

Discerning Heart Failure: New Treatment Approaches for Preserved or Reduced Ejection Fraction Subtypes

HIGHLIGHTS

- › Filling the Gaps in Guideline-Directed Care
- › Heart Failure Population Health Considerations
- › CE Sample Posttest

Discerning Heart Failure: New Treatment Approaches for Preserved or Reduced Ejection Fraction Subtypes

Release date: May 24, 2021

Expiration date: June 15, 2022

Estimated time to complete activity: 2.0 hours

Type of activity: Application

Medium: Print with internet-based posttest, evaluation, and request for credit

Fee: Free

This activity is supported by an educational grant from Merck Sharp & Dohme Corp.

Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or healthcare professional interested in scientific advances for combination therapies in the treatment of heart failure.

Activity Overview

The number of Americans older than 20 years with heart failure (HF) has significantly increased in the past 10 years, with projections estimating more than 8 million American adults will be diagnosed with HF by 2030. Patients with HF with reduced ejection fraction (HFrEF) and those with preserved ejection fraction (HFpEF) require different treatments. Managed care pharmacists and clinicians must be familiar with diagnostics and treatment strategies associated with each subtype. Heart disease is a leading cost driver in healthcare, with costs attributed to medication management of comorbidities, complications due to nonadherence, and hospitalizations. Managed care professionals must be familiar with emerging evidence and where these agents may fit into the HF treatment paradigm, as well as current treatment guidelines, and ensure the implementation of these protocols within their institutions.

Statement of Educational Need

The high cost of heart failure for patients and the healthcare system is an ongoing challenge, especially for patients who have heart failure with preserved ejection fraction (HFpEF). These patients incur high morbidity, mortality, and hospital admission rates. Treatment for HFpEF is limited, and treatments used for heart failure with reduced ejection fraction (HFrEF) have historically been trialed in patients with HFpEF. However, these conditions have varying pathophysiology, indicating a

need to approach each subtype differently. In recent years, there has been increased research interest into mechanisms of action and pathways in patients with HFpEF. It is imperative that managed care professionals utilize clinical trial results of medications under investigation to expand their knowledge of recommended treatment pathways. Adhering to existing pathways and understanding where emerging agents may fit into the heart failure treatment paradigm will support the healthcare team in providing optimal clinical and cost-effective care for patients. Managed care professionals and pharmacists involved in care need to understand the impact that updated clinical guidance for existing and emerging medications will have in the treatment of patients with HFpEF and HFrEF.

Educational Objectives

Upon completion of this activity, participants will be able to:

- Explain the incidence and prevalence of heart failure (HF), the difference between heart failure with preserved or reduced ejection fraction (HFpEF or HFrEF), diagnostic testing, and prognosis.
- Classify traditional treatments for HFpEF and HFrEF, the lack of medications for HFpEF, and innovative treatment approaches currently in clinical trials.
- Calculate the high cost of hospitalizations and emergency department visits, reduced quality of life, and treatment challenges for patients diagnosed with HF.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care*[®], managed care professionals will increase their knowledge of heart failure with reduced and preserved ejection fraction and new therapies in the treatment landscape.

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Filling the Gaps in Guideline-Directed Care

Christopher Betz, PharmD, BCPS, FKSHP, FASHP

Introduction and Heart Failure Overview

Nationally, the medical community continues to focus on decreasing readmission rates for heart failure (HF). HF affected an estimated 6 million American adults in 2018. Its prevalence increases significantly with ages older than 80 years.¹ Cardiologists categorize HF into primarily 2 groups: HF with reduced ejection fraction (HFrEF, formerly called systolic HF) and HF with preserved ejection fraction (HFpEF, formerly called diastolic HF). HFrEF indicates that a patient's left ventricular ejection fraction (LVEF)—a marker of underlying pathophysiology—is less than 40% on echocardiography. HFrEF has traditionally been the most well-recognized type of HF.²⁻⁵

HFpEF refers to patients with HF symptoms, impaired left ventricular relaxation, probable increased left ventricular chamber stiffness, and an LVEF greater than 50% on echocardiography.⁶ Patients with HFpEF tend to be older than those with HFrEF. They often have underlying comorbidities of hyperlipidemia, diabetes, atrial fibrillation, anemia, and chronic obstructive pulmonary disease. Patients with HFpEF often experience diastolic dysfunction, reduced compliance (ease of filling a chamber of the heart with blood), ventricular hypokinesia, and a triad of symptoms including shortness of breath, excessive fatigue, and exercise intolerance.⁷ Among patients with HF who are hospitalized, statisticians indicate that approximately half have reduced ejection fraction (EF) and the other half have preserved EF.^{2,5}

The astute reader will have identified a gap between the LVEF cutoff numbers for HFrEF and HFpEF. The *2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized with Heart Failure* acknowledges this group, labeling them patients with midrange ejection fraction (HFmrEF, LVEF 40 to 50). In the newly issued *Universal Definition and Classification of Heart Failure; A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure (Universal Definition and Classification of Heart Failure)*, this group is called HF with mildly reduced EF (HFmrEF).⁵ Management draws on components of both HFrEF and HFpEF.²

ABSTRACT

As American clinicians have tried to reduce heart failure rehospitalizations and improve care for patients with heart failure with reduced ejection fraction (HFrEF), the population of patients who have heart failure with preserved ejection fraction (HFpEF) has emerged as needing attention. Although HFrEF and HFpEF share some characteristics, treatment approaches are different, and treatment options for HFpEF are more limited. All patients would benefit from guideline-directed medical treatment. The FDA has expanded the indications for sacubitril/valsartan to encompass both patients with HFrEF and selected patients with HFpEF, and the sodium-glucose cotransporter-2 inhibitors to reduce heart failure hospitalizations and the risk of cardiovascular death in symptomatic patients with HFrEF. It has also approved vericiguat, an oral soluble guanylyl cyclase activator. In addition, investigators are examining possible uses of omecamtiv mecarbil and nonsteroidal aldosterone antagonists in heart failure. Addressing heart failure is a team effort, and such teams need overlapping expertise, innovative approaches, and resources that support and sustain their efforts. Team members should familiarize themselves with the American College of Cardiology 2021 Update to the 2017 Expert Consensus Decision Pathway as a means to offer the best care to the patients that they serve.

Am J Manag Care. 2021;27:S183-S190

For author information and disclosures, see end of text.

HF's prevalence is expected to increase 46% before 2030, resulting in more than 8 million Americans with HF.¹ According to the Atherosclerosis Risk in Communities (ARIC) study, a prospective epidemiologic study conducted in 4 US communities' surveillance data, women experience slightly higher new-onset HF than men, with Black patients experiencing greater numbers of hospitalizations. HFpEF is more common in women, while HFrEF is common in men.^{7,8} ARIC surveillance data from 2005 through 2014 indicated that 11.6 people were hospitalized for HF for every 1000 residents. It also showed increased rates of HF hospitalizations, primarily driven by HFpEF, thus making HFpEF an emerging concern.⁸

Diagnosis and Its Challenges

HF, a progressive condition, begins with risk factors for cardiac dysfunction and proceeds to asymptomatic changes in cardiac structure and function. It evolves into clinical HF, disability, and death. Clinicians use 2 grading systems to classify patients. First, the recently published *Universal Definition and Classification of Heart Failure* proposes classifying HF based on its progressive pathophysiology⁵:

- Stage A: At-risk for heart failure
- Stage B: Pre-heart failure
- Stage C: Heart failure
- Stage D: Advanced heart failure

Treatment goals differ based on the stage of the patient's HF.⁹ In stage A, patients are at risk for, but do not have, HF and goals are to establish a heart healthy lifestyle, prevent vascular and coronary disease, and prevent left ventricular structural abnormalities. These patients have risk factors for HF (eg, atherosclerotic disease, diabetes, hypertension, metabolic syndrome, obesity). At stage D, the goals are palliative: to control symptoms, improve health-related quality of life, reduce hospital readmissions, and establish patients' end-of-life goals. The American Heart Association posts a flow chart that concisely summarizes the stages (which have not been changed to the consensus statement's terminology, but are similar), patient profiles, and recommended therapies at www.heart.org/-/media/files/health-topics/heart-failure/rahf-guidelines-toolkit-algorithm.pdf?la=en.⁹

TABLE 1. The New York Heart Association's Functional Classification¹³

Class I: No limitation of physical activity
Class II: Slight limitation of physical activity
Class III: Marked limitation of physical activity
Class IV: Unable to perform any physical activity without symptoms of heart failure (HF), or symptoms of HF at rest

Data from various sources indicate survival after onset of HF in older adults has improved. But improvements in HF survival have not been level across all demographics. In the ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalizations were 10.4%, 22%, and 42.3%, respectively. Five-year case fatality rates were higher in Black patients than White patients.¹⁰ Among Medicare beneficiaries, the overall 1-year HF mortality rate declined slightly from 1998 to 2008; however, the rate still approached 30%.¹¹

Patients with HFrEF may present with a variety of symptoms, but most are nonspecific.¹² Typical symptoms include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and dependent edema. Abdominal bloating, right upper-quadrant discomfort, and early satiety—all nonspecific symptoms—may indicate right-sided HF. Clinicians use a second classification system, the New York Heart Association's (NYHA) functional classification (see [Table 1](#)¹³), to grade symptom severity. Specific signs of HF include elevated jugular venous pressure, positive abdominojugular reflux, S3 (gallop rhythm), and laterally displaced apical impulse; these symptoms indicate a higher degree of congestion (volume overload) and higher risk of hospitalization or death.^{12,14}

Assessment of a chest x-ray, electrocardiogram, and B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide (BNP/NT-proBNP) levels are appropriate in patients presenting with HF symptoms. Natriuretic peptide levels can exclude or support an HF diagnosis and predict the patient's prognostic trajectory. In patients with chronic HFrEF, a decrease in NT-proBNP to 1000 pg/mL or less during treatment has been linked to lower risk of HF hospitalization or cardiovascular (CV) death. The diagnosis should then be confirmed via transthoracic echocardiography.¹²

Treatment of HFrEF: Standard of Care

HF is usually associated with multiple comorbidities, necessitating the use of multiple medications. [Table 2](#)^{3,4} summarizes the standard of care for HFrEF, listing nonpharmacologic, pharmacologic, and invasive strategies depending on the severity of the patient's disease.^{3,4,15-17} Various guidelines detail what to use first based on the patient's classification or functional status.

Guideline-directed Medical Therapy Advancements Sacubitril/valsartan

Several vasoactive peptides (eg, adrenomedullin, bradykinin, natriuretic peptides, and substance P) are key to HF's pathogenesis and progression. Nephilysin, also called neutral endopeptidase, is a metalloprotease that inactivates many vasoactive peptides.¹⁸ Clinicians need to be aware that angiotensin II is a nephilysin substrate, and nephilysin inhibitors raise angiotensin levels. For this reason, guidelines indicate nephilysin inhibitors must be administered with an angiotensin receptor blocker (ARB) and not given with angiotensin-converting enzyme inhibitors (ACEIs),

as coadministration increases risk of angioedema.¹⁹ Angiotensin receptor-neprilysin inhibitors (ARNIs) have been associated with improvement in diastolic function, left ventricular function, quality of life, and burden of ventricular arrhythmias. Currently, one angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan, is available.

The randomized controlled prospective comparison of ARNI versus ACEI, PARADIGM HF, study examined sacubitril/valsartan in patients with chronic HFrEF. The investigators enrolled patients with NYHA class II to IV symptoms with an EF less than 40% (but reduced it to less than 35%, 1 year into the trial). Participants had to have stable ACEI or ARB doses and be taking other background guideline-directed medical therapy (GDMT). Participants could not have histories of angioedema, eGFR less than 30 mL/min/1.73m², symptomatic hypotension or systolic blood pressure (SBP) less than 100 mm Hg, or current decompensated HF.²⁰

In participants treated with sacubitril/valsartan, the primary outcomes of CV death or HF hospitalization had an absolute risk reduction of 4.7% (hazard ratio (HR), 0.80; 95% CI, 0.73-0.87; *P* < .001) when compared with enalapril-treated patients. The number needed to treat to prevent 1 CV death or HF hospitalization over 27 months was 21. Also, each individual outcome within the composite end point including CV death (HR, 0.80; 95% CI, 0.71-0.89; *P* < .001) and hospitalization for worsening HF (HR, 0.79; 95% CI, 0.71-0.89; *P* < .001), as well as the secondary end point of death from any cause (HR, 0.84; 95% CI, 0.76-0.93; *P* < .001), met statistical significance. Sacubitril/valsartan-treated patients were more likely to experience symptomatic hypotension (14.0% vs 9.2%; *P* < .001), but the investigators did not identify worsening renal function. Angioedema was similar in both arms.²⁰

The 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure recommended an ARNI, ACEI, or ARB to reduce morbidity and mortality in patients with chronic HFrEF (with ARNIs preferred).¹⁶ They also recommended transitioning patients with NYHA class II to III symptoms who tolerated an ACEI or ARB to an ARNI, basing the recommendation on reduced morbidity and mortality.¹⁶ The 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction (2021 ECDP) indicates that clinical studies and prescribers' clinical experience suggest that initiating an ARNI without previous patient exposure to an

ACEI or ARB is safe and effective.³ Common adverse reactions include hypotension, hyperkalemia, cough, dizziness, and renal failure.²¹

Clinicians had historically started patients on neprilysin inhibitors while they were community dwelling. The Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute HF Episode (PIONEER-HF) trial found that clinicians in hospital settings could safely start patients hospitalized for acute decompensated HF on an ARNI as well. This multicenter trial enrolled patients hospitalized for HFrEF from day 2 until day 10 following initial presentation and evaluated the time-averaged reduction in NT-proBNP concentration from baseline through weeks 4 and 8. Prior to randomization, patients were required to have an SBP greater than or equal to 100 mm Hg in the past 6 hours and no intravenous (IV) inotropes in the past 24 hours. Patients received either sacubitril/valsartan or enalapril twice daily with initial dosing adjusted according to SBP. Patients with an SBP between 100 and 119 mm Hg were initiated on sacubitril/valsartan 24/26 mg twice daily or enalapril 2.5 mg twice daily. Patients with an SBP greater than or equal to 120 mm Hg were started on sacubitril/valsartan 49/51 mg twice daily or enalapril 5 mg twice daily. Patients who received sacubitril/valsartan had a significantly greater reduction in time-averaged NT-proBNP concentration when compared with enalapril (-46.7% vs -25.3%; ratio of change, 0.71; 95% CI, 0.63-0.81; *P* < .001). In addition, the rates of worsening renal function, hyperkalemia, angioedema, and symptomatic hypotension

TABLE 2. Treatments Used as Standard of Care for Heart Failure^{3,4}

Intervention Type	Possible Interventions
Nonpharmacologic therapies	<ul style="list-style-type: none"> • Dietary sodium and fluid restriction • Physical activity as tolerated • Oxygen and noninvasive positive pressure ventilation • Weight monitoring
Guideline-directed medical therapy	<ul style="list-style-type: none"> • Aldosterone antagonists • Angiotensin-converting enzyme inhibitors • Angiotensin receptor-neprilysin inhibitors • Angiotensin receptor blockers • β-blockers • Digoxin • Diuretics • Hydralazine/isosorbide dinitrate • Ivabradine • Sodium-glucose cotransporter-2 inhibitors • Vericiguat
Avoid drugs that may exacerbate heart failure:	
<ul style="list-style-type: none"> • Nonsteroidal anti-inflammatory drugs • Calcium channel blockers • Most antiarrhythmic drugs 	
Guideline-based device therapy	<ul style="list-style-type: none"> • Implantable cardioverter-defibrillators (ICDs) • Biventricular pacing/cardiac resynchronization therapy (CRT) • Combination ICD/CRT devices • Ventricular assist devices

did not differ significantly between the groups within this trial.²² Since symptomatic hypotension was the only adverse effect that occurred with great frequency within a previous trial, the investigators' decision to maintain the lowest dose of sacubitril/valsartan (24/26 mg twice daily) in patients with an SBP from 100 to 119 mm Hg appears to have mitigated this risk.^{20,22}

Sodium-Glucose Cotransporter-2 Inhibitors

The sodium-glucose cotransporter-2 (SGLT2) inhibitors have recently emerged as a novel therapy in the care of patients with HF. SGLTs block reabsorption of filtered glucose in the proximal renal tubule causing urinary glucose excretion. After the publication of the 2017 ACC Expert Consensus Decision Pathway, the FDA approved SGLT2 inhibitors for treatment of HFrEF patients.³ Results from 2 pivotal studies, DAPA-HF and EMPEROR-Reduced, showed that SGLT2 inhibitors exhibit a beneficial class effect in patients with HFrEF.²³ The DAPA-HF study and the EMPEROR-Reduced demonstrated SGLT2 inhibitors' utility in HF.^{24,25}

The DAPA-HF trial followed randomly assigned patients with chronic HFrEF (N = 4744) treated with dapagliflozin or placebo for an average of 18.2 months. All patients received appropriate neurohormonal antagonists as background treatments. More than 90% received renin-angiotensin system inhibitors and β -blockers, and more than 70% took mineralocorticoid receptor antagonists. Approximately half of the patients had diabetes at baseline, and more than 40% did not have underlying ischemic heart disease.²⁴

In this patient population, the composite outcome of CV death, hospitalization for HF, or an urgent visit for worsening HF requiring IV therapy occurred in 16.3% of patients taking dapagliflozin and 21.2% of patients taking placebo (HR, 0.74; 95% CI, 0.65-0.85; $P < .001$). In addition, each efficacy outcome within the composite occurred statistically significantly less often in the population receiving dapagliflozin versus placebo. The composite outcome occurred with similar regularity in patients with diabetes (HR, 0.75; 95% CI, 0.63-0.90) as without diabetes (HR, 0.73; 95% CI, 0.60-0.88).²⁴ Subsequent to DAPA-HF, Jhund et al reevaluated the trial data to determine if dapagliflozin also had appreciable effects on recurrent events within the composite end point as opposed to first events. Using the Lin Wei Yang Ying model to determine the rate of recurrent HF hospitalizations and CV deaths, the authors found that the rate ratio of dapagliflozin was statistically significant (HR, 0.75; 95% CI, 0.65-0.88; $P < .0002$). This showed that the effect of dapagliflozin in patients with HFrEF did not simply diminish first events, but also reduced subsequent events as well.²⁶

The double-blind, placebo-controlled EMPEROR-Reduced trial randomized 3730 patients with class II to IV HFrEF with or without diabetes to receive 10 mg daily or placebo. Patients in this trial also received GDMT as background.²⁵ The investigators followed the participants for a median of 16 months. Empagliflozin reduced

the primary end point, a composite of CV death or HF hospitalization significantly (HR, 0.75; 95% CI, 0.65-0.86; $P < .001$). The event rates were 15.8 and 21/100 patient-years in the empagliflozin and placebo groups, respectively. This translated to a number needed to treat of 19, which the investigators attributed to a lower risk of HF hospitalization. Empagliflozin-treated patients also experienced a significantly slower annual rate of decline in eGFR (a secondary outcome) and lower risk of serious renal outcomes.²⁵

Empagliflozin's benefits were similar among patients receiving currently recommended drugs, including an ARNI whether or not they had diabetes. Adverse effects associated with HF drugs were similar in both arms, but patients in the SGLT2 inhibition arm were more likely to develop uncomplicated urinary tract infections.²⁵

The 2021 ECDP includes an update on when to add, switch, and titrate all HFrEF patients to maximally tolerated and ideal target doses of SGLT2 inhibitors.³ It recommends initiating patients with stage C HFrEF with ARNI/ACEI/ARB (ARNI preferred) and an evidence-based β -blocker. Additionally, diuretics should be used as needed. Selected patients who meet specific criteria—HFrEF (EF at or below 40%) with or without diabetes and NYHA class II to IV—are treated with SGLT2 inhibitors as additional secondary agents.³

Among patients with HF, SGLT2 inhibitors have been well tolerated. The FDA-approved product labeling indicates that common adverse effects include genital yeast infections, including vulvovaginal candidiasis and balanitis, frequent urination, and urinary tract infection.²⁷⁻²⁹ Canagliflozin, dapagliflozin, and empagliflozin should be discontinued at least 3 days before scheduled surgery.²⁷⁻²⁹ SGLT2 inhibitors are dosed once daily. They have few drug interactions, but canagliflozin is a P-glycoprotein substrate.²⁷ SGLT2 inhibitors are contraindicated in patients with type 1 diabetes, patients who are lactating, and those on dialysis.²⁷⁻²⁹ Dapagliflozin may be prescribed in patients with eGFR at or above 30 mL/min/1.73m² and empagliflozin may be prescribed in patients with eGFR at or above 20 mL/min/1.73m².^{28,29}

In the aforementioned studies, infections were common during early treatment.²³ Adverse effects (AEs) in HF trials in which many patients did not have diabetes were less severe than in trials enrolling patients with diabetes. In DAPA-HF, discontinuation due to serious AEs was similar between arms. Other serious AEs included volume depletion (1.2% and 1.7%, $P = .23$) and renal AEs (1.6% and 2.7%) in the dapagliflozin and placebo groups, respectively. Dapagliflozin-treated patients experienced no notable excess AEs.²⁴ In EMPEROR-REDUCED, uncomplicated genital tract infection was reported more frequently in the empagliflozin group. AEs identified often in previous trials including hypotension, volume depletion, renal dysfunction, bradycardia, and hyperkalemia were not identified as concerns in this trial.²⁵

The ECDP warns that patients may be at risk for genital mycotic infections, ketoacidosis in patients with diabetes, acute kidney

injury, urosepsis, pyelonephritis, and Fournier gangrene. SGLT2 inhibitors should also not be prescribed to women who are pregnant or breastfeeding. Patients who develop acute kidney injury from treatment with SGLT2s may need to be held until the eGFR improves to above 30 mL/min/1.73m² with dapagliflozin and above 20 mL/min/1.73m² with empagliflozin. Because SGLT2 inhibitors may enhance volume depletion, dose reduction of loop diuretics may be warranted dependent on the volume status of the patients being treated.³

Vericiguat

The FDA approved vericiguat, an oral soluble guanylyl cyclase activator, in January 2021 for patients with HFrEF with worsening disease to reduce risk of CV death and HF hospitalization, following a hospitalization for HF, or need for outpatient IV diuretics, in adults with symptomatic chronic HF and EF less than 45%.^{30,31}

Activation of guanylyl cyclase increases cGMP, which leads to natriuresis, diuresis, and vasodilation. In the VICTORIA randomized double-blind placebo-controlled trial, patients were given vericiguat titrated to a 10-mg target dose or placebo in addition to GDMT.³² Enrolled patients had symptomatic chronic HF (NYHA class II, III, or IV) and an EF of 45% or less within the previous 12 months. They also had elevated natriuretic peptide levels within 1 month of randomization. Patients were excluded if they had an SBP less than 100 mm Hg, had an implantable left ventricular assist device, or were on concomitant long-acting nitrates, soluble guanylate cyclase stimulators (eg, riociguat), phosphodiesterase type 5 inhibitors (eg, sildenafil), or IV inotropes. In addition, enrollment required objective evidence of worsening HF in the form of a hospitalization within the past 3 to 6 months or the use of IV diuretics without hospitalization. In the vericiguat arm, 35.5% of participants experienced the primary outcome (a composite of death from CV causes or first hospitalization for HF) compared with 38.5% of the placebo arm (HR, 0.90; 95% CI, 0.82-0.98; $P = .02$). Secondary outcomes included CV deaths (16.4% vs 17.5% [HR, 0.93; 95% CI, 0.81-1.06]), all-cause death (20.3% vs 21.2%), HF hospitalization (27.4% vs 29.6% [HR, 0.90; 95% CI, 0.83-0.98; $P = .02$]), and serious AE (32.8% vs 34.8% in vericiguat-treated participants and placebo-treated participants, respectively). The positive composite end point was primarily driven by improvements in HF hospitalizations, but the trial's 1-month duration may have diminished the authors' ability to find a difference in deaths from CV causes. Hypotension (9.1%) and anemia (7.6% and 5.7%) in the vericiguat and placebo groups, respectively, were common AEs.³²

Vericiguat could be considered as an adjunct therapy to reduce the risk of HF hospitalization in symptomatic patients with objective evidence of worsening HF. This could include patients who receive outpatient IV diuretics as a means to prevent worsening HF and subsequent hospitalization.

HFpEF: Many Unmet Needs

Few randomized, controlled studies have shown clinical benefits in the use of medications to treat HFpEF, substantiating experts' designation of this condition as having many unmet needs. HFpEF is a heterogeneous condition, although some cardiologists divide it broadly into 3 groups: exercise-induced elevation of left ventricular filling pressures (lowest risk, difficult to diagnose), volume overload (more common, easier to recognize), or right HF (highest risk, poor prognosis).^{22,33} Regardless of HFpEF's cause or presentation, clinicians and patients need to treat/monitor blood pressure and volume and address modifiable risk factors aggressively.^{4,17}

There are many similarities and differences among patients with HFpEF and HFrEF. Smoking increases risk of both HFpEF and HFrEF, and both are associated with accelerated cognitive decline and an equal likelihood of rehospitalization. Physical activity lowers risk of developing HFpEF, but not HFrEF. Atrial fibrillation is marginally more prevalent in patients with HFpEF (HR, 2.34; 95% CI, 1.48-3.70) than those with HFrEF (HR, 1.32; 95% CI, 0.83-2.10). Patients with HFpEF are more likely to be women, obese, anemic, and have hypertension.¹

Clinicians should approach HFpEF differently than they do HFrEF.³³ Although β -blockers, ACEIs, and cardiac resynchronization are effective in HFrEF, in HFpEF these interventions do not lead to statistically significant improvements in morbidity and to date no therapies have been shown to improve mortality in HFpEF. Patients with HFpEF have no or minimal left ventricular dilatation, yet therapies that improve mortality in HFrEF also reverse its associated left ventricular dilatation. The 2013 ACCF/AHA Guideline for the Management of Heart recommended several approaches to manage HFpEF that remained largely unchanged in the 2017 update^{3,4}:

- Control blood pressure
- Use diuretics to relieve symptoms due to volume overload
- Manage atrial fibrillation according to published guidelines
- Using ACEIs, ARBs, and β -blockers is reasonable to control blood pressure
- Aldosterone antagonists can be considered to reduce hospitalizations in patients with an EF \geq 45%, elevated BNP levels, or HF admission within a year
- The use of ARBs might be considered to reduce hospitalizations

The 2017 Focused Update included an update to only one treatment recommendation: the use of aldosterone antagonists. The Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) trial initially showed that spironolactone did not reduce the composite end point of CV death, aborted cardiac arrest, or hospitalization for the management of HF at its conclusion and initial publication.³⁴ However, the investigators found considerable regional variability among the trial participants. Therefore,

they conducted a post hoc analysis and found a 4-fold difference in the incidence of the primary end point in the Americas (HR, 0.83) when compared with Russia/Georgia (HR, 1.10), which led to the guideline change listed above.^{3,4}

In February 2021, the FDA approved an expanded indication for sacubitril/valsartan.²¹ This was due to the findings of the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial. PARAGON-HF was a randomized, double-blind, active-comparator trial. This trial enrolled 4822 patients aged 50 years or older with symptomatic HF, an EF at or exceeding 45% in the past 6 months, elevated natriuretic peptides, evidence of structural heart disease, and background diuretic therapy. The investigators randomized participants to sacubitril/valsartan titrated to a target dose of 97/103 mg twice daily or valsartan titrated to a target dose of 160 mg twice daily. The primary outcome was a composite of total HF hospitalizations and CV death over roughly 3 years. Within the sacubitril/valsartan group, 894 events occurred; 1009 events occurred within the valsartan group (rate ratio, 0.87; 95% CI, 0.75-1.01; $P = .06$). Therefore, sacubitril/valsartan did not significantly lower the incidence of the primary end point. However, among the subgroup of patients with an EF between 45% and 57%, there was a significant improvement in the primary end point (rate ratio, 0.78; CI, 0.64-0.95), which led the FDA to approve the expanded indication.³⁵

To further evaluate the overall efficacy of sacubitril/valsartan in relationship to a patient's underlying LVEF, Solomon et al conducted a pooled analysis of patients enrolled within the PARADIGM-HF and PARAGON-HF trials. Patients were divided into groups by LVEF less than or equal to 22.5%, greater than 22.5% to 32.5%, greater than 32.5% to 42.5%, greater than 42.5% to 52.5%, greater than 52.5% to 62.5%, and greater than 62.5% to determine if there were any differences in event rates for first HF hospitalization or CV death, HF hospitalization, CV death, noncardiovascular death, and all-cause mortality. The investigators found variability in the event rates among patients in the prespecified LVEF groups treated with sacubitril/valsartan compared with an ACEI or ARB. The patients with the lowest LVEFs had greatest reduction in clinical end points (LVEF <42.5%). However, all end points failed to meet statistical significance once the LVEF was above or at 42.5%. This was most consistent in the primary composite end point of first hospitalization and CV death (LVEF \leq 22.5%: HR, 0.77; 95% CI, 0.63-0.94; $P = .012$; LVEF \geq 22.5% to 32.5%: HR, 0.81; 95% CI, 0.71-0.92; $P = .001$; LVEF >32.5% to 42.5%: HR, 0.81; 95% CI, 0.69-0.94; $P = .005$). This analysis showed the benefits of sacubitril/valsartan when compared with ACEIs or ARBs varied by LVEF, but that the benefits did occur in patients with HFmrEF.³⁶

The labeling for sacubitril/valsartan now indicates it can be used to reduce the risk of CV death and HF hospitalization in adult patients with chronic HF. It acknowledges that patients with LVEF

below normal have benefited most. This expands the population of patients with HF to include some whose EF is preserved. The labeling also states LVEF is a variable measure and clinical judgment should be used in deciding whom to treat.²¹

Reaching Beyond Standard of Care

With so many medications, cardiac devices, surgical options, and lifestyle adaptations, patient-centered HF care is complicated. Educating, monitoring, and engaging patients who have HF takes a village of healthcare providers, many of whom are specialists. The average patient's advancing age and comorbid cardiac and noncardiac conditions also pose problems (more than half of Medicare beneficiaries with HF have 4 or more noncardiovascular comorbidities and more than 25% have 6 or more).³⁷ Finding approaches that are effective and, more importantly, able to be tolerated or lack drug interactions with patients' critical medications requires a skilled medical team. In addition, care delivery inefficiencies and misunderstandings further increase risk for suboptimal care.³

Streamlined transitions of care have been challenging for many facilities. One innovative program developed to improve transitions and 30-day readmission rates engaged a transitions-of-care pharmacist, community paramedics, and advanced care practitioners.³⁸ Because patients with HF use emergency department services frequently, community paramedics were assigned to make home visits; during those visits they conducted physical assessments, provided disease and medication education, and administered in-home IV medication. Paramedics worked closely with the transitions-of-care pharmacist and advanced care practitioners. Over 7 months, the readmission rate for 86 participants enrolled in this HF collaborative care study was 10.5%. In comparison, among 596 discharged patients with HF who received usual care in the same period, 23.5% were readmitted to the hospital.³⁸

This study, although small, demonstrates principles promulgated in the 2021 ECDP.³ The HF team needs considerable and overlapping expertise in diagnosis, treatment (with an emphasis on titration and adherence), and patient education. They need to be knowledgeable about HF's psychosocial impact, palliative care, and comorbid conditions. Beyond these primarily clinical skills, they need reliable inpatient and outpatient electronic medical records that communicate with each other; reliable, cost-effective electronic devices, wearable activity monitors, and secure mobile technologies.³

Investigational Approaches, Emerging Therapies Cardiac Myosin Activator

Medications that increase cardiac contractility in HF have tended to have mechanism-related AE profiles. Omecamtiv mecarbil (OM) is a first-in-class cardiac myosin activator. It increases cardiac contractility by binding to the catalytic S1 domain of cardiac myosin. It has

reduced heart rate, peripheral vascular resistance, mean left arterial pressure, and left ventricular end-diastolic pressure in animal models. Additionally, preclinical and clinical studies suggest OM may improve cardiac output and stroke volume, decrease ventricular wall stress, reverse ventricular remodeling, promote sympathetic withdrawal, and initiate systolic wall thickening. Three trials have evaluated OM's tolerability, kinetics, and efficacy in the management of HF.³⁹⁻⁴²

The Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF)⁴⁰ is a phase 3, international, multicenter, randomized, double-blind, placebo-controlled, event-driven CV outcomes study that enrolled 8256 patients. Eligible patients with chronic HFrEF symptoms aged 18 to 85 years were either hospitalized for HF, or had an urgent medical visit for HF (urgent clinic visit, emergency department visit, or hospitalization) within 12 months of screening. Patients were randomly assigned to receive OM twice daily or placebo. At a median of 21.8 months, CV death or HF event (the primary outcome) occurred in 37% of the OM-treated patients and in 39.1% of placebo-treated patients (HR, 0.92; 95% CI, 0.86-0.99; $P = .03$). OM did not produce a significant effect on CV death (HR, 1.01; 95% CI, 0.92-1.11), first hospitalization for HF (HR, 0.95; 95% CI, 0.87-1.03), or death from any cause (HR, 1.00; 95% CI, 0.92-1.09).⁴⁰

Emerging Aldosterone Antagonists

Aldosterone antagonists have been associated with several treatment-limiting AEs. Aldosterone increases water retention and potassium reabsorption and induces proinflammatory activity, creating progressive fibrotic damage in the heart and kidney. As noted above, aldosterone receptor blockers can slow some components of HF progression. Hyperkalemia, however, is common. Investigators are working on a new generation of nonsteroidal mineralocorticoid receptor antagonists that might reduce the potential for hyperkalemia.^{43,44} Apararenone, esaxerenone, and finerenone are currently in clinical trials.^{43,44}

Dual SGLT1/SGLT2 Inhibitor

The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial recently evaluated sotagliflozin, an oral SGLT1/SGLT2 inhibitor, for use in patients with diabetes with recent worsening HF.⁴⁵ Inhibiting SGLT2 diminishes renal glucose reabsorption, while inhibiting SGLT1 impairs glucose reabsorption within the gastrointestinal tract. SOLOIST-WHF was designed to determine if an SGLT1/SGLT2 inhibitor would reduce the risk of CV death, HF hospitalization, or urgent clinic visits for HF in patients with type 2 diabetes and recent worsening HFrEF or HFpEF when given shortly after an acute HF exacerbation. This multicenter, double-blind trial enrolled 1222 patients with diabetes who were recently hospitalized for worsening

HF. Patients received sotagliflozin 200 mg daily (titrated to 400 mg daily if tolerated) or placebo and were followed for roughly 9 months. The primary end point occurred in 51% of patients on sotagliflozin and 76.3% of patients taking placebo (HR, 0.67; 95% CI, 0.52-0.85; $P < .001$). CV death was not statistically significantly different between arms (10.6% vs 12.5%; HR, 0.84; 95% CI, 0.58-1.22). The trial's results were consistent across subgroups including patients with HFrEF or HFpEF. However, the trial closed early and was not powered to determine if these benefits would occur in a larger study population. Nonetheless, the SOLOIST-WHF trial has opened the door for further study of SGLT inhibitors in patients with HFpEF.⁴⁵ However, the FDA refused to approve a New Drug Application for sotagliflozin on March 3, 2021, for the indication as an adjunct therapy in type 1 diabetes, which was submitted by Sanofi in partnership with Lexicon before Sanofi left the partnership. Therefore, sotagliflozin faces additional regulatory hurdles if it is to be eventually utilized in the management of HF.⁴⁶

Conclusions

The changing demographics of patients hospitalized with HF and the disease's increasing prevalence creates a sense of urgency to find new and better treatment approaches. Recent research and FDA approvals suggest that pharmacists and managed care administrators need to examine their protocols and prior authorization processes to ensure that the care they provide is in keeping with current evidence and guideline recommendations.

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Funding source: This activity is supported by an educational grant from Merck Sharp & Dohme Corp.

Author disclosure: Dr Betz has no relevant financial relationships with commercial interests to disclose.

Author information: Acquisition, analysis, and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of manuscript.

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Heart Failure Population Health Considerations

Jeenal Patel, PharmD, BCGP

Economic Burden

The burden of heart failure (HF) in the United States is considerable. In 2012, total costs for HF were estimated to be \$30.7 billion, with two-thirds attributed to direct medical costs.¹ Without improvements to the cost of care by the year 2030, costs are predicted to reach \$69.8 billion (127% increase). This equates to approximately \$244 for each US adult.¹ This projected increase is due to an aging population and epidemiologic factors such as obesity, hypertension, diabetes mellitus, and coronary artery disease.² In addition to the overall rise in number of HF cases, the complexity of the disease appears to be increasing as more comorbidities generally lead to more clinical events and hospitalizations for both HF and other causes.³

Incidence of HF increases with age and is associated with poor mortality, as older adults diagnosed with HF have a 5-year mortality approaching 50%.⁴ In 2014, HF was the primary cause of 1.1 million emergency department (ED) visits, 1 million hospitalizations, and 84,000 deaths.⁴ HF was a comorbidity or contributing cause in an additional 4.1 million ED visits, 3.4 million hospitalizations, and 231,000 deaths and was associated with significantly higher costs compared with patients without HF as a listed comorbidity.⁴ In 2014, the estimated mean cost of HF hospitalizations was \$11,552, with a total estimated cost of more than \$11 billion.⁴ Although HF greatly affects older adults, the costs are also significant when treating HF comorbidities and HF exacerbations in younger populations, totaling \$1 billion in inpatient costs, which may be rising.¹

A 2020 systematic review across HF literature in the United States between 2014 and 2020 aimed to assess the quality of published evidence and provide a narrative synthesis of current data. The review found that the median cost for HF-specific hospitalizations was \$13,418 (interquartile limit [IQL], \$11,125-\$15,667) per patient. Patients with comorbidities had a slightly higher cost at \$14,015 (IQL, \$11,769-\$20,373).⁵ The 30-day post-discharge cost following a worsening HF admission was estimated at \$6283 per patient. A patient readmitted over a 30-day period following an HF hospitalization showed an estimated cost of \$15,732 per patient in the same hospital and \$25,879 per patient at a different hospital. Average

ABSTRACT

The United States has an increasing number of patients with heart failure (HF) who experience significant disease burden as well as contribute to high economic healthcare costs and usage of healthcare resources. HF costs are currently estimated at \$30.7 billion. If no improvements are made to current treatment outcomes, it is expected to grow to \$69.8 billion by the year 2030. Hospital admissions account for the driving factor of direct medical costs. There has been increased focus on decreasing HF-related hospital readmission rates in the United States for the past decade; however, few interventions have positively affected hospital readmission rates. Some transitional care programs have been successful at positively affecting readmissions, though not all programs have demonstrated improvement of end points. These mixed program outcomes show the importance of evaluating HF-related transitional care program components for future directions. Newly approved treatments for HF with preserved ejection fraction may improve clinical outcomes for these patients. Pharmacists and physicians can help improve access to HF medications by assisting patients on how to navigate manufacturer assistance programs, submitting complete and well-supported prior authorization forms when needed, and encouraging the use of pharmacy price matching and price checkers.

Am J Manag Care. 2021;27:S191-S195

For author information and disclosures, see end of text.

annual outpatient healthcare costs were estimated at \$8487 for medical/surgical, \$2178 for diagnostic costs, \$550 for behavior costs, \$2904 for pharmacy costs, and \$973 for other costs. The median cost per ED visit was \$1441 (IQL, \$829-\$1933). The annual estimated cost for patients with home healthcare was \$2227 per patient per year. Based on median data, HF hospitalizations contributed to 65% of all medical HF costs over a 1-year treatment period post hospitalization.⁵

In addition to direct medical costs, it is important to evaluate the social care costs. Absenteeism, presenteeism, and informal care are all indirect costs from the physical and social limitations experienced by HF patients. These factors present a significant disease burden for patients and their families. The total loss of earnings attributed to HF morbidity and mortality is estimated at \$12.4 billion for 2020 in the United States. One-third of patients also often need informal care of approximately 45 hours per week. The estimated annual cost of informal care is \$836 per patient. This systematic review highlights the disease burden and high healthcare usage of patients with HF.⁵

In general, the overall costs associated with heart failure with reduced ejection fraction (HFrEF) is well known compared with patients diagnosed with heart failure with preserved ejection fraction (HFpEF). A study in Germany and Australia focused on assessing total costs in a young cohort of patients with HFpEF including medications, number of primary care and specialist visits, and hospitalizations. This analysis suggested that economic burden is typically lower than anticipated in the HFpEF population because the prevention and treatment of comorbidities early on can reduce costs.⁶

Quality Measures

HF is a progressive condition with poor outcomes leading to at least 1 million hospitalizations every year, with more than half of those patients being readmitted and 30% dying within 1 year.⁷ A recent cohort suggests hospitalizations may be on the rise. A 2021 analysis evaluated hospital admissions between January 2010 and December 2017 and found the rate of overall hospitalizations, unique patient hospitalizations, and post-discharge HF readmissions declined between 2010 and 2014 but showed an increase between 2014 and 2017.⁸ As hospitalizations are a major contributor to increased healthcare usage and poorer clinical outcomes, this recent finding supports the continued need to evaluate which HF therapies and treatment strategies have demonstrated improved quality measures.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were previously the mainstays of therapy due to their improved clinical outcomes until 2015, when a first-in-class therapy was introduced to the market.² Sacubitril/valsartan contains a neprilysin inhibitor and ARB and is used in patients with New York Heart Association (NYHA) functional class II to IV symptoms.² Sacubitril/valsartan trials have shown its ability

to reduce risk of cardiovascular death and first HF hospitalizations among patients with HFrEF by 20% compared with traditional ACEI therapy with enalapril.²

To evaluate the real-world efficacy outside of a traditional trial setting, a 2019 study aimed to compare hospitalization and healthcare costs among stable patients with HFrEF treated with sacubitril/valsartan versus traditional ACEI or ARB therapy in clinical practice. This retrospective study was conducted using claims data from October 1, 2014 to September 30, 2016, from a large population representative database containing de-identified medical and pharmacy claims data and linked enrollment information for individuals enrolled in US commercial and Medicare Advantage health plans. This analysis found that the mean standard deviation (SD) number of post-index per-patient per-month (PPPM) hospitalizations was lower in the sacubitril/valsartan versus the ACEI/ARB cohort for HF hospitalizations (0.01 [0.06] vs 0.03 [0.10]; $P = .003$) and all-cause hospitalizations (0.05 [0.11] vs 0.11 [0.20]; $P < .001$). In addition to lower hospitalizations, the sacubitril/valsartan was also associated with lower hospital costs. Patients treated with ACEI/ARB versus sacubitril/valsartan had mean (SD) PPPM costs that were more than 4 times higher for HF hospitalization (\$1122 [\$7290] vs \$248 [\$1588]; $P = .048$) and more than 3 times higher for all-cause hospitalization (\$2770 [\$9189] vs \$810 [\$2921]; $P < .001$).²

Patients who decline and develop a worsening HF event (WHFE), such as escalating HF signs or symptoms requiring intravenous diuretic therapy in the outpatient setting or hospitalization, have higher rates of recurrent HF hospitalizations and mortality.⁷ A 2020 study evaluated the healthcare resource usage and healthcare costs in patients with chronic HFrEF following a WHFE versus those with a chronic HFrEF who remain stable. The retrospective study used claims from IBM MarketScan Commercial and Medicare Supplemental databases from January 1, 2015 to December 31, 2018. An HFrEF index date was identified and evaluated patients 12 months before this date and continued to follow them 12 months after to identify WHFEs based on the presence of HF-related hospitalization and/or intravenous diuretic use. The study found that the adjusted mean total HF-related cost of care PPPM during the worsening assessment period was $\$383 \pm \1064 for patients with stable chronic HFrEF and $\$3647 \pm \7636 for patients with chronic HFrEF following a WHFE ($P < .0001$). The mean total all-cause cost of care PPPM was $\$2195 \pm \4572 for patients with stable chronic HFrEF and $\$8657 \pm \$13,150$ for patients with chronic HFrEF following a WHFE ($P < .0001$). Hospitalizations were the primary driver in all-cause costs for patients with chronic HFrEF following a WHFE, while the main driver in all-cause costs was outpatient visits for those patients with stable chronic HFrEF.⁷ This study highlights the need to improve outcomes of patient with chronic HFrEF following a WHFE.

In an effort to address the lack of studies demonstrating improvement in mortality in patients with HFpEF, a 2018 systematic review

and meta-analysis aimed to review the clinical trials and identify treatment effects on mortality, HF hospitalization, functional status, and biomarkers in this patient population.⁹ The review included 25 randomized controlled trials between January 1996 and May 2016 and comprised data for 18,101 patients. It found that all-cause mortality was reduced with β -blocker therapy compared with placebo (RR, 0.78; 95% CI, 0.65-0.94; $P = .008$). No effect was demonstrated with ACEIs, aldosterone receptor blockers, mineralocorticoid receptor antagonists, or other drug classes when compared with placebo. No drug class demonstrated a reduction in HF hospitalizations when compared with placebo.⁹ This review reveals the difference of treatment efficacies among patients with HF_{rEF} and HF_{pEF}.

Readmissions

HF is the leading cause of hospitalizations among older adults, and Medicare beneficiaries with HF have the highest readmission rate of any condition.⁴ Approximately one-quarter of patients hospitalized with HF are readmitted within 30 days of discharge, and mortality rates of those patients within the first year after hospital discharge approach 30%.¹⁰ With a worldwide prevalence of 26 million patients with HF, there is a critical need for global attention, research, and quality improvement initiatives to improve the quality of care and clinical outcomes for the HF population.¹⁰ In response, the United States focused on efforts to reduce preventable readmissions. Hospital HF readmissions are a priority quality measure because reimbursement policies such as the Hospital Readmissions Reduction Program were implemented to incentivize hospitals to reduce readmission rates by decreasing Medicare reimbursement for hospitals with higher than predicted readmissions rates.¹¹ Despite this increased focus on readmissions and resulting reimbursement incentive, a 2016 study that evaluated HF readmissions found no statistically significant change in 30-day mortality rates between 2009 (7.8%) and 2012 (7.6%; $P = .71$).¹¹

To combat the lack of successful interventions, a 2018 observational qualitative study aimed to uncover the reason for poor HF readmission rates from the patient perspective. Understanding the patient and caregiver challenges to HF home management and perceived reasons for readmissions may provide insight to address these gaps in care. The study included patients with HF from 2 hospitals and included those hospitalized for HF at least twice within 30 days and those who had been recently discharged after their first HF admission. The patients participated in open-ended, semi-structured interviews. Two major themes were discovered, the home management as a struggle between adherence and adaptation, and hospital readmission as a rational choice in response to distressing symptoms. Discharge instructions were provided to patients, but they reported adapting, rather than adhering, to the recommendations. One reason for adapting included uncertainty regarding the recommendations for diet, fluid management, and

physical activity and patients reported they would have benefited from more knowledge about the disease process and anticipatory guidance. Some patients reported comorbidities contributed an additional obstacle by difficulties consolidating their medications and different diet instructions provided by different providers. Socioeconomic factors also contributed as patients with limited resources made medication decisions based on what medications or food they were able to afford. Some patients also reported feelings of hopelessness from perceived lack of progress despite medication adherence. These cyclic feelings of despair affected their home management by decreased adherence, worsening symptoms, and intensification of negative emotions. Patients also reported frustration with their limitations and restrictions including dependence on others to perform activities of daily living, difficulty leaving their homes due to decreased physical capacity, or frequent urination caused by diuretics. The other main theme of readmission as a rationale choice was often a joint decision made between patients and their families. This was mainly due to difficulty in distinguishing symptoms that were truly life-threatening with those that could be safely managed at home. Readmission was regarded as the safest choice and not viewed as a negative action.¹² This study helps to identify educational gaps and reveals the need for better care-coordination to truly impact hospital readmission rates and resulting clinical outcomes.

Additional avenues are being explored and implemented including care coordination and transition programs, such as those that facilitate the hospital-to-home transition and provide in-home aftercare.⁴ These referral programs have been associated with slightly lower (1%) relative 30-day risk adjustment readmission rates.¹¹ A recent successful transitional program was implemented at the Phoenix VA Medical Center. The multidisciplinary program was implemented to encourage early post-discharge hospital follow-up in patients with HF and included new clinical slots, predischARGE nurse visits that provided blood pressure cuff and scale, and cardiologist supervision. To determine success of the program, they compared a proportion of patients in both groups who were scheduled for and completed a cardiology appointment within 7 days after hospitalization. A Cox model evaluated effectiveness during the intervention period of 30-day composite outcomes including all-cause ED visits, all-cause hospitalizations, or death. Data for 261 patients were analyzed. The study found that after adjusting for significant clinical predictors (non-White ethnicity, left ventricular ejection fraction $\leq 40\%$, hemoglobin, systolic blood pressure, BNP [log]; $P < .1$ with outcome), the postintervention period was associated with a reduced hazard of the 30-day composite end point (HR, 0.59; 95% CI, 0.37-0.96; $P = .04$).¹³ They also found that the program was associated with a 3.3 times higher rate of referral for 7-day HF follow-up as well as observed a 41% lower risk of ED visits, rehospitalizations, or death during the intervention period.¹³

It is important to evaluate the individual measures of transitional care programs as not all programs have been deemed successful. A 2020 retrospective cohort study examined the association of individual HF-transitional care program components and their bundle with the primary outcomes of all-cause 30-day inpatient or observation stay readmission.¹⁴ It reviewed inpatient encounters for HF at 13 Kaiser Permanente Southern California hospitals between January 1, 2013 and October 31, 2018, who were followed up from discharge until 30 days, readmission, or death. The program included a home health visit or telehealth visit from a registered nurse within 2 days of hospital discharge, an HF care-manager call within 7 days, and a clinic visit with a physician or nurse practitioner within 7 days. They found the 30-day readmission rate to be 18.1%. Both the home health visit within 2 days of discharge (HR, 1.03; 95% CI, 0.96-1.10) and the 7-day HF case-manager call (HR, 1.08; 95% CI, 0.99-1.18) were not associated with a lower rate of admission when compared with no call or visit. However, the completion of a 7-day clinic visit was found to be associated with a lower readmission rate (HR, 0.88; 95% CI, 0.81-0.94) when compared with no clinic visit. There were no synergistic effects of all 3 components compared with a clinic visit alone (HR, 1.05; 95% CI, 0.87-1.28).¹⁴ This study demonstrates the need to continually evaluate what components make a successful transitional care program to improve overall quality of care and positively impact HF-related hospital readmissions for future endeavors.

Evaluating Place of Therapy for New Agents for Heart Failure and Patient Access

One recent major breakthrough in the treatment of HF is that the 2021 update to the 2017 Expert Consensus Decision Pathway ACC Guidelines now recommend therapy with an angiotensin receptor-neprilysin inhibitor (ARNI) even for patients who have not been previously treated with an ACEI/ARB.¹⁵ These recommendations are due to favorable study results in patients with newly diagnosed HF who were initially started on ARNI therapy experiencing a greater reduction in natriuretic peptide concentration, comparable safety data, and significant improvements in early clinical outcomes when compared with enalapril.¹⁵ Another inclusion to the recent ACC update was recognizing the approval of a sodium-glucose cotransporter-2 (SGLT2) inhibitor and adding the class to the armamentarium of medications available for the treatment of patients with HF_rEF. Dapagliflozin has demonstrated a reduction in cardiovascular death and HF hospitalization in patients with and without type 2 diabetes. Empagliflozin also demonstrated a reduction in HF hospitalization/cardiovascular death in patients with HF_rEF with and without diabetes. In recognition of these advances, the guidelines recognize a beneficial class effect in patients with HF_rEF. The updated treatment algorithm recommends SGLT2 inhibitors as add-on therapy for patients already on an ARNI/ACEI/

ARB, an evidence-based β -blocker, and as-needed diuretic agents for patients meeting estimated glomerular filtration rate criteria with NYHA class II to IV.¹⁵

In addition to the change in treatment recommendations are suggestions for managing costs and access to HF medications. Medications are the second most important cost for patients with HF after hospital costs, accounting for 15.6% of direct costs.¹⁵ The guidelines recommend a variety of cost containment measures to support patients with this significant financial burden. Prescribers should be aware of patient insurance and potential limitations when determining the most appropriate medication therapies. Using generic medications whenever possible is one strategy for reducing costs. Common generic HF drugs include digoxin, β -blockers, ACE inhibitors, and ARBs. Patients may be incentivized to “shop around” for the best priced generic medications; however, this could have negative health implications when a single pharmacy is not overseeing a patient’s medications to be able to account for potential drug–drug and drug–disease interactions. Pharmacists, social workers, and physicians should work together to identify co-pay assistance programs, encourage pharmacy price matching, and using online price checkers to encourage patients to use a single pharmacy and identify which pharmacy offers the best pricing for patients’ medications.¹⁵

The ACC 2021 update also addresses medication access to new HF therapies. Newer therapies for HF_rEF are costly and often entail higher monthly co-payments and more steps may be involved in the process of obtaining them. For example, prior authorizations may be required that could be perceived as a potential barrier of initiating a therapy the prescriber feels most appropriate for a patient. Providing all the necessary information that supports the use of the requested medication in the selected patient and including clinical evidence and relevant patient-specific factors will reduce the risk of multiple correspondences with the payer that will delay medication initiation. Patient assistance programs are also available for newer agents. Pharmacists can help patients navigate through the usage management process and manufacturer assistance programs to help improve access to these therapies. If a patient has no income to provide as a requirement for assistance programs, many agencies accept a signed letter from the clinician indicating the patient has no known income, though this option is often not clearly apparent on manufacturer websites or materials.¹⁵

In February 2021, the FDA approved sacubitril/valsartan for a new indication to treat patients with HF_pEF. This marks the first approved therapy for this population. Previous therapy had been aimed at symptom management and treatment of comorbidities. This approval comes from the FDA’s Cardiovascular and Renal Drugs Advisory Committee after reviewing results from the PARAGON-HF trial where sacubitril/valsartan fell just short of meeting the primary end point. The committee found it was worthy of some indication

based on trial results.¹⁶ It is still to be determined what impact this will have on clinical practice as this is not part of the current guidelines; however, this approval does have promise if additional studies demonstrate improvement in quality measures and similar cost-effectiveness as demonstrated in patients with HFREF.

Additionally, in January 2021, the FDA approved vericiguat, a first-in-class soluble guanylate cyclase stimulator, for HFREF. A phase 3 trial included 5050 patients with NYHA class II, III, or IV with an ejection fraction of less than 45%. Patients were assigned to placebo or vericiguat treatment groups and followed for the primary outcome of composite death from cardiovascular causes or first hospitalization for HF. For the median follow-up period of 10.8 months, death from cardiovascular causes or first hospitalization for HF occurred in 897 patients (35.5%) in the vericiguat group versus 972 patients (38.5%) in the placebo group (HR, 0.90; 95% CI, 0.82-0.98; $P = .02$).¹⁷ This emerging treatment will add an additional pathway to consider when evaluating treatment options for patients. The growing number of target and therapy lists may add complication to HF treatment management for both patients and care teams. It is important for healthcare decision makers to continue to make guideline-directed medical therapy the foundation of HF care, and the therapy with the highest expected benefit, based on large randomized trials, shall be prioritized for HFREF.¹⁵ This includes ARNIs, evidence-based β -blockers, aldosterone antagonists, and SGLT2 inhibitors for all populations. Additional first-line therapies may also be considered such as hydralazine/isosorbide dinitrate for self-identified African Americans and ivabradine as a second-line medication for select populations where an individual has a resting heart rate greater than or equal to 70 beats per minute in sinus rhythm despite maximally tolerated β -blocker therapy.¹⁵

Conclusions

HF contributes a significant disease and economic burden to the United States. Its prevalence is on the rise with the growing aging population. These patients often have multiple comorbidities that contribute to treatment complexity and create obstacles in patient home health management. Even with a focus on readmissions and implementation of programs to incentivize hospitals to meet 30-day readmission benchmarks, hospitals are still challenged at developing solutions to effectively target hospital readmissions and improve clinical outcomes. Some transitional care programs have shown to be successful, while others have not, which demonstrate the continued need to identify the most impactful components of programs for program replication. In 2015 the introduction of sacubitril/valsartan changed the current landscape of disease treatment

and has shown favorable disease and economic outcomes. However, more novel therapies are needed in order to continue to impact the treatment landscape of HF and change the current trajectory of HF prevalence and growth trends in the United States and globally. ■

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Funding source: This activity is supported by an educational grant from Merck Sharp & Dohme Corp.

Author disclosure: Dr Patel has no relevant financial relationships with commercial interests to disclose.

Author information: Concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; provision of study materials; and final approval of manuscript.

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Medical writing and editorial support provided by: Jenna Wood, PharmD

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Discerning Heart Failure: New Treatment Approaches for Preserved or Reduced Ejection Fraction Subtypes

Release date: May 24, 2021

Expiration date: June 15, 2022

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Sample of Online Posttest

Choose the best answer for each of the following:

1. In terms of hospitalizations for heart failure (HF), what is the estimated ratio of admission due to HF with preserved ejection fraction (HFpEF) to HF with reduced ejection fraction (HFrEF)?
 - A. 40:60
 - B. 50:50
 - C. 70:30
 - D. 80:20
2. In which of the following ways are HFrEF and HFpEF similar?
 - A. Patients who engage in physical activity lower their risk for HFpEF and HFrEF.
 - B. Patients with HFpEF and HFrEF are at equal risk for noncardiovascular death.
 - C. Patients with HFpEF and HFrEF are at risk for accelerated cognitive decline.
 - D. Patients with HFpEF and HFrEF respond well to ivabradine and phosphodiesterase-5 inhibitors.
3. Which statement accurately describes the recent labeling change for sacubitril/valsartan?
 - A. This drug increases cardiac contractility by binding to the catalytic S1 domain of cardiac myosin.
 - B. Patients must now have estimated glomerular filtration rate (eGFR) above 30 mL/min, creatinine level less than 2.5 mg/dL, and potassium level less than 5 mEq/L.
 - C. The labeling removes previous language that indicated concurrent administration of an angiotensin-converting enzyme inhibitor (ACEI) is no longer contraindicated.
 - D. Left ventricular ejection fraction (LVEF) is a variable measure and clinicians should use clinical judgment when deciding whom to treat.
4. In which patient with HFpEF would it be UNSAFE to add spironolactone to their HF treatment regimen?
 - A. A woman with a history of angioedema
 - B. A man with an eGFR of 25 mL/min
 - C. A woman with a serum creatinine of 1.5 mg/dL
 - D. A man with a serum potassium of 4.5 mEq/dL
5. TB is a 68-year-old White man with a history of ischemic cardiomyopathy who presents to clinic with New York Heart Association (NYHA) class II symptoms. He has an allergy to digoxin, which manifested as a rash, and a past medical history of HFrEF (for which he was hospitalized 1 month ago), hypertension, and non-ST segment elevation myocardial infarction. His vitals include BP 118/75 mm Hg, HR 68 bpm, RR 16, T_{max} 98.5, height 5'9", and weight 225 lb. His weight has not changed since hospitalization and his physical exam does not reveal any sign or symptoms of edema. TB's most recent echocardiogram showed an LVEF of 30% and today's labs include an NT-proBNP of 1100 pg/mL. His current oral medication regimen includes sacubitril/valsartan 97 mg/103 mg twice daily, carvedilol 50 mg twice daily, furosemide 20 mg daily, spironolactone 25 mg daily, dapagliflozin 10 mg daily, aspirin 81 mg daily, and atorvastatin 80 mg daily. Which of the following would be most appropriate to add to TB's regimen to reduce his risk of subsequent HF hospitalizations?
 - A. Digoxin
 - B. Ivabradine
 - C. Hydralazine and isosorbide dinitrate
 - D. Vericiguat

6. Which statement is TRUE regarding HF prevalence trends and economic burden of disease in the United States?

- A. The development of new therapies for the treatment of HF has positively affected HF prevalence trends in most recent years, resulting in a downward trend in number of HF cases in the United States.
- B. The greatest contributors to the economic burden of HF are direct medical costs, accounting for two-thirds of overall costs.
- C. Pharmacy costs are the main driver of the economic burden of HF, which is estimated to account for 80% of overall costs.
- D. Absenteeism, presenteeism, and informal care are all direct costs from the physical and social limitations experienced by patients with HF.

7. Which statement is TRUE regarding currently approved treatment therapies for HF?

- A. Although sacubitril/valsartan has shown successful results in clinical trials leading to approval, it has not yet demonstrated real-world effectiveness in quality measures such as cardiovascular death or hospitalizations.
- B. Sacubitril/valsartan is only approved for patients with HF stages with reduced ejection fraction with NYHA functional classes II to IV.
- C. Sodium-glucose cotransporter-2 inhibitors have demonstrated reduction in HF hospitalizations and cardiovascular death in patients with HFrEF with and without diabetes. This class is now a guideline-recommended treatment for patients with HFrEF regardless of diabetes as a comorbid condition.
- D. Sacubitril/valsartan should be reserved for patients whose treatment has failed with an ACEI or angiotensin receptor blocker before initiation.

8. Which statement is TRUE regarding 30-day HF readmission rates?

- A. The implementation of incentivized Medicare reimbursement policies for hospitals based on HF readmission benchmarks has proven to be effective across the country at positively impacting readmission rates and clinical outcomes.
- B. Approximately 25% of patients hospitalized with HF are hospitalized within 30 days of discharge.
- C. Transitional care programs that provide care coordination and facilitate the hospital to home transition and provide in-home aftercare can be an effective tool at positively impacting admission rates; however, not all programs have demonstrated success and it is important to continually evaluate individualized components of successful programs.
- D. There are numerous reports that patients view readmission as a negative outcome and often report being too afraid to admit themselves into the hospital for lack of judgment from healthcare providers.

9. Which statement is true regarding healthcare resource utilization following a worsening HF event (WHFE)?

- A. All-cause costs are significantly greater for patients with HFrEF who experience a WHFE compared with patients with stable HFrEF.
- B. HF-related costs for patients with HFrEF who experience a WHFE are equal to the costs of patients with stable HFrEF.
- C. The main primary driver of all-cause costs in patients with HFrEF following a WHFE are outpatient visits.
- D. Patients with HFrEF who experience a WHFE have lower recurrent hospitalizations and mortality compared with patients with stable HFrEF.

10. Patient challenges to HF management and perceived reasons for readmission include which of the following?

- A. Centers for Medicare & Medicaid Services Hospital Readmissions Reduction Program guideline penalties
- B. Lack of access to medical and pharmacy claims data
- C. Socioeconomic factors such as limited resources and food affordability
- D. Lack of reimbursement incentive

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