I-PRESERVE trial found no statistical difference in primary or secondary end points. Given the neurohormonal hypothesis for diastolic dysfunction, the lack of important findings was disappointing. Despite these results, ARBs, together with ACE inhibitors, are commonly prescribed to manage uncontrolled HTN in patients with diastolic dysfunction in the hope that benefit beyond blood pressure reduction will be gained.

5. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospitalization admission in elderly patients with heart failure (SENIORS) trial. Eur Heart J 2005;26:215–25.

   Although several large randomized trials showed a mortality benefit with β-blockers in patients with HF, the effects of β-blockers in elderly patients with a broad range of left ventricular EF values were unknown. The SENIORS trial was designed to assess the role of nebivolol (titrated to 10 mg/day) compared with placebo in 2128 elderly patients (older than 70 years) with systolic and diastolic dysfunction. The mean duration of follow-up was 21 months. The mean age of patients enrolled was 76 ± 5 years; 37% were women, and the mean EF was 36% (with 35% having an EF greater than 35%). The primary composite end point of all-cause mortality or cardiovascular hospitalization was significantly reduced (HR = 0.86; p=0.039). A primary limitation of this trial was that it was in a mixed population of patients with both systolic (65%) and diastolic (35%) dysfunction, and β-blockers in systolic dysfunction had already been shown to reduce mortality. In addition, diastolic dysfunction was defined as EF greater than 35%, rather than greater than 40% to 45%, which comprises a small portion of patients with systolic dysfunction. In a prespecified subanalysis, the effect of EF (less than 35% vs. greater than 35%) was assessed, and the effect of nebivolol on the primary end point was similar (HR = 0.86; 95% confidence interval, 0.72–1.04; p=0.720 for subgroup interaction). Although this trial showed efficacy and safety of β-blockers in elderly patients with HF, the limitations of the trial precluded drawing definitive conclusions regarding the role of β-blockers in patients with HF and preserved EF. The ongoing Randomized Trial to Assess the Effects of Beta-Blockers in Diastolic Heart Failure: Japanese Diastolic Heart Failure aims to assess the role of carvedilol in patients with HF and preserved EF (EF greater than 40%) only.

6. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al; Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667–77.

   Before this trial, it was common practice to restore and maintain sinus rhythm in patients with atrial fibrillation and HF primarily to minimize the contribution of atrial fibrillation to the development of HF symptoms and acute decompensation. The AFFIRM trial provided important information regarding the treatment strategy of rate control versus rhythm control in patients with atrial fibrillation at high risk of stroke and death. More than 75% of patients had a normal EF, and about 25% had a history of HF. The AF-CHF trial was a multicenter, randomized trial addressing the role of rate control versus rhythm control in patients with EF less than 35% and symptoms of HF. A total of 1376 patients were enrolled (682 in the rhythm-control group and 694 in the rate-control group) and were observed for a mean of 37 months. The primary outcome, time to cardiovascular death, was not significantly different between the two treatment groups (HR = 1.06; p=0.59). Nor was there a significant difference in additional end points, including all-cause mortality, cardiovascular mortality, arrhythmia, worsening HF, and stroke. Overall, these results suggest that a routine strategy of rhythm control does not reduce the rate of death, stroke, or worsening HF in patients with concomitant HF and atrial fibrillation. Given these findings and the many complexities (e.g., adverse effects, including some that are life threatening; drug interactions; difficult acquisition) associated with antiarrhythmic therapies used to achieve rhythm control, the strategy of rate control is preferred unless atrial fibrillation contributes to HF symptoms or acute decompensation of HF, necessitating rhythm control.

7. Køber L, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H, et al. Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678–87.

