

New Therapies for Heart Failure: A Managed Care Perspective

HIGHLIGHTS

- › Heart Failure With Reduced Ejection Fraction: Clinical and Economic Burden and Insights Into Current and Emerging Treatments
- › Heart Failure Without a Reduced Ejection Fraction
- › Defining a Path Toward Improved Heart Failure Care

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OVERVIEW

This supplement to *The American Journal of Managed Care*[®] includes 3 articles that examine the challenges and opportunities of treating heart failure (HF) from a managed care perspective and provide an overview of treatment approaches for HF with reduced ejection fraction and HF with preserved ejection fraction; it culminates in a discussion of ways to improve access to care for all patients with HF.

TABLE OF CONTENTS

Participating Faculty	S178
Introduction	
Addressing the Clinical and Economic Impact of Heart Failure	S179
Reports	
Heart Failure With Reduced Ejection Fraction: Clinical and Economic Burden and Insights into Current and Emerging Treatments	S180
<i>Sounok Sen, MD</i>	
Heart Failure Without a Reduced Ejection Fraction	S187
<i>Sant Kumar, MD; and Mitchell A. Psotka, MD, PhD</i>	
Defining a Path Toward Improved Heart Failure Care	S195
<i>Nihar R. Desai, MD, MPH; and Katherine A. A. Clark, MD, MBA</i>	

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Addressing the Clinical and Economic Impact of Heart Failure

Heart failure (HF) imposes one of the highest burdens of any medical condition in the United States.¹ It is a chronic condition affecting approximately 6 million adults in the United States, and it is associated with more than 83,000 deaths annually, according to data from 2015 to 2018.² Furthermore, the prevalence of HF is expected to rise to over 8 million (or 1 in 33) US adults by 2030, mirroring the aging population.^{2,3} Despite substantial recent advances in medical therapy for HF, associated morbidity remains high, and quality of life (QOL) of affected patients is poor.⁴ The clinical burden of HF is exacerbated by the occurrence of severe comorbid conditions (present in over 70% of patients) that are independently associated with increased risk of death, functional limitation, and QOL impairment.⁵ The 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America Guideline for the Management of Heart Failure reflects our improved understanding of HF pathogenesis, patient phenotypes, and use of effective therapies.⁶ Despite these advances, adoption of guideline-directed medical therapy (GDMT) remains suboptimal for several reasons (eg, insufficient uptake by health care providers) and/or patient-related issues (eg, medication adverse effects, low adherence to medications, socioeconomic factors).⁷⁻¹⁰ This supplement includes 3 articles that examine the challenges and opportunities of treating HF from a managed care perspective and provides an overview of treatment approaches for HF with reduced ejection fraction.¹¹⁻¹³ It ultimately culminates in a discussion of ways to improve access to care for all patients with HF. ■

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Heart Failure With Reduced Ejection Fraction: Clinical and Economic Burden and Insights Into Current and Emerging Treatments

Sounok Sen, MD

Introduction

Heart failure (HF) is defined as a clinical syndrome, although a lack of consensus around a clear definition has led to challenges in characterizing the disease within clinical practice and clinical research. At present, there remains substantial heterogeneity in the diagnostic criteria for HF, which may include metabolic, hemodynamic, and symptom-based parameters. Most HF trials include patients who are identified using a threshold of left ventricular ejection fraction (LVEF) or specific New York Heart Association (NYHA) functional class categories (classes I-IV indicating symptom severity).¹ However, the Heart Failure Society of America (HFSA) recently proposed a universal definition and classification of HF that is based on symptoms and/or signs resulting from a structural and/or functional cardiac abnormality and that is supported by elevated natriuretic peptide levels and/or evidence of pulmonary or systemic congestion (**Figure 1**).²

The latest joint guideline from the American College of Cardiology (ACC), American Heart Association (AHA), and HFSA for the management of HF gives treatment recommendations according to this modified version of the classic definition of HF.³ The new classification defines HF with reduced ejection fraction (HFrEF) as LVEF 40% or less, and patients with HF and an EF above 40% and below 50% are classified as having HF with mildly reduced EF.³ Patients with a previous diagnosis of HFrEF but with a follow-up LVEF of more than 40% are now described as having HF with improved EF. This change reflects the dynamic nature of HFrEF, where improvement or deterioration can occur over time.

HF imposes one of the highest disease burdens of any condition in the United States, with around 6.5 million Americans 20 years or older reported to be affected.⁴ This figure was calculated using data from 2011 to 2014, and it continues to grow, largely as a result of aging of the population. From 2012 to 2030, the prevalence of HF is projected to increase by 46% to more than 8 million people at least 18 years of age.⁴

Although the survival of patients with HF has improved in recent decades, 1-year mortality remains high at 29.6%.⁵ Similarly, data from the Atherosclerosis Risk in Communities study showed

ABSTRACT

Heart failure (HF) imposes a large and growing burden on the population, with a prevalence that is projected to increase to more than 8 million adults by 2030. The high risk of morbidity and mortality associated with HF is further exacerbated by the frequent presence of comorbidities. The coexistence of HF and comorbid conditions can result in emergency department visits and hospitalizations that not only affect patients and their families but also pose a growing economic burden on health care systems. The largest costs arise from hospitalization for HF, with outpatient care and associated medication costs comprising the second largest component. For patients with HF with reduced ejection fraction (HFrEF), defined as left ventricular ejection fraction of 40% or less, remarkable improvements in outcomes have been observed in recent decades due to the availability of disease-modifying therapies. However, the management of HFrEF remains suboptimal, with many patients either not receiving guideline-directed medical therapy (GDMT) or experiencing delays in receiving target doses. Since this can result in preventable hospitalizations and deaths, action is needed to ensure rapid initiation of GDMT. Optimal treatment can be hindered by such patient factors as the presence of comorbidities and socioeconomic barriers that include the cost of multiple treatments. Furthermore, poor treatment adherence is common among patients with HF. Measures aimed at tailoring therapies to individual patients and reducing medical costs are important to increase the uptake of and adherence to therapy and therefore improve clinical outcomes.

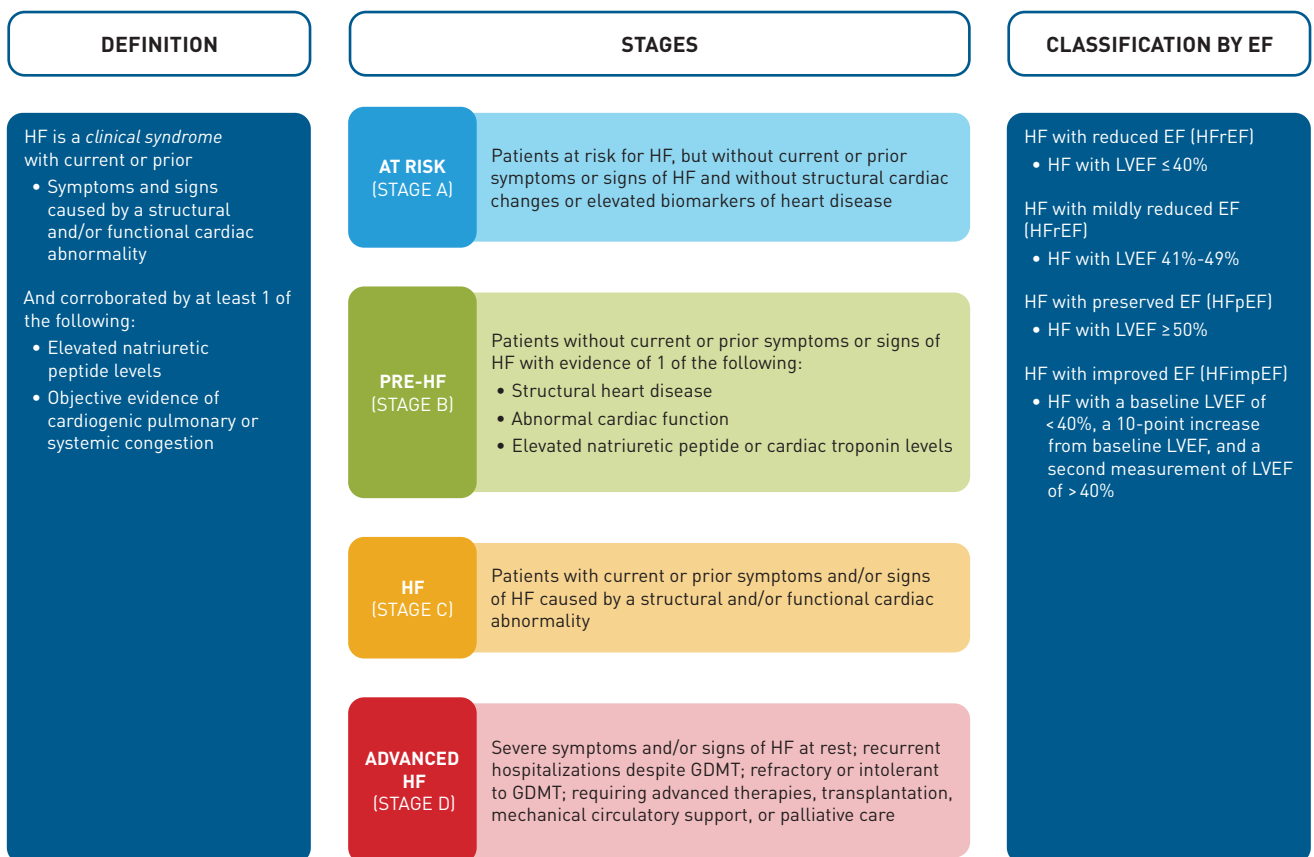
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A plain language summary of this article is available at
<https://www.ajmc.com/view/HF-NewTherapiesManagedCare-PLS>

TAKEAWAY POINTS

- › Heart failure (HF) imposes a large and growing economic burden on individuals and health care systems.
- › Frequent emergency department visits and hospitalizations account for the largest proportion of health care costs.
- › Current management is suboptimal, and many patients do not receive guideline-directed medical therapy. Adverse effects and costs of treatment can contribute to poor patient adherence.
- › Action is needed to improve access to effective therapies for HF to improve clinical outcomes and reduce hospitalizations.
- › Tailoring therapies to individual patients and reducing medical costs can help improve the medical management of HF so that wider society can benefit from recent advances in treatment.

FIGURE 1. Universal Definition and Classification of HF²

Language matters! The new universal definition offers opportunities for more precise communication and description with terms including **persistent HF** instead of "stable HF," and **HF in remission** rather than "recovered HF."

EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction.

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30-day, 1-year, and 5-year case fatality rates after hospitalization to be 10.4%, 22%, and 42.3%, respectively.⁶ The clinical burden of HF is further increased by the frequent presence of comorbid conditions, including hypertension, hyperlipidemia, cardiac arrhythmias, coronary artery disease, type 2 diabetes (T2D), chronic obstructive airway disease, mental depression, and chronic kidney disease.⁷ Over 70% of patients with HF have comorbid conditions that independently increase the risk of morbidity, reduce quality of life, and increase mortality.⁸ Furthermore, the coexistence of HF and comorbid conditions can result in emergency department visits and hospitalizations that not only have an impact on patients and their families but also on the health care system as a whole.

Economic Burden

HF imposes a large and growing economic burden on health care systems, mostly as a result of aging of the population.⁹ Associated total medical costs from 2012 to 2030 are projected to increase from \$21 billion to \$53 billion.¹⁰ The estimated annual health care costs for HF—which include direct and indirect costs—are expected to reach \$70 billion by 2030.¹⁰ The majority of these costs result from hospitalization for HF, which occurs frequently among affected patients.^{11,12} For each person with HF, the annual costs of care are estimated to be almost \$30,000, half of which is accounted for by the cost of inpatient care, and a further quarter due to outpatient care.⁹ Approximately 30% to 40% of individuals with HF have a history of hospitalization.^{10,11,13} Furthermore, a study of national trends for inpatient HF care reported that 1.2 million hospitalizations occurred among 924,000 patients in 2017.¹⁴ Following hospital admission, patients with HF are at increased risk of all-cause readmission, which is estimated to be around 20% within 30 days of initial hospital admission.^{15,16} Outpatient care, including medication costs, is the second largest component of health care expenditures in HF.¹² Other direct costs include rehabilitation, nursing care, and informal care.¹² Given the health care costs associated with HF, measures aimed at reducing symptoms and improving long-term outcomes for patients with HF may have important benefits for both the health care system and for individual patients.

Current Treatments

Over the past 2 decades, there have been remarkable improvements in outcomes for patients with HFrEF, largely due to changes in clinical practice based on the results of several landmark trials of treatments involving renin-angiotensin system blockade¹⁷⁻²³ and β -blockade.²⁴⁻²⁶ The use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or angiotensin-neprilysin inhibitors (ARNIs) is now recommended as first-line therapy for patients with HF and HFrEF (Figure 2).³ This recommendation is based on results from large-scale clinical trials of both ACEIs and

ARBs in the management of HFrEF, which demonstrated significant reductions in mortality and morbidity versus standard care.¹⁷⁻²³

For patients with chronic symptomatic HFrEF with NYHA class II or III symptoms who can tolerate ACEI or ARB therapy, current guidelines advise switching to treatment with an ARNI due to evidence of improved morbidity and mortality with their use.^{3,27} Additionally, an ARNI is recommended for de novo treatment of HFrEF based on evidence that use of these agents enhances health status and improves prognostic markers and LV remodeling parameters when compared with ACEI or ARB therapy.^{3,28} β -blockers are also recommended for patients with current or previous symptoms of HFrEF; specifically, use of bisoprolol, carvedilol, or sustained-release metoprolol succinate improves LVEF and clinical status and reduces HF symptoms, hospitalizations, and mortality.^{3,24-26} These agents are also associated with improvements in LVEF, reduction in HF symptoms, and improved clinical status.²⁹⁻³¹ Use of mineralocorticoid receptor antagonists (MRAs), members of the third group of agents recommended for patients with HFrEF, is associated with a reduced risk of mortality and hospitalizations.³²⁻³⁴ More recently, a fourth group of agents, the sodium-glucose cotransporter 2 inhibitors (SGLT2is), has produced benefits in patients with HF irrespective of the presence of T2D.^{35,36} The outcomes of 2 landmark trials (DAPA-HF [NCT03036124] and EMPEROR-Reduced [NCT03057977]) showed that inhibition of SGLT2 was associated with an approximate 25% reduction in a composite of cardiovascular death or HF hospitalization and an approximate 30% reduction in HF hospitalization when compared with placebo.³⁵⁻³⁷ Furthermore, the risk of a decline in renal function (as indicated by a composite of chronic dialysis, renal transplantation, or a $\geq 50\%$ sustained reduction of estimated glomerular filtration rate) was significantly reduced by SGLT2 inhibition.³⁷ Results of the DELIVER trial (NCT03619213) have shown that inhibition of SGLT2 can improve outcomes for patients with HF and mildly reduced or preserved EF (LVEF $> 40\%$) with fewer worsening HF events and cardiovascular deaths and a reduced symptom burden when compared with placebo.³⁸

Based on current evidence, clinical guidelines strongly recommend the use of these 4 groups of disease-modifying agents— β -blockers, ARNI, MRAs, and SGLT2is—as first-line treatments for HFrEF.³ Patients should receive multiple medications, as tolerated, to improve clinical outcomes. To ensure that patients are discharged on optimal therapy, guideline-directed medical therapy (GDMT) for HFrEF should be initiated during hospitalization following clinical stabilization.³

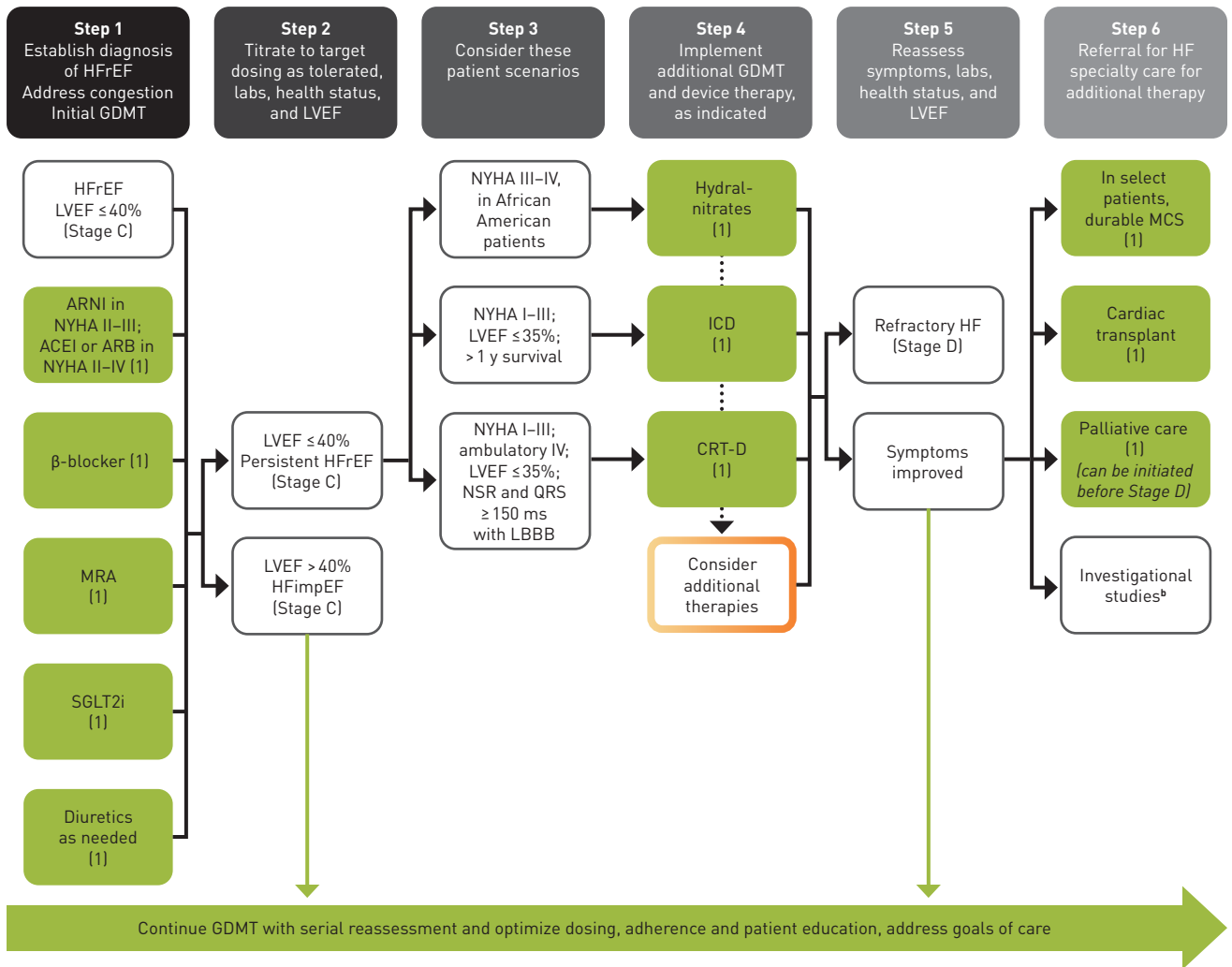
For patients with HFrEF (class III-IV) who self-identify as being Black, the addition of a combination of hydralazine and isosorbide dinitrate to optimal medical therapy is recommended.³ This guidance is based on the findings of 2 pivotal clinical trials showing that this combination was associated with reduced symptoms, morbidity, and mortality in Black patients.³⁹⁻⁴¹ However, the benefits observed in these

trials were higher than those typically achieved in clinical practice, and this regimen has not been widely used due to difficulties with treatment adherence, possibly related to treatment adverse effects.^{3,42}

Heart rate reduction with the selective sinus node *I_f* current inhibitor, ivabradine, is also recommended for the management of patients with HFrEF (NYHA class II-III).³ The latest ACC/AHA/HFSA

guideline recommends the addition of ivabradine to GDMT that includes a β -blocker at the maximum tolerated dose for patients with HFrEF (LVEF $\leq 35\%$) who are in sinus rhythm with evidence of an elevated resting heart rate (≥ 70 beats/min).³ For these individuals, ivabradine use reduces the risk of HF hospitalizations and cardiovascular death.⁴³

FIGURE 2. Treatment of Symptomatic or Advanced HFrEF (Stages C and D)^{3a}



ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; COR, class of recommendation; CRT-D, cardiac resynchronization therapy with defibrillation; GDMT, guideline-directed medical therapy; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hydral-nitrates, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

*Colors correspond to class of recommendation: green = class 1 (strong evidence for benefit); yellow = class 2b (moderate evidence for benefit); orange = class 2b (weak evidence for benefit). Treatment recommendations for patients with HFrEF are displayed. Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication. Medication doses should be increased to target as tolerated.

^bParticipation in investigational studies is appropriate for stage C, NYHA class II and III HF.

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The role of standard GDMT is less well-established for patients with advanced HFrEF due to limited clinical experience in this population. The use of sacubitril/valsartan is not currently endorsed by practice guidelines for use in patients with class IV HFrEF, and the results of a recent clinical trial of sacubitril/valsartan versus valsartan in patients with advanced HFrEF (class IV), HFN-LIFE (NCT02816736), showed that adding sacubitril as assessed by NT-proBNP levels provides no benefit.⁴⁴ Therapeutic options for advanced HF include durable mechanical support with LV assist devices (LVADs) and transplant in addition to palliative care.³ Survival for patients with advanced HF (class IV) has substantially improved in recent years with the introduction of new-generation LVADs.⁴⁵

Optimizing Existing Therapies

To date, clinical management of HFrEF has generally involved initiating treatments in a sequence that largely follows the chronological order of published pivotal trials (ie, starting with ACEIs or ARBs, then adding a β -blocker, then an MRA, switching to an ARNI, and finally adding an SGLT2i).⁴⁶ This approach also involved a cautious and gradual increase in dosage until the recommended level was reached before adding another therapy. More recently, it was suggested that patient outcomes could be improved and hospitalizations could be reduced by using alternative approaches to treatment sequencing.⁴⁷⁻⁵¹ However, the optimal approach to sequencing of therapy has not been established.

The ACC/AHA/HFSA guideline states that GDMT is the foundation of care for patients with HFrEF and should be started as soon as possible after diagnosis.^{3,52} However, accelerated initiation of therapy could be beneficial; the effects of individual agents are independent and additive, with each drug conferring benefit soon after initiation (within 30 days).^{3,46,51} A modeling study based on data from pivotal trials showed that simply shortening the time to gradually increase the dose of each drug reduced the occurrence of hospitalizations and deaths.⁴⁶ This finding is to be expected given the known early benefits associated with the 4 first-line agents. However, changing the sequencing of administration to start with either an SGLT2i or an MRA allowed rapid attainment of target doses and was associated with the greatest benefits in terms of hospitalization and mortality. In contrast, starting 2 drugs simultaneously produced only modest additional benefit.

Despite the existence of clinical guidelines, current evidence suggests that the management of HFrEF remains suboptimal.¹³ An analysis of data from the CHAMP-HF registry, which included US outpatients with HFrEF who were receiving at least 1 oral treatment for HF, identified substantial gaps in the use of GDMT.⁵² Among patients eligible for treatment, a substantial proportion was not prescribed ACEI/ARB/ARNI treatment, a β -blocker, or MRA therapy (27%, 33%, and 67%, respectively). When medications were prescribed, only a minority of patients received target doses (an

ACEI/ARB, 17%; an ARNI, 14%; a β -blocker, 28%), although most received target doses of an MRA (77%). Furthermore, for patients eligible for all classes of medication, only 1% simultaneously received target doses of an ACEI/ARB/ARNI, a β -blocker, and an MRA, and less than 25% received any dose of all 3 medications. An analysis of CHAMP-HF registry data also showed that even if patients with HFrEF did receive GDMT, they frequently experienced delays in receiving target doses of treatment.⁵³

Failure to start GDMT in the hospital means that the majority of patients (> 75%) will not receive appropriate therapy within the next year as outpatients.⁵⁴ Since delaying treatment by even a few weeks can result in preventable hospitalizations and deaths, the use of simultaneous or rapid-sequence initiation of quadruple therapy should be considered a high priority. In the PROMPT-HF trial (NCT04514458), investigators evaluated the use of targeted and tailored electronic health record–based alerts aimed at improving GDMT use in eligible outpatients with HFrEF.⁵⁵ The results showed that use of the alerting system was associated with significantly higher uptake of GDMT at 30 days versus usual care; it represents a low-cost intervention that could be rapidly integrated into clinical care.

Importantly, the likelihood of receiving target doses of GDMT can be reduced by several patient factors, including the presence of comorbidities particularly, renal disease and socioeconomic barriers (eg, the cost of multiple treatments, the ability of patients to attend frequent office visits for treatment optimization).⁵² Out-of-pocket expenses can be a barrier to quadruple therapy for some patients.⁵⁶ This burden is likely to increase following the addition of information concerning newer therapies, such as ARNIs and SGLT2is, to clinical guidelines. In a recent analysis of data from the Medical Expenditure Panel Survey, one-third of patients with HF experienced subjective financial hardship from medical bills, with 13.2% being unable to pay medical bills at all.⁵⁷ The risk of financial hardship was greatest for patients 65 years or younger (possibly related to their ineligibility for Medicare coverage) and for individuals with less education.^{56,57} High financial burden can have an adverse impact on health outcomes, because affected patients are more likely to miss clinic visits, report poorer quality of life, have a sedentary lifestyle, and experience housing instability.⁵⁷

These findings indicate an urgent need for increased efforts to reduce out-of-pocket costs for patients with HF and evaluation of cost as a patient-reported outcome in future clinical trials. Involvement of specialist cardiac pharmacists can help in addressing the cost implications of treatment for patients, improving adherence with GDMT, and optimizing clinical outcomes, which, in turn, reduces the risk of HF exacerbations and hospital admissions.⁵⁶ According to results of the survey discussed above, the high prevalence of financial hardship among patients despite insurance coverage (ie, only 2.4% of patients with HF were uninsured vs 9% of patients without HF)

emphasizes the need to improve the quality of insurance coverage, particularly as newer drugs for HF are becoming available.⁵⁷

The ACC/AHA/HFSA guideline recommends an individualized approach to the initiation and titration of GDMT for HFrEF. Treatment optimization should be undertaken as soon as possible, taking account of symptoms, vital signs, functional status, tolerance, renal function, electrolyte levels, comorbidities, underlying cause of HF, and availability of follow-up.³ However, further research is needed to determine how to individualize treatment for specific causes of HFrEF and to assess the role of genetic and other individual factors in patient management.

Overall, the highest risk for decompensation requiring readmission is seen in the days and weeks following hospital discharge.¹⁶ Therefore, referral to multidisciplinary HF disease management programs is recommended for patients with recurrent hospitalizations for HFrEF to reduce the risk of further hospitalization.³ In addition, follow-up in the early postdischarge period can help to optimize understanding of changes to the care plan resulting from hospital admission, and this has been associated with a reduced risk of subsequent rehospitalization.³

Future Treatments

Since poor adherence to treatment is common among patients with HF, it is important that clinicians have a range of therapeutic options to consider for individual patients to reduce the risk of symptom exacerbations, disease progression, and hospitalizations.⁵⁸ The search for a treatment that can increase myocardial performance has continued for many decades, although no drug that directly improves systolic function has been shown to improve clinical outcomes, including survival.⁵⁹ However, 1 such agent, the selective cardiac myosin activator omecamtiv mecarbil, has been shown to improve cardiac function in patients with HFrEF, although this drug is not currently approved by the FDA for clinical use. In a clinical study, GALACTIC-HF (NCT02929329), patients with an LVEF of 35% or less who were receiving GDMT and device therapy who were given omecamtiv mecarbil had a lower incidence of a composite of a HF event or death from cardiovascular causes when compared with a placebo group.⁶⁰

The effect of vericiguat, a novel oral soluble guanylate cyclase stimulator, has also been recently evaluated in patients with HFrEF. Vericiguat was compared with placebo in relatively high-risk patients with HFrEF (LVEF < 45%) who were recently hospitalized or received intravenous diuretic therapy and were receiving GDMT.⁶¹ In this population of patients with HFrEF and poor prognosis, treatment with vericiguat was associated with reductions both in hospitalization for HF and in cardiovascular death. These encouraging findings will need further evaluation to determine the future role of this agent in the management of HFrEF. Research is also needed to develop methods to assess treatment adherence in

clinical practice and to evaluate interventions that can improve clinical outcomes and readmission rates.⁵⁸

Conclusions

In view of the current suboptimal treatment of patients with HFrEF, our approach toward medical management that combines access, affordability, and initiatives to initiate and titrate therapies with proven benefits at a patient, health system, and societal level should be reconsidered.¹³ Further research is needed to determine how to implement therapies that have proven benefits in HFrEF so that patients and the wider society can benefit from recent advances in medical care. An improved understanding of patient-level costs associated with HF therapies and measures that reduce these costs are important to increase the uptake of and adherence to therapy and to optimize clinical outcomes. ■

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Heart Failure Without a Reduced Ejection Fraction

Sant Kumar, MD; and Mitchell A. Psotka, MD, PhD

Introduction

Heart failure (HF) burdens a large and increasing proportion of the population in the United States and causes substantial clinical impact and financial expenditure. Here we review the epidemiology, diagnosis, management, and financial burden of HF with a left ventricular ejection fraction (LVEF) of 50% or more, also known as HF with a preserved ejection fraction (HFpEF). We aim to cover what is known, reveal current gaps in knowledge, and highlight where future evidence generation is needed.

Definition and Diagnosis of HFpEF

As defined in the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guideline for the management of HF, "HF is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood."¹ The clinical syndrome consists of symptoms such as dyspnea on exertion, reduced ability to exercise, fatigue, and lower extremity swelling. These symptoms limit physical activity, worsen debility, and impair employment and recreational engagement, and they may lead to hospitalization.

LVEF is used to broadly characterize HF, because most historical clinical trials that included LVEF as an enrollment criterion and a factor for clinical care and guidelines have since adopted it as a descriptor. However, because it is a label defined by historical context, there is variability to the LVEF that distinguishes HF subtypes, including HFpEF.² Current US guidelines define HFpEF as HF with an LVEF of at least 50%.^{1,3} This point of LVEF delineation, recently ranging from 40% to 55%, has varied over time.⁴ LVEF is influenced by sex, age, body mass, and method of measurement, which may cause clinicians to question its accuracy, but it generally can be consistently estimated within a range of 5% to 10%.⁵ Although some patients with HF with improved LVEF (ie, patients whose LVEF has improved from < 40% to \geq 50%) can have an LVEF of at least 50%, the treatment of these patients and their response is similar to those of patients with HF with a reduced ejection fraction (HFrEF) (LVEF \leq 40%); this situation is not included in this discussion.

ABSTRACT

Heart failure (HF) substantially impacts the health and financial security of an increasing proportion of the US population. It worsens debility and quality of life and may lead to hospitalization and death. HF is a clinical syndrome with diverse symptomatic presentations. Physicians generally divide patients with HF into 2 groups: those with a left ventricular ejection fraction (LVEF) greater than or equal to 50% and those with an LVEF less than 49%. This review focuses on the group of patients whose LVEF is greater than or equal to 50%. This classification of HF is referred to as HF with a preserved ejection fraction (HFpEF). Few beneficial therapies have been identified for this condition, possibly because of its heterogeneous etiologies (eg, myocardial, vascular, metabolic, and other physiologic derangements). Clinicians should focus on diagnosing, treating, and preventing the etiologies that are known to cause HFpEF. Results from a small proportion of randomized controlled trials have shown therapeutic benefit for small molecules, although limited, if any, demonstrