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EDUCATIONAL OBJECTIVES

GOAL: To discuss the natural history, current guideline recommended drug treatment, pertinent monitoring, and pharmacy team role in modern heart failure.

After participating in this activity, pharmacists will be able to:

- Discuss heart failure's complexity and its poor outcomes (rehospitalization, premature death) and the underlying reasons
- Identify recent changes to national evidence-based guidelines with an emphasis on medication and monitoring
- Outline the pharmacist's role in identifying patients who are undertreated, and develop ways to engage the interdisciplinary team effectively
- Discuss patient counseling tips for improving adherence to heart failure medication therapy and lifestyle changes

After participating in this activity, pharmacy technicians will be able to:

- Recall the basics of heart failure
- Discuss the importance of medication adherence for heart failure treatment
- Identify medications used in evidence-based guidelines
- Describe when to refer HF patients to the pharmacist for recommendations and counseling

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Heart failure: Pumping up knowledge, circulating new approaches

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Abstract Heart failure is a syndrome occurring with increasing frequency that is associated with higher rates of death and hospitalizations. Guidelines are available to help drive management of heart failure with reduced ejection fraction (HFrEF). The cornerstones of evidence-based therapy include angiotensin-converting enzyme inhibitors (ACEI), beta blockers, and mineralocorticoid receptor antagonists. Recent updates to guidelines now recommend angiotensin receptor–neprilysin inhibitors in lieu of ACEI. Angiotensin receptor blockers can be used in patients who do not tolerate ACEI, and the combination of hydralazine plus isosorbide dinitrate should be given to self-identified black patients. Ivabradine can be used in patients on ACEI and beta blockers who have a resting heart rate above 70 bpm. Digoxin can be added to standard therapy to further lower hospitalization rates. Given all of these pharmacologic choices, the pharmacy team (pharmacists and technicians) play a huge role in the multidisciplinary management of heart failure patients. This includes inpatient, clinic, transitions-of-care, and community settings, and involves such activities as medication reconciliation, disease state, medication, dietary education, and direct patient care management.

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Introduction

Heart failure (HF) is defined as a clinical syndrome of reduced cardiac function, resulting in lower cardiac output and signs/symptoms of fluid overload. It is classified according to the left ventricular ejection fraction (LVEF) as either HF with preserved ejection fraction (HFpEF; LVEF ≥50%) or reduced ejection fraction (HFrEF; LVEF <40%).[1] These designations have previously been referred to

IMAGE: SHUTTERSTOCK / GEMPHOTO

as "diastolic" and "systolic" HF, respectively. Patients with LVEF between 40% and 49% are generally considered as HFpEF, but may be subclassified as borderline/intermediate or recovered (those previously with HFrEF whose LVEF has improved).[2]

According to a 2017 update by the American Heart Association providing the latest statistics on heart disease and stroke, approximately 6.5 million adults in the United States have HF, a number that is expected to exceed 8 million by the year 2030.[3] Prevalence increases with age, with a greater rate of growth in women than in men, and the prevalence of HFrEF and HFpEF are similar, each representing approximately 50% of patients with HF.[4,5]

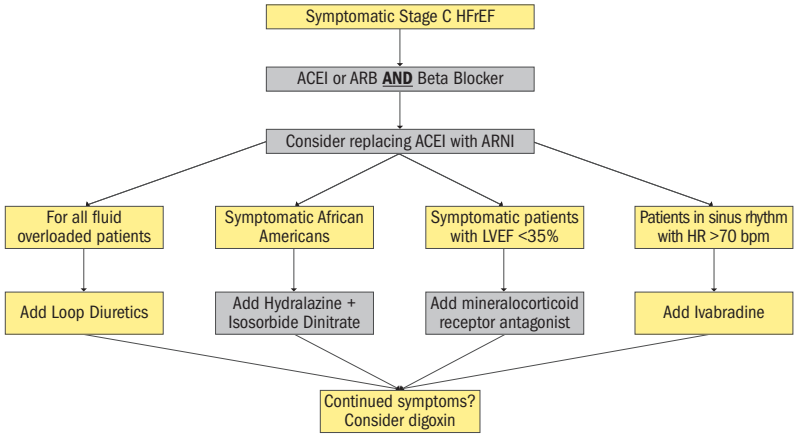
Etiology of HF is diverse, including both cardiovascular and noncardiovascular causes. These can include, but are not limited to, ischemic heart disease (eg, myocardial infarction [MI]), long-standing uncontrolled hypertension, valvular heart disease, arrhythmias, substance abuse (eg, cocaine, alcohol), and medications (oncologic therapies, immunomodulators, antiarrhythmics, nonsteroidal anti-inflammatory drugs).[6] Other known risk factors for developing HF include diabetes, chronic kidney disease, obesity, anemia, and low socioeconomic status.[7–11]

The rate of mortality remains high, with nearly half of patients dying within 5 years of initial diagnosis.[12] These rates, however, have improved with modern pharmacotherapeutic and device therapies.[13] The majority of these deaths are due to either cardiovascular causes or worsening HF.[14,15] Hospitalizations remain a challenge in HF patients, with 1 in 4 Medicare recipients readmitted for HF within 30 days of a hospitalization and nearly 50% readmitted within 6 months.[16] Data from the Olmsted County study show that hospitalizations for HF are common (1.3 per person-year, on average), with 63% of these due to noncardiovascular causes.[17] Interestingly, the overall hospitalization rate did not differ between the years 2000 and 2010 and was similar between EF categorizations. Rates of hospitalization peak in the immediate timeframe following discharge, plateau, and then increase again toward end of life.[18] This suggests there could be an opportunity for pharmacy team members to impact this financially burdensome complication of HF at the time of and shortly following hospital discharge. Commonly reported precipitating factors related to HF admission include cardiac ischemia, arrhythmias, uncontrolled hypertension, as well as dietary and medication nonadherence.[19]

FIGURE

Treatment algorithm for patients with symptomatic stage C heart failure with reduced ejection fraction

(shaded boxes indicate therapies shown to reduce mortality).



Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; ARB, angiotensin II receptor blocker; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LVEF, left ventricular ejection fraction. Reproduced courtesy of William L. Baker, PharmD.

Source: Ref 1,2

Current heart failure guidelines and treatment recommendations

Guidelines for the management of HF were last fully updated by the American College of Cardiology Foundation/American Heart Association in 2013, with a targeted update published in conjunction with the Heart Failure Society of America (HFSA) in 2016.[2,20] A complete guideline was also published in 2016 by the European Society of Cardiology (ESC).[1] Heart failure includes the following stages: stage A, individuals at high risk for developing HF but without existing structural heart disease or HF symptoms; stage B, patients with structural heart disease (eg, prior MI, left ventricular [LV] systolic dysfunction, or asymptomatic vascular disease) but without current or prior symptoms; stage C, individuals with structural heart disease and either current or prior symptoms; and stage D, patients with refractory HF requiring specialized interventions. Patients with HF are also classified based on their functional capacity (New York Heart Association [NYHA] functional classification). There are 4 NYHA functional classifications: class I patients are asymptomatic with no limitations in physical activity; class II patients have slight limitations in activity level, developing symptoms of HF with ordinary physical activity; class III patients are markedly limited in activity level, developing symptoms with less than ordinary activity (eg, activities of daily living [ADLs]); and class IV patients are unable to perform physical activity without symptoms or have symptoms at rest.

The backbone of HFrEF pharmacotherapy is the combination of an angiotensin-converting enzyme inhibitor (ACEI) and a beta blocker, unless contraindicated (see Figure and Table).[1,2] All patients with stage B HFrEF should be treated with an ACEI and a beta blocker to prevent the

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TABLE **Drugs and Doses for Treating Stage C Heart Failure with Reduced Ejection Fraction**

DRUG	INITIAL DAILY DOSE	MAXIMUM DOSE	MEAN DOSE ACHIEVED IN TRIALS	MONITORING/ADVERSE EFFECTS
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS				
Captopril	6.25 mg 3 times daily	50 mg 3 times daily	112.7 mg daily	BP; electrolytes (potassium, BUN, SCr) at baseline, at 2 weeks, and after dose titration Adverse effects: cough, angioedema, first-dose hypotension, increased SCr
Enalapril	2.5 mg twice daily	10–20 mg twice daily	16.6 mg daily	
Fosinopril	5–10 mg once daily	40 mg once daily	N/A	
Lisinopril	2.5–5 mg once daily	20–40 mg once daily	32.5–35.0 mg daily	
Perindopril	2 mg once daily	8–16 mg once daily	N/A	
Quinapril	5 mg twice daily	20 mg twice daily	N/A	
Ramipril	1.25–2.5 mg once daily	10 mg once daily	N/A	
Trandolapril	1 mg once daily	4 mg once daily	N/A	
ANGIOTENSIN RECEPTOR BLOCKERS				
Candesartan	4–8 mg once daily	32 mg once daily	24 mg daily	BP; electrolytes (potassium, BUN, SCr) at baseline, at 2 weeks, and after dose titration Adverse effects: first-dose hypotension, increased SCr
Losartan	25–50 mg once daily	50–150 mg once daily	129 mg daily	
Valsartan	20–40 mg twice daily	160 mg twice daily	254 mg daily	
BETA BLOCKERS				
Bisoprolol	1.25 mg once daily	10 mg once daily	8.6 mg daily	BP; heart rate; ECG Adverse effects: worsening HF symptoms, dizziness, depression, sexual dysfunction
Carvedilol	3.125 mg twice daily	25–50 mg twice daily	37 mg daily	
Metoprolol succinate	12.5–25 mg once daily	200 mg once daily	159 mg daily	
MINERALOCORTICOID RECEPTOR ANTAGONISTS				
Eplerenone	25 mg once daily	50 mg once daily	42.6 mg daily	BP; electrolytes (potassium) at baseline, at 2–3 days, and within 1 week of initiation and dose titration Adverse effects (for spironolactone): gynecomastia or breast tenderness, menstrual changes, hirsutism
Spironolactone	12.5–25 mg once daily	25 mg once or twice daily	26 mg daily	
ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITOR				
Sacubitril/ valsartan	100 mg (49/51 mg) twice daily	200 mg (97/103 mg) twice daily	375 mg (combined) daily	BP; electrolytes (potassium, BUN, SCr) at baseline, at 2 weeks, and after dose titration Adverse effects: hypotension, angioedema, hyperkalemia
HYDRALAZINE PLUS ISOSORBIDE DINITRATE				
Fixed-dose combination	37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily	BP; heart rate Adverse effects: headache, hypotension, tachycardia, systemic lupus erythematosus (for hydralazine)
Hydralazine, isosorbide dinitrate	Hydralazine: 25–50 mg 3–4 times daily Isosorbide dinitrate: 20–30 mg 3–4 times daily	Hydralazine: 300 mg daily in divided doses Isosorbide dinitrate: 120 mg daily in divided doses	N/A	
Ivabradine	5 mg twice daily	7.5 mg twice daily	N/A	HR; ECG Adverse effects: bradycardia, atrial fibrillation, visual disturbances

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; ECG, electrocardiogram; HF, heart failure; HR, heart rate; N/A, not available; SCr, serum creatinine. *Source: Ref 1,2*

development of symptomatic HF (eg, stage C HFrEF). This includes patients with and without a history of acute coronary syndrome or MI. For stage B HFrEF patients who are unable to tolerate an ACEI, an angiotensin II receptor blocker (ARB) should be considered instead, unless contraindicated.

For symptomatic patients with stage C HFrEF, additional evidence-based therapies should be considered. In the absence of severe renal impairment (eg, estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or hyperkalemia (potassium level <5.0 mEq/L), a mineralocorticoid receptor antagonist (MRA) should be added to the combination of an ACEI or ARB and beta blocker for all patients with NYHA class II through IV symptoms to reduce morbidity and mortality. The recently approved angiotensin receptor–neprilysin inhibitor (ARNI) is recommended in place of an ACEI, in conjunction with evidence-based beta blockers and MRAs, to further lower mortality in patients with HFrEF and NYHA class II or III symptoms. The combination of hydralazine and isosorbide dinitrate is recommended in self-identified black patients with NYHA class III or IV symptoms despite treatment with an ACEI, beta blocker, and MRA. Use of ivabradine is recommended for symptomatic patients (NYHA class II or III) in sinus rhythm who have a resting heart rate 70 bpm or higher despite receiving a beta blocker. Digoxin can be added to ACEI (or ARB), beta blocker, and MRA therapy to further prevent hospitalizations in symptomatic patients in sinus rhythm. Lastly, diuretics can be used to improve symptoms and exercise capacity associated with volume overload regardless of the underlying therapies being used. Additional details on each drug class are provided here.

ACE inhibitors are the cornerstone of HF therapy and have been shown to reduce mortality and morbidity in patients with HFrEF.[21] These benefits appear to be a class effect and may be the result of reductions in progression of LV remodeling.[22] These should be initiated at a low dose and titrated up, with the target being those doses used in clinical trials. This is particularly important with ACEIs, as studies have shown improved outcomes (although no all-cause mortality benefit) when higher doses were achieved.[23] They should be used with caution in patients with low blood pressure (systolic blood pressure <80 mm Hg), elevated potassium levels (>5.0 mEq/L), bilateral renal artery stenosis, or marked increases in serum creatinine levels (3 mg/dL). Kidney function and serum potassium levels should be monitored within 1 to 2 weeks of drug initiation or dose increase. Potential adverse events with ACEIs could include renal impairment, low blood pressure, high potassium, and dry cough.

PAUSE AND PONDER

If so many drug therapies have been shown to improve outcomes in heart failure, why are frequent hospitalizations still a major problem?

Beta blockers reduce mortality and morbidity in symptomatic HFrEF when added to ACEIs.[24] Unlike with ACEIs, 1 of 3 specific beta blockers (bisoprolol, carvedilol, metoprolol) should be used, because these are the only agents shown to afford beneficial effects. Suppression of the sympathetic nervous system in heart failure patients not only results in a pronounced halt (and regression) of LV remodeling but also lowers heart rate and prevents sudden cardiac death.[25] Beta blockers should be started at low doses in individuals who are clinically stable and devoid of volume overload, and slowly titrated up at 2-week intervals. Doses shown to improve outcomes in clinical trials should be targeted. This slow approach to dose titration can increase the likelihood of a patient achieving their target dose. Although patients can start on both ACEIs and beta blockers at the time of HF diagnosis, the former does not need to be at target dose before the latter is instituted. Adverse events from use of beta blockers include fluid retention and worsening of HF, fatigue, low blood pressure, and low heart rate or heart block. The risk of low blood pressure can be mitigated by separating the timing of the administered beta blocker and ACEI doses.

The MRAs spironolactone and eplerenone have been shown to reduce mortality and HF hospitalization across the disease spectrum when added to ACEIs and beta blockers.[26–28] Aldosterone levels are elevated in HF, leading to endothelial dysfunction, hypertrophy and myocardial fibrosis, sympathetic activation, and sodium and water retention. These physiologic effects are attenuated with MRA use.[29] When MRAs are started in patients on ACEIs and beta blockers, however, serum potassium levels need to be closely monitored because of their propensity to cause hyperkalemia (potassium >5.0 mEq/L). Potassium levels should be checked at day 3, day 7, and at least monthly for the first 3 months after initiation of an MRA. Renal function must also be watched because MRAs are eliminated through the kidney. MRAs should be avoided in patients with serum creatinine above 2.5 mg/dL or eGFR below 30 mL/min/1.73 m^2. Recent evidence shows that patients who have been initiated on an MRA in the outpatient setting have appropriate laboratory follow-up in only 3% of cases versus 25% when they are initiated as an inpatient.[30] This represents an opportunity for pharmacists to improve the safety of these agents by ensuring proper follow-up and monitoring. Factors associated with increased risk of hyperkalemia with MRAs include poor renal function, history of diabetes, concomitant use of ACEIs or ARBs, and higher age.[31] Other adverse events of spironolactone include gynecomastia or breast pain (incidence ~10%) due to its nonselective steroidal blocking proper-

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ties. Because eplerenone is more selective then spironolactone for the aldosterone receptor, however, it does not cause gynecomastia.

ARBs have been shown to lower mortality and HF hospitalization rates in patients who cannot tolerate ACEIs for reasons other than hyperkalemia or renal insufficiency.[32,33] Although the combination of an ARB plus an ACEI improves outcomes versus ACEI alone, the risk of adverse events is increased and should be reserved for those unable to take an MRA.[34] The choice of specific ARB to use in a patient is less restrictive than the beta blockers, but should include one of the agents evaluated in clinical trials (candesartan, losartan, valsartan). Recommendations for initiation and monitoring of ARBs are similar to the ACEIs as are the adverse events, with the exception of the chronic cough due to lack of pharmacologic effect on bradykinin production.

The newest class of agents to show mortality reduction in HFrEF are the ARNIs, as represented by sacubitril/valsartan, which is recommended in patients who tolerate ACEIs or ARBs.[35] Neprilysin is an endopeptidase responsible for the degradation of vasodilatory substances such as bradykinin and natriuretic peptides. By inhibiting neprilysin, sacubitril maximizes the benefits of these substances and, when combined with the ARB valsartan, minimizes the risk of developing angioedema (due to bradykinin accumulation).[36] The ARNIs should be used in patients who have tolerated an ACEI or ARB, have symptomatic HFrEF, elevated plasma neuroendopeptidase levels (brain natriuretic peptide [BNP] ≥150 pg/mL or N-terminal pro b-type natriuretic peptide [NT-proBNP] ≥600 pg/mL), adequate renal function (eGFR ≥30 mL/min/1.73 m^2), and remain symptomatic despite treatment with an ACEI, beta blocker, and MRA. Adverse events of hypotension occurred more with ARNI, while renal impairment, hyperkalemia, and cough occurred more with enalapril. Angioedema, which was infrequent overall (0.3% of study population), occurred in more patients treated with ARNI than enalapril, but the difference was not statistically significant. Thus, blood pressure, kidney function, and potassium require monitoring, and patients should be counseled about the signs and symptoms of angioedema.

If the decision is made to switch from an ACEI to an ARNI, at least 36 hours are needed after ACEI withdrawal before the ARNI is started (to minimize angioedema risk). The dose of 100 mg twice daily (sacubitril 49 mg/valsartan 51 mg) should be given for 1 to 2 weeks, then increased to 200 mg (sacubitril 97 mg/valsartan 103 mg) twice daily if tolerated. For ACEI or ARB-naïve patients, those previously on low doses of ACEI or ARB, or patients with significant renal (eGFR <30 mL/min/m^2) or hepatic impairment, a lower starting dose (50 mg; sacubitril 24 mg/valsartan 26 mg) of ARNI is recommended, but the goal dose (200 mg twice daily) remains the same. Even if the higher dose of ARNI cannot be achieved, outcomes are improved versus those with lower-dose enalapril.[37]

The combination of hydralazine and isosorbide dinitrate has been shown to reduce mortality in self-identified black (African American) patients with HFrEF in addition to ACEI, beta blockers, and MRAs.[38] This combination was earlier shown to be inferior to the ACEI enalapril in a general population, but does improve hemodynamics versus placebo.[39,40] The beneficial effects of this combination on hemodynamics in HF is complex and involves nitroso–redox balance.[41] In African American patients receiving an ACEI/ARB, beta blocker, and MRA, or in non-African American patients who cannot tolerate an ACEI or an ARB, the combination of hydralazine and isosorbide dinitrate can be beneficial. A challenge with this therapy is the need for thrice-daily dosing of 2 separate drugs, or as a single combination product. This significantly increases the pill burden in patients already receiving a high number of medications. Adverse events associated with this combination include headache, dizziness, hypotension, and gastrointestinal complaints. Hydralazine has also been associated with a lupus-like syndrome.

Ivabradine represents another novel mechanism by inhibiting the I_f (funny channel) in the sinoatrial node, slowing nodal firing and lowering heart rate.[42] Elevated heart rate at hospital discharge in heart failure patients has been associated with higher risks of both death and rehospitalization.[43] A clinical trial showed that use of ivabradine in HFrEF patients in sinus rhythm with a resting heart rate lower than 70 bpm, despite receiving maximally tolerated beta blockers, ACEI, and MRA, lowered HF hospitalizations but not all-cause mortality.[44] For most patients, the starting dose of ivabradine is 5 mg twice daily administered with meals. Both symptomatic and asymptomatic bradycardia were more common in patients treated with ivabradine. Thus, heart rate needs to be monitored closely during initiation and dose titration. Further, ivabradine should not be used in individuals with significant sinoatrial or atrioventricular block without a concomitant pacemaker. It is also a CYP3A4 substrate and should not be used with inducers or moderate to strong inhibitors. Some studies also suggest an association between ivabradine use and new-onset atrial fibrillation.[45] Therefore, if atrial fibrillation develops in patients taking ivabradine, the drug should be discontinued. Visual disturbances including the development of phosphenes were also more common in patients treated with ivabradine.

Digoxin has been used for hundreds of years to treat cardiovascular ailments. Specific to HF, digoxin improves symptoms, quality of life, and prevents hospitalizations. No mortality benefits, however, have been seen in placebo-controlled trials.[46–48] It is most beneficial in patients in sinus rhythm with symptomatic HFrEF to reduce hospitalizations. Although using digoxin in patients with concomitant HF and atrial fibrillation may be beneficial to slow rapid ventricular rates, observational studies have suggested higher mortality and hospitalization rates in this population.[49] Serum concentrations of digoxin should be kept between 0.5 ng/mL and 0.9 ng/mL, because this range

as a goal level has shown lower mortality rates, with values above 1.2 ng/mL showing higher mortality.[50] This is especially important for pharmacists to closely monitor and intervene to optimize dosing to achieve desired serum concentrations, given that many labs still report values outside this target range as normal.[51] Simplified dosing nomograms, including web- and mobile-based adaptations, have been developed to aid clinicians in optimizing the digoxin dose for patients with HFrEF.[52,53] Females, older patients, and those with renal insufficiency are especially susceptible to having higher serum digoxin concentrations. Digoxin also has drug–drug interactions with agents such as amiodarone, quinidine, verapamil, and macrolide antibiotics. Pharmacy team members on the front lines can recognize these potential interactions and undertake interventions accordingly. Adverse events of note with digoxin include nausea and vomiting, ventricular and atrial arrhythmias, bradycardia, heart block, mental status changes, and alterations in visual color fields.

Despite the lack of placebo-controlled clinical trial data showing improvement in HF outcomes, diuretics are recommended to reduce signs and symptoms of congestion.[54] Loop diuretics, due to their more potent natriuretic effects, are recommended for HF patients with volume overload rather than thiazide agents. The goal of diuretic therapy is to achieve and maintain clinical euvolemia with the lowest dose possible. This requires frequent monitoring of signs and symptoms of volume overload, particularly daily weight measurements, which allows patients to self-adjust their diuretic dose. Detailed reviews of diuretics can be found elsewhere.[55,56] One of the biggest challenges with chronic diuretic management in HF patients is the development of resistance. Potential mechanisms can include reduced drug absorption, low protein binding, distal tubule sodium reabsorption, and drug–drug interactions.[56,57] Pharmacy team members can help prevent and treat this common complication through timely identification and management. Beyond resistance, other common adverse events with diuretics include electrolyte abnormalities (low potassium, magnesium sodium, calcium; high glucose; uric acid), renal insufficiency, and (rarely) ototoxicity. These drugs require continuous monitoring of clinical volume status and laboratory values of electrolytes and renal function.

Role of the pharmacy team in heart failure management

Heart failure is a condition that requires multidisciplinary management to achieve optimal clinical outcomes.[58] This includes not only cardiologists but also primary care physicians, nurses, dieticians, social workers, physiotherapists, and pharmacists.[1] It is well known that pharmacists play an integral role in the management of patients with cardiovascular disease, including HF.[59,60] As described earlier, chronic HF management requires a large number of pharmacologic agents. When these are added to other comorbid chronic conditions, the number of drugs a patient can be taking is large. This type of polypharmacy can be problematic for patients and potentially impact medication adherence. The pharmacy team can play a major role in ensuring the safe and effective use of these medications with the aim of improving outcomes. Regardless of practice setting, pharmacists are skilled to identify and prevent adverse drug reactions, medication errors, drug interactions, and medication nonadherence in patients with HF.[61] Additionally, pharmacists may identify patients with HFrEF who may be untreated (eg, not prescribed evidence-based medications like a beta blocker) or undertreated (eg, not receiving target doses of evidence-based therapies or, for stage C patients, not prescribed additional evidence-based medications like an MRA). Many of these interventions are made through routine services provided by pharmacists such as therapeutic drug monitoring and medication reconciliation.[61] In fact, data suggest that pharmacist care activities reduce all-cause and HF hospitalizations when part of a multidisciplinary team.[62] For these reasons, the ESC, HFSA, and American College of Clinical Pharmacy (ACCP) advocate for the inclusion of clinical pharmacists as part of the multidisciplinary HF team across the continuum of care.[61]

Although the impact of inpatient clinical pharmacists on outcomes in patients with HF has not been well researched, several studies have demonstrated clinical and economic value associated with inclusion of clinical pharmacists on multidisciplinary teams caring for patients with cardiovascular disease, including HF.[63–65] The most common and impactful pharmacy services are drug information, therapeutic consultation to resolve drug-related problems, order clarification and formulary maintenance, identification and resolution of drug interactions and therapeutic duplication, and quality improvement.[61,65] Additionally, pharmacists may play a role in improving HF-related quality metrics.[61,66]

Pharmacists in both inpatient and outpatient settings play an important role during transitions of care for HF patients. Given the frequency of HF hospitalizations and the complexity of medication regimens, many drug-related problems occur during care transitions. Medication history taking and medication reconciliation are among the most basic pharmacy services provided by pharmacists, yet these remain among the most impactful in decreasing medications discrepancies, adverse drug reactions, and healthcare utilization.[67–72] A recent ACCP white paper outlines several roles for pharmacists in all settings during transitions of care.[73] For inpatient pharmacists, these include participation in medication reconciliation, patient care rounds, patient and caregiver education, involvement in the discharge process, and post-discharge follow-up. Community and ambulatory care pharmacists may also participate in post-discharge follow-up, patient education, clarification of medication discrepancies, and review of medications set up for automatic refills. Further, consultant and home health care pharmacists should play a role (eg, medication

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reconciliation). Although the quality of studies is low, HF transitions-of-care programs involving pharmacists are associated with improved adherence, exercise tolerance, and a lower incidence of clinical events including HF readmissions and mortality.[74] Key components of successful programs are provision of patient education, collaboration with other providers, and post-discharge phone follow-up.[75–80]

Outpatient clinical pharmacists caring for patients with HF provide many of the same services as inpatient clinical pharmacists, most often in collaboration with other providers but also in pharmacist-managed clinics such as titration and medication monitoring clinics.[61] Studies evaluating the impact of outpatient pharmacists on HF care have demonstrated improvements in the utilization of evidence-based HF medications, medication adherence, and patient symptoms, as well as lower rates of nonfatal HF events including HF readmissions.[76,81–83]

The community pharmacist can play a key role in the care of patients with HF. Given the quantity of medications prescribed for HF and other comorbidities and the frequency of medication refills, HF patients are more likely to interact with a community pharmacist than with any other provider. As a result, community pharmacists have frequent opportunities to positively impact HF care by correcting medication problems, resolving barriers to drug access, and by educating patients and caregivers on the safe and effective use of their HF medications as well as self-care.

As already discussed, it is recommended that community pharmacists play a role during care transitions by clarifying medication discrepancies and reviewing medications scheduled for automatic refills.[73] During HF hospitalizations, several medication changes may be made to a patient's HF drug regimen. Clarifying these changes with the patient and/or provider, including review of existing refills on file such as medications scheduled for automatic refills, can prevent drug-related problems. Preventable problems may include improper drug selection (eg, use of discontinued ACEI), therapeutic duplication (eg, taking 2 loop diuretics inadvertently), and drug–drug interactions/potential adverse drug reactions (eg, use of both ARNI and ACEI instead substituting ARNI for ACEI).

Community pharmacists are also often the first to identify potential barriers to medication access (eg, financial, insurance) and can help both patients and providers resolve these (eg, substitution of less costly evidence-based medications, assisting with insurance prior authorizations). In a recent pilot study, community pharmacists, using a simple clinical tool, identified 1 or more signs or symptoms of worsening HF in 62% of patients, which could prove to be another effective mechanism to prevent unnecessary HF readmissions.[84]

Dietary and pharmacotherapy counseling tips

The ACCP Cardiology Practice and Research Network recently developed a best practices model for discharge counseling patients with HF or MI.[85] Although this model is geared toward discharge counseling, many of the counseling points and methods can be applied to all HF patient education encounters. Several general principles should be followed by pharmacists during patient education encounters. Education of patients with HF and their caregivers should be an ongoing process in which pharmacists in both inpatient and outpatient settings should routinely participate. Each teaching session should include an assessment of both baseline knowledge and existing barriers to patient education, including readiness to learn, to allow for individualization of teaching points and methods.[85,86] Whenever possible, interventions should be directed to remove or address existing barriers (eg, use of pillboxes to address nonadherence related to forgetfulness, recommendations for less costly medications in the presence of financial barriers, and use of translators or printing instructions in a patient's native language if needed). Pharmacists should engage caregivers whenever possible, because many patients with HF have cognitive impairment that may limit retention and comprehension of educational points.[85,86] Patients should be offered a variety of teaching methods, including use of written materials, videos, telephone calls, group discussions, etc., that may improve patient education encounters. Pharmacists should consider use of the "teach back" method, particularly if there is uncertainty regarding the patient or caregiver's understanding of HF educational points.

Patients and caregivers should be provided specific HF self-care recommendations throughout educational encounters.[85,86] Optimal self-care education includes definition of HF and clarification of its cause, recognition of signs and symptoms of worsening HF and plan for responding to them, recognition and management of risk factors for HF progression, discussion of dietary restrictions including low-sodium diet and minimization of alcohol intake, recommendations for activity level and exercise, and emphasis on treatment adherence and strategies to promote it.[86] Skill building is an essential component of self-care management. For example, because of the paucity of data, specific restrictions on sodium intake are not recommended, but reasonable targets are less than 1.5 to 3 g/day.[6] Perhaps more important than specific sodium restrictions are skill-building exercises such as reading and interpreting food labels and sorting foods based on their sodium content (eg, low sodium and high sodium).[85,86] Daily self-measurement and documentation of weights and development of an action plan if significant weight changes are observed are additional self-care skills that should be emphasized.

Heart failure self-care education must include a thorough review of medications and reinforcement of behavioral strat-

egies that optimize medication adherence.[85] For each medication, patients and caregivers should be able to identify the name, indication, expected benefit, dose, dosing schedule, anticipated duration of therapy, appropriate storage, and what to do if a dose is missed. Patients should be taught common and serious adverse effects for each of the medications and screened for the presence of these at each encounter. Drug–drug and drug–food interactions should be reviewed with patients as well. In addition to medication-specific educational points, patients should also be taught behaviors that optimize adherence, including carrying an updated list of current medications, bringing all medications to all healthcare appointments, and identification of a medication "system" that allows for easy tracking and promotion of medication adherence. Similarly, patients should be educated to develop a plan for scheduling and obtaining medication refills. Finally, it may be beneficial during educational encounters to have patients read instructions from a medication label to provide an opportunity to assess health literacy and intervene if necessary.[85]

Although specific educational points for heart failure medications are beyond the scope of this review, there are some noteworthy points to emphasize. When initiating and titrating beta blockers in patients with HFrEF, the need to monitor for signs and symptoms of worsening HF should be emphasized, because it is during this period when patients are most susceptible to this adverse effect. Nocturnal diuresis is a frequent reason for nonadherence with diuretic therapy. Therefore, patients should be educated to optimize their dose administration times to minimize nocturnal diuresis. Finally, given the frequency of hyperkalemia associated with MRA therapy in patients with HFrEF, patients should be counseled regarding the need for and frequency of serial monitoring of potassium concentrations as well as awareness of their dietary potassium intake.[85]

Conclusion

Heart failure is a complex syndrome that results in impaired cardiac function, poor end-organ perfusion, and is associated with substantial morbidity and mortality. Thankfully, there are numerous evidence-based medications that improve outcomes in patients with HFrEF. Recently, the new drugs ARNI and ivabradine have been approved to improve HF-related outcomes. Pharmacists have a unique skill set and play a key role on multidisciplinary teams that care for patients with HF in all settings.

References are available online at *www.drugtopics.com/cpe.* •

TEST QUESTIONS

FOR PHARMACISTS

1. Which one of the following drugs/classes has been shown to reduce mortality in patients with HFrEF?
- **a.** Angiotensin receptor–neprilysin inhibitors
- **b.** Digoxin
- **c.** Ivabradine
- **d.** Loop diuretics

2. What is the goal serum digoxin level when treating HFrEF?
- **a.** 0.1–0.5 ng/mL
- **b.** 0.5–0.9 ng/mL
- **c.** 1.2–2.0 ng/mL
- **d.** 0.5–2.0 ng/mL

3. Which of the following agents has been shown to reduce mortality specifically in African American patients with HFrEF?
- **a.** Candesartan
- **b.** Eplerenone
- **c.** Hydralazine/isosorbide dinitrate
- **d.** Ivabradine

4. Ivabradine has been associated with which of the following adverse events?
- **a.** Angioedema
- **b.** Atrial fibrillation
- **c.** Lupus-like syndrome
- **d.** Torsade de Pointes

5. Compared with eplerenone, spironolactone has a higher risk of causing which adverse event?
- **a.** Acute kidney injury
- **b.** Gynecomastia
- **c.** Hyperkalemia
- **d.** Dry cough

6. Which of the following beta blockers has proven mortality reduction in patients with HFrEF?
- **a.** Atenolol
- **b.** Carvedilol
- **c.** Metoprolol tartrate
- **d.** Propranolol

7. How many hours needs to pass between when an ACE inhibitor is stopped and sacubitril/valsartan can be started?
- **a.** It can be started immediately
- **b.** 12 hours
- **c.** 24 hours
- **d.** 36 hours

8. In which of the following populations can an angiotensin II receptor blocker be used?
- **a.** As initial therapy in all patients
- **b.** In patients who cannot tolerate a mineralocorticoid receptor antagonist
- **c.** In patients who cannot tolerate an ACEI
- **d.** In patients who cannot tolerate a beta blocker

9. Which of the following is a warning of caution for the use of ACEIs in HFrEF?
- **a.** Serum potassium >5.0 mEq/L
- **b.** Serum creatinine >1.5 mg/dL
- **c.** Systolic blood pressure <110 mm Hg
- **d.** Unilateral renal artery stenosis

10. Which of the following would be a preferred initial 3-drug regimen in a white patient with HFrEF?
- **a.** Digoxin, furosemide, spironolactone
- **b.** Lisinopril, bumetanide, losartan
- **c.** Valsartan, bisoprolol, furosemide
- **d.** Lisinopril, carvedilol, furosemide

11. Which of the following pharmacist activities has been associated with lower rates of medication discrepancies, adverse drug reactions, and healthcare utilization?
- **a.** Medication history taking
- **b.** Medication use evaluation
- **c.** Order verification
- **d.** Quality improvement activities

12. A 53-year-old white male with HFrEF and NYHA class II symptoms presents a new prescription for sacubitril 49 mg/valsartan 51 mg twice daily along with a discount card to obtain the first month free. The patient was previously treated with enalapril 10 mg twice daily, carvedilol 25 mg twice daily, and spironolactone 25 mg daily. Which of the following interventions by the community pharmacist would be best for this patient?
- **a.** Contact prescriber to recommend a less costly alternative to sacubitril/valsartan
- **b.** Contact prescriber to recommend ivabradine instead of sacubitril/valsartan

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c. Review and cancellation of automatic refills for enalapril
d. Schedule sacubitril/valsartan for automatic refills every month

13. A 72-year-old female with HFrEF and NYHA class III symptoms and preserved renal function presents a new prescription for ivabradine 5 mg twice daily explaining that she was recently hospitalized for heart failure 1 month ago. She cannot afford her copay ($150). Which of the following interventions by the community pharmacist would be best for this patient?

a. Contact the prescriber and suggest digoxin as a less costly alternative to ivabradine
b. Measure the patient's heart rate to determine the need for ivabradine
c. Recommend the patient discuss this with her physician and place prescription on hold
d. Screen the patient for signs and symptoms of worsening heart failure to determine need for ivabradine

14. An 87-year-old female with HFrEF and chronic kidney disease presents to the pharmacy requesting refills of her heart failure medications, which include lisinopril 10 mg daily, metoprolol succinate 200 mg daily, digoxin 0.25 mg daily, and furosemide 80 mg twice daily. She asks for a recommendation for an OTC antiemetic, complaining of nausea and vomiting she attributes to recent visual changes. Which of the following interventions should the community pharmacist consider?

a. Suggest she go to the emergency department to be evaluated for dehydration
b. Recommend bismuth subsalicylate as an antiemetic, suggesting she separate it by at least 2 hours from her other medications
c. Dispense her heart failure medications but suggest she contact her primary care provider for her nausea and vomiting
d. Contact the prescriber to voice concern about potential digoxin toxicity

15. Which of the following is a key component of successful transitions-of-care programs for heart failure patients that involve pharmacists?

a. Assessment of medication adherence
b. Assessment of patients' signs and symptoms of heart failure by community pharmacists
c. Meds-to-beds programs
d. Patient education

16. Which of the following should the pharmacist do at the beginning of each heart failure patient education session?

a. Assessment of barriers to patient education
b. Incorporate technology (eg, videos, mobile applications, web-based)
c. Promote the benefits of automatic refills for heart failure medications
d. Review daily weight logs kept by the patient

17. A 67-year-old male with HFrEF and dementia asks to speak to the pharmacist about his heart failure medications. Which of the following interventions should the pharmacist consider during this counseling session to enhance success?

a. Encourage self-care as part of the counseling session
b. Engage the patient's caregiver
c. Recommend the use of pill boxes
d. Use both written and video-based educational materials

18. Which of the following patient education points is more important regarding sodium restriction in a patient with HFrEF?

a. Limit to <1.5 g/day b. Limit to <3 g/day
c. Teach the patient to read food labels and sort foods based on sodium content
d. Teach the patient to utilize salt substitutes instead of sodium

19. Which of the following strategies can be used by pharmacists to assess health literacy?

a. Administer a brief health literacy survey
b. Ask patients if they understand your instructions or if they have any questions
c. Ask patients to explain heart failure to you
d. Have patients read instructions from a medication label

20. Which of the following is an important counseling point that should be emphasized for a 57-year-old male with HFrEF being started on a beta blocker?

a. Potential for erectile dysfunction
b. Self-measurement of vital signs
c. Self-monitoring for signs and symptoms of worsening heart failure
d. What to do if a dose is missed

FOR PHARMACY TECHNICIANS

1. Which of the following is a mineralocorticoid receptor antagonist?

a. Captopril b. Eplerenone
c. Ivabradine d. Valsartan

2. Which of the following beta blockers has evidence showing mortality reduction in heart failure?

a. Atenolol b. Carvedilol
c. Metoprolol tartrate d. Nadolol

3. Which of the following statements about treatment of acute pain with opioids is true?

a. <60% b. <50%
c. <40% d. <30%

4. For which of the following drugs is monitoring of serum drug concentrations required?

a. Digoxin b. Ivabradine
c. Sacubitril d. Spironolactone

5. Which drug class should be used first to treat HFrEF?

a. ACEIs b. ARBs
c. Hydralazine/isosorbide dinitrate
d. MRAs

6. Which of the following patients with HFrEF is more likely to have problems with medication adherence due to poor retention and comprehension of educational points?

a. Patient with cognitive impairment
b. Patients with language barriers
c. Patients recently discharged from the hospital
d. Young patients

7. Medication nonadherence is a common precipitating factor for which of the following outcomes?

a. Disease progression
b. Heart failure hospitalization
c. Increased cost of care
d. Increased mortality

8. Which of the following patients with HFrEF should be referred to the pharmacist for patient education and counseling?

a. All patients treated with beta blockers
b. Only patients who ask to speak to the pharmacist
c. Patient recently discharged from the hospital
d. Patient requesting routine refills of heart failure medications

9. Which of the following patients with HFrEF should be referred to the pharmacist for patient education and counseling?

a. Non-English-speaking patient
b. Patient prescribed bumetanide twice daily
c. Patient who does not possess a list of their current heart failure medications
d. Patient who verbalizes she cannot afford her newly prescribed sacubitril/valsartan

10. A 47-year-old female recently diagnosed with HFrEF asks the technician dispensing her refills for metoprolol succinate and ramipril how long she will likely be taking these medications. Which of the following actions should the technician take?

a. Explain that these medications may be discontinued if her heart function improves
b. Explain that these medications will likely be lifelong
c. Refer the patient to the pharmacist for patient education and counseling
d. Refer the patient to the prescribing physician who can answer more appropriately