   Atrial fibrillation is a significant cause of morbidity and mortality in HF. Class III antiarrhythmic agents are beneficial in maintenance of and/or conversion to normal sinus rhythm in patients with atrial fibrillation. Unfortunately, several of these agents have contraindications or cause significant toxicities. Dronedarone is a multichannel blocker with properties similar to

amiodarone; however, it lacks the iodine moiety thought to contribute to many of the toxicities associated with amiodarone. Dronedarone decreases recurrent atrial fibrillation after cardioversion by 25% (vs. placebo). In the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) trial, 627 patients hospitalized with new or worsening HF with NYHA class III or IV symptoms were randomized to dronedarone 400 mg two times/day or placebo for a median follow-up of 2 months. The trial was terminated early for safety reasons. The primary end point of all-cause mortality or hospitalization for worsening HF was not significantly different; however, all-cause mortality was higher in the dronedarone group (8% vs. 3.7%, p=0.03). These findings raised concern that dronedarone contributes to worsening HF, although the mechanism of this is unclear. The results of this trial led to a black box warning and contraindication to the use of dronedarone in patients with NYHA class IV HF or with NYHA class II–III HF and a recent decompensation requiring hospitalization or referral to an HF specialist.

8. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668–78.

   No currently available antiarrhythmic agent has reduced the hospitalization rate caused by cardiovascular events in patients with atrial fibrillation. The ATHENA trial randomized 4628 patients to dronedarone 400 mg orally two times/day or placebo. Patients studied met at least one of the following inclusion criteria: age 70 years or older; HTN; DM; previous stroke, transient ischemic attack, or systemic embolism; left atrial diameter 50 mm or more; and left ventricular EF 40% or less. Patients also had to have electrocardiography showing atrial fibrillation or flutter within 6 months of randomization. Because of a lower than expected mortality rate, inclusion criteria were adjusted to allow patients older than 75 years to be eligible, regardless of risk factors. Mean follow-up was 21 months. The primary end point of first hospitalization caused by cardiovascular events or all-cause mortality was significantly decreased in the dronedarone group (31.9% vs. 39.4%; p<0.001). This decrease was primarily attributable to a decrease in hospitalization because there was no difference in all-cause mortality. The treatment discontinuation rate was high in both groups (30%) but was similar to other antiarrhythmic trials. Although this study showed an improvement in clinical outcomes, dronedarone has been criticized for its low rate of converting patients to normal sinus rhythm.

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   Optimization of HF treatment is currently based on physician preference and patient tolerance. B-type natriuretic peptide has a known diagnostic value in HF, but its role in general management is less clear. The STARS-BNP trial randomized 220 patients with NYHA class II–III symptoms and a left ventricular EF less than 45% to either BNP-guided titration of HF therapies or traditional management. Medical therapy was increased with the goal of reducing plasma BNP concentrations to less than 100 pg/mL; drugs were adjusted according to investigator judgment. In both groups, about 40% of the changes were related to diuretic dosage; however, ACE inhibitor and β-blocker use increased in the intervention group. There was also a significant drop in the rate of HF-related deaths or hospitalizations. There was no significant difference in all-cause mortality or all-cause hospitalization. Given the positive findings of this study, larger trials of similar design are under way.

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    Therapy guided by BNP monitoring seems appealing in all patients with HF, but particularly so in older patients who are less physically active and in whom symptoms are considered less reliable. The TIME-CHF trial randomized 499 patients 60 years or older with a history of HF hospitalization within the past year and elevated BNP concentrations (400 pg/mL or more if younger than 75 years, 800 pg/mL or more if 75 years or older) to symptom-guided or intensified BNP-guided management for 18 months. Therapy was titrated on the basis of guidelines to reduce symptoms to NYHA class II or less (symptom-guided therapy) or BNP concentration of 2 times the upper limit of normal or less and symptoms of NYHA class II or less (BNP-guided therapy). The primary outcome, survival at 18 months with no all-cause hospitalization, was no different between groups. Quality of life improved in both groups, but these improvements were similar. The secondary end point of survival free of hospitalization for HF was higher in the BNP-guided therapy group. The subgroup of patients younger than 75 years showed benefit from the BNP-guided therapy, suggesting this approach has benefit in younger patients with HF. However, there was no difference in the reduction of BNP concentrations between the two treatment groups. Unlike the results of the STARS-BNP study, the results of this study suggest that the use of serial BNP monitoring in HF management is of limited value.

11. Chow SL, Dorsch MP, Dunn SP, Jackevicius CA, Page RL 2nd, Trujillo T, et al. Key articles related to complementary and alternative medicine in cardiovascular disease. Part 1. Pharmacotherapy 2010;30:1e–49e.

    Complementary and alternative medicine has become increasingly popular in the United States. Clinicians need to be aware of evidence supporting or disputing the use of these agents. This document cites

key articles for therapy used in cardiovascular disease, including HF, arrhythmia, dyslipidemia, chronic and acute HF, HTN, coronary artery disease, cerebrovascular accidents, and peripheral vascular disease. The variety of therapies addressed include coenzyme Q10, dark chocolate, fish oil (omega-3 fatty acids), folic acid and B vitamins, garlic, gingko biloba, hawthorn, tea (black and green), vitamin D, and vitamin E.

12. GISSI-HF Investigators; Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. Lancet 2008;372:1223–30.

    Sudden cardiac death continues to account for up to one-half of fatal events in HF. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione trial showed a decreased mortality rate, mainly because of prevention of sudden death, in patients taking PUFAs after an MI versus placebo. The GISSI-HF trial randomized 6975 patients to 1 g of PUFA 9850-882 eicosapentaenoic acid and docosahexaenoic acid or placebo. Patients included had NYHA class II–IV HF and could have any left ventricular EF. When left ventricular EF was greater than 40%, the patient was required to have a recent hospitalization (within 1 year) for HF. The two coprimary end points were time to death and time to death or hospitalization for cardiovascular reasons. Patients were monitored for a median of 3.9 years. There was no significant difference in time to death. However, the combined end point was significantly decreased in the PUFA group (absolute risk reduction = 2.3%). This moderate benefit was smaller than expected; however, all patients received optimal drug management. In addition, the benefit was consistent across all predefined subgroups. Of interest, the risk of sudden death was not statistically different between groups, suggesting a broader mechanism of action in patients with HF than in patients with MI. Adequate-sized trials in primary prevention are not yet available.

13. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319–31.

    Oral tolvaptan is indicated for hypervolemic or euvolemic hyponatremia. The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure dose-ranging trial compared once-daily tolvaptan doses of 30 mg, 60 mg, and 90 mg with placebo for up to 60 days. Treatment with tolvaptan significantly increased serum sodium and decreased body weight on the first day of treatment compared with placebo. Although the risk of worsening HF was similar in the tolvaptan and placebo groups, a post hoc analysis showed that tolvaptan reduced the risk of 60-day mortality in patients with CKD or severe systemic congestion. The EVEREST trial randomly assigned 4133 patients with NYHA class III or class IV HF to tolvaptan or placebo in addition to standard drugs if they presented with acute exacerbation of HF within the past 48 hours. Although this trial enrolled patients with acute HF with and without hyponatremia, patients with hyponatremia experienced significant improvements in sodium concentrations as early as the first day of treatment. Diuresis was associated with changes in body weight and significant improvements in symptoms and signs of congestion. The trial failed to show a significant improvement with tolvaptan compared with placebo in global clinical status by day 7 or discharge. In addition, tolvaptan failed to improve 2-year all-cause mortality, cardiovascular mortality, or HF rehospitalization. However, in a subgroup analysis of patients with hyponatremia (serum sodium less than 130 mEq/L) at baseline, treatment with tolvaptan significantly reduced the risk of cardiovascular morbidity and mortality compared with placebo (HR = 0.60; $p<0.05$). A future prospective trial should evaluate tolvaptan treatment of patients with HF and hyponatremia.

14. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436–48.

    Anemia is a strong predictor of survival and hospitalization in patients with HF. Proinflammatory cytokines can lead to decreased iron absorption and decreased release of iron from total body stores. In addition, poor nutrition can lead to iron deficiency. It has been hypothesized that iron supplementation is beneficial in patients with HF regardless of whether they are classified as having anemia. Small trials have shown a benefit of intravenous iron. The Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial randomized 459 patients with symptomatic HF and documented iron deficiency (baseline hemoglobin between 9.5 g/dL and 13.5 g/dL) in a 2:1 ratio to either ferric carboxymaltose or placebo. Ferric carboxymaltose was given in 200-mg doses weekly for 8–12 weeks (depending on iron deficit) and then every 4 weeks for 24 weeks. For the Patient Global Assessment, the primary end point, 50% of the iron-treated patients reported they were much or moderately improved compared with 28% of the placebo group. In addition, NYHA functional class was improved, with 47% of the iron-treated group classified as I or II compared with 30% of the placebo group. Significant improvements were seen in the distance on the 6-minute walk test and in general quality of life. Trial limitations include a high dropout rate and the subjectivity of the primary end points. In addition, it is unclear whether iron replacement must be intravenous or whether oral therapy might provide a similar benefit. Regardless, iron therapy represents a new possible therapeutic option in HF management.

# Self-Assessment Questions

1. A 45-year-old man has New York Heart Association (NYHA) class II nonischemic cardiomyopathy caused by long-standing, uncontrolled hypertension (HTN). The patient was previously given the option of receiving an implantable cardioverter defibrillator (ICD) because of repeated syncopal events; however, he refused placement of this device. His current heart failure (HF) drug regimen includes furosemide 40 mg orally two times/day and lisinopril 5 mg orally once daily. The patient is being referred to the HF specialty clinic with dyspnea on moderate exertion. **Which one of the following drugs, if added to his regimen, would be most likely to reduce all-cause mortality?**
   A. Metoprolol succinate 25 mg orally daily.
   B. Losartan 12.5 mg orally daily.
   C. Spironolactone 12.5 mg orally daily.
   D. Digoxin 0.125 mg orally daily.

2. A 53-year-old African American man with idiopathic dilated cardiomyopathy presents to the clinic with dyspnea on minimal exertion. Physical examination reveals normal neck veins, regular heart rate and rhythm, lungs clear to auscultation, and only trace edema. The patient is currently at his baseline dry weight. His HF drug regimen includes furosemide 80 mg orally two times/day, enalapril 10 mg orally two times/day, and metoprolol extended release 150 mg orally once daily. His vital signs include blood pressure 110/67 mm Hg and heart rate 53 beats/minute. His laboratory values are potassium 5.2 mEq/L, blood urea nitrogen 17 mg/dL, and serum creatinine (SCr) 2.1 mg/dL, which are all stable from his recent clinic visits. **Which one of the following is the best approach to treating this patient's HF?**
   A. Initiate amlodipine 5 mg orally daily, decrease furosemide to 40 mg orally two times/day.
   B. Initiate spironolactone 25 mg orally daily.
   C. Initiate hydralazine 37.5 mg and isosorbide dinitrate 20 mg orally three times/day.
   D. Increase metoprolol extended release to 200 mg orally daily.

3. A 23-year-old woman developed postpartum cardiomyopathy within 6 weeks of giving birth to her first child about 1 year ago. Her medical history includes only type 2 diabetes mellitus (DM) diagnosed before pregnancy with documented poor response to dietary counseling. She was hospitalized 4 days ago with symptoms of shortness of breath at rest, orthopnea, and pitting edema. Her drug regimen consists of furosemide 40 mg orally two times/day, enalapril 5 mg orally two times/day, and glyburide extended release 20 mg orally once daily. She will be discharged from the hospital after aggressive intravenous diuretic administration for fluid overload. Having returned to her dry weight, she is now asymptomatic. The patient's laboratory values on admission included glycosylated hemoglobin 11.2 mg/dL and SCr 1.8 mg/dL. **Which one of the following is the best option to manage this patient's DM?**
   A. Continue glyburide extended release 20 mg/day orally once daily.
   B. Initiate metformin 500 mg orally two times/day.
   C. Initiate rosiglitazone 2 mg/day orally once daily.
   D. Initiate insulin glargine 10 units/day subcutaneously once daily.

4. A 54-year-old man has been hospitalized six times in the past 6 months for acute decompensated HF caused by drug and dietary nonadherence. He was last admitted 1 month ago. His medical history includes NYHA class III cardiomyopathy (left ventricular EF 30%), DM, and stage 3 chronic kidney disease. His prescribed drugs include lisinopril 10 mg orally daily, carvedilol 25 mg orally two times/day, furosemide 40 mg orally two times/day, and insulin glargine 35 units. **Which one of the following counseling points, reviewed with the patient at discharge, would be most likely to minimize the frequency of his hospitalizations?**
   A. Restrict fluids to less than 1 L/day and sodium to less than 1 g/day.
   B. Obtain influenza vaccine 0.5-mL intramuscular injection as soon as possible.
   C. Weigh himself daily and contact the health care team if weight increases.
   D. Recognize deescalating symptoms and titrate downward the angiotensin-converting enzyme (ACE) inhibitor dosage.

**Questions 5–8 pertain to the following case.**
R.F., a 54-year-old African American man with systolic dysfunction, presents with a 2-week history of increased lower extremity edema and shortness of breath that limits his normal daily activities. His weight has increased by 4.5 kg over the past 3 days. His physical examination is notable for blood pressure 148/72 mm Hg, heart rate 88 beats/minute, respiratory rate 24 breaths/minute, rales, and 3+ lower extremity edema. His

laboratory values include sodium 138 mEq/L, potassium 5.4 mEq/L, blood urea nitrogen 35 mg/dL, SCr 0.9 mg/dL, and digoxin 2.1 ng/mL. His medical history is significant for HTN, gout, and chronic obstructive pulmonary disease (COPD). His current drugs include lisinopril 20 mg/day, diltiazem extended release 120 mg two times/day, digoxin 0.25 mg/day, allopurinol 100 mg/day, colchicine 0.6 mg two times/day, and salmeterol/fluticasone 250/50 two puffs two times/day. R.F. began taking naproxen 220 mg three times/day about 7 days ago for pain associated with gout.

5. **Which one of the following drugs pairs is most likely to have contributed to R.F.'s fluid overload?**

   A. Diltiazem and naproxen.
   B. Lisinopril and digoxin.
   C. Salmeterol/fluticasone.
   D. Allopurinol and colchicine.

6. R.F. is counseled on salt and fluid restriction. **Which of the following pharmacologic options would be best to add to manage R.F.'s fluid overload?**

   A. Hydrochlorothiazide 50 mg orally daily.
   B. Furosemide 40 mg orally two times/day.
   C. Metolazone 2.5 mg orally daily.
   D. Spironolactone 25 mg orally daily.

7. **Once optimal fluid status has been achieved, which one of the following would best manage R.F.'s HTN?**

   A. Discontinue diltiazem and initiate amlodipine 5 mg orally daily.
   B. Initiate metoprolol 25 mg orally daily.
   C. Discontinue diltiazem and initiate metoprolol 25 mg orally daily.
   D. Initiate prazosin 2 mg orally daily.

8. **Which one of the following drug changes would best decrease cardiac morbidity for R.F.?**

   A. Increase lisinopril to 40 mg orally daily.
   B. Reduce digoxin to 0.125 mg orally daily.
   C. Initiate spironolactone 25 mg orally daily.
   D. Initiate candesartan 4 mg orally daily.

**Questions 9–11 pertain to the following case.**
G.G., a 71-year-old woman with a history of ischemic cardiomyopathy, presents to the clinic with symptoms consistent with NYHA class IV HF. Her medical history includes hyperlipidemia, DM, myocardial infarction (MI), and hypothyroidism. G.G. has shortness of breath at rest, two-pillow orthopnea, and occasional paroxysmal nocturnal dyspnea. Her physical examination is positive for 1+ pitting edema in her ankles and minimal jugular venous distention. Her vital signs include blood pressure 105/70 mm Hg and heart rate 91 beats/minute. Laboratory results include potassium 3.6 mEq/L, blood urea nitrogen 39 mg/dL, and SCr 1.4 mg/dL. G.G.'s current drugs are levothyroxine 0.05 mg/day, furosemide 40 mg two times/day, lisinopril 20 mg/day, potassium chloride 20 mEq/day, atorvastatin 40 mg/day, aspirin 81 mg/day, insulin glargine 46 units at bedtime, and insulin aspart 6 units before meals.

9. **Which one of the following would best manage G.G.'s hypokalemia?**

   A. Continue furosemide 40 mg orally two times/day and potassium chloride 20 mEq/day.
   B. Increase furosemide to 80 mg orally two times/day, continue potassium chloride 20 mEq/day.
   C. Continue furosemide 40 mg orally two times/day, initiate spironolactone 25 mg orally daily.
   D. Increase furosemide to 80 mg orally two times/day, initiate spironolactone 25 mg orally daily.

10. **Which one of the following is the most useful self-monitoring parameter for G.G. to use in early identification of fluid accumulation?**

    A. Number of pillows used at night.
    B. Shortness of breath.
    C. Weight change.
    D. Abdominal girth with tape measure.

11. G.G. is interested in complementary drug options because she prefers natural products to drugs. **In addition to her standard HF therapy, which of the following complementary drug therapies is the best treatment option for G.G.?**

    A. Garlic.
    B. Omega-3 fatty acids.
    C. Coenzyme Q10.
    D. Vitamin E.

12. A 45-year-old man with a history of uncontrolled HTN and DM is hospitalized for an acute MI. During his hospital stay, echocardiography shows a left ventricular ejection fraction (EF) of 25%; however, he has no HF signs and symptoms, and physical examination reveals no edema. Both an ACE inhibitor and a β-blocker were initiated before discharge. **Which one of the following would best provide additional mortality benefit for this patient?**

    A. Candesartan 8 mg orally once daily.
    B. Furosemide 20 mg orally two times/day.
    C. Digoxin 0.125 mg orally two times/day.
    D. Spironolactone 25 mg orally once daily.

13. A 54-year-old African American man recently received a diagnosis of nonischemic cardiomyopathy. His medical history is notable for COPD and HTN. Current drugs include salmeterol one inhalation two times/day, fluticasone 88 mcg inhaled two times/day, furosemide 80 mg two times/day, enalapril 20 mg two times/day, and spironolactone 25 mg/day. Today, he presents with fatigue, shortness of breath on exertion and low-grade fever. On physical examination, the patient has no rales, wheezes, or crackles, and he denies productive cough, chest pain, or palpitations. His general chemistry panel and complete blood cell count are within normal limits. **Which one of the following would be most helpful in determining the etiology of this patient's symptoms?**

    A. Electrocardiography.
    B. Chest radiograph.
    C. B-type natriuretic peptide (BNP).
    D. Troponin.

**Questions 14 and 15 pertain to the following case.**
R.P. is a 43-year-old white woman with a history of nonischemic cardiomyopathy and hypothyroidism presents with palpitations, shortness of breath, and fatigue. Her physical examination is notable for blood pressure 138/72 mm Hg, heart rate 98 beats/minute, respiratory rate 22 breaths/minute, irregular heart rate and rhythm, and trace lower extremity edema. Echocardiography shows left ventricular EF 25% to 30%, dilated left atrium, dilated left ventricle, and mild mitral regurgitation. R.P.'s laboratory values include sodium 140 mEq/L, potassium 3.9 mEq/L, blood urea nitrogen 56 mg/dL, SCr 1.1 mg/dL, thyroid-stimulating hormone 1.4 mIU/mL (normal range 0.34–5.66 mIU/mL), and normal hepatic enzyme concentrations. Her electrocardiography shows atrial fibrillation. Her drugs include lisinopril 10 mg orally daily, levothyroxine 150 mcg orally daily, and metoprolol extended release 50 mg orally daily.

14. **Which one of the following is the most appropriate strategy for initial management of R.P.'s atrial fibrillation?**

    A. Initiate diltiazem continuous release 120 mg orally daily.
    B. Increase metoprolol extended release to 100 mg orally daily.
    C. Initiate dronedarone 400 mg orally two times/day before meals.
    D. Initiate dofetilide 500 mcg orally every 12 hours.

15. R.P.'s symptoms initially improve; however, she returns to the clinic 3 months later with symptomatic atrial fibrillation that is limiting her daily activities. Her physical examination is notable for blood pressure 105/68 mm Hg, heart rate 60 beats/minute (rest) and 90 beats/minute (exercise), and respiratory rate 22 breaths/minute. Pertinent laboratory values include sodium 139 mEq/L, potassium 3.9 mEq/L, blood urea nitrogen 48 mg/dL, SCr 0.9 mg/dL, thyroid-stimulating hormone 1.79 mIU/mL, and normal hepatic enzymes. Electrocardiography shows atrial fibrillation. Her current drugs are lisinopril 20 mg orally daily, carvedilol 12.5 mg orally two times/day, and warfarin 5 mg orally daily. **Which one of the following additions to her regimen would best manage R.P.'s atrial fibrillation?**

    A. Sotalol 80 mg orally every 12 hours.
    B. Dronedarone 400 mg orally two times/day before meals.
    C. Dofetilide 500 mcg orally every 12 hours.
    D. Digoxin 0.125 mcg orally daily.

16. A 45-year-old man presents with hypertensive cardiomyopathy, classified as NYHA class I/II. His drugs include enalapril 20 mg and carvedilol 50 mg, both orally every 12 hours. He started carvedilol 3 months ago, and his left ventricular EF increased from 42% to about 55%. His physical examination is notable for blood pressure 157/85 mm Hg and heart rate 80 beats/minute. His laboratory values are potassium 5.1 mEq/L and SCr 0.9 mg/dL. **Which one of the following would optimize this patient's therapy?**

    A. Discontinue carvedilol 50 mg orally two times/day.
    B. Add losartan 25 mg orally daily.
    C. Add amlodipine 5 mg orally daily.
    D. Add verapamil sustained release 120 mg orally daily.

**Questions 17–19 pertain to the following case.**
M.M., a 26-year-old man with idiopathic cardiomyopathy (NYHA class III/IV), is now ready for discharge after hospitalization for HF exacerbation secondary to fluid overload. He has been hospitalized six times in the past year for HF exacerbations. His drugs at discharge include furosemide 80 mg orally two times/day, potassium chloride 40 mEq orally daily, ramipril 5 mg orally daily, and metoprolol extended release 100 mg orally daily. M.M.'s laboratory values include potassium 4.5 mEq/L and creatinine 1.4 mg/dL, which are both at his baseline. His BNP concentration at discharge is 3220 pg/mL.

17. **Which of the following would be most effective in reducing M.M.'s risk of rehospitalization?**

A. A follow-up with a primary care physician within 2 months of discharge.
B. Measurement of serial BNP concentrations.
C. Referral to an HF specialist within 2 months of discharge.
D. Referral to a dietitian for dietary counseling.

18. About 1 month after discharge, M.M. states that he feels well. His physical examination shows euvolemia, and his laboratory values remain stable. His ramipril dosage has been increased to 5 mg orally two times/day. Vital signs today include blood pressure 120/80 mm Hg and heart rate 90 beats/minute. **Which one of the following is the best choice to optimize M.M.'s therapy?**

A. Initiate spironolactone 12.5 mg orally daily.
B. Increase ramipril to 10 mg orally two times/day.
C. Initiate eplerenone 25 mg orally daily.
D. Increase metoprolol extended release to 150 mg orally daily.

19. Six months later, M.M. presents to the clinic with general fatigue and weakness. Physical examination shows blood pressure 106/70 mm Hg, heart rate 62 beats/minute, no rales or jugular venous distention, and trace lower extremity edema. Drugs include ramipril 5 mg orally two times/day, furosemide 80 mg orally two times/day, metoprolol extended release 200 mg orally daily, and spironolactone 12.5 mg orally daily. **Which one of the following is the most reasonable next step for M.M.?**

A. Check iron studies.
B. Check a BNP concentration.
C. Empirically increase furosemide to 120 mg orally two times/day.
D. Empirically treat with intravenous iron.

20. A 66-year-old man presents with HF with preserved EF (EF = 55%). His history and physical examination are negative for signs and symptoms of fluid overload. Current cardiovascular drugs include bumetanide 4 mg orally two times/day, potassium chloride 40 mEq orally two times/day, digoxin 0.125 mg orally daily, ramipril 5 mg orally daily, and metoprolol controlled release 200 mg orally daily. **Which one of the following drugs in this patient's regimen is most likely to reduce his chance of hospitalization?**

A. Ramipril.
B. Metoprolol.
C. Digoxin.
D. Bumetanide.

21. As the clinical pharmacist providing care for patients on an inpatient HF service, you are asked by the medical director to assist with meeting core performance measures for HF. **Which one of the following components of an HF management program would have the greatest impact on meeting core performance measures?**

A. Use of standardized HF service notes in the medical chart to document contraindications to β-blockers.
B. Counseling HF service patients on signs and symptoms of bleeding while taking warfarin.
C. Use of standing orders that include echocardiography for every patient.
D. Counseling HF service patients on the importance of abstaining from illegal substances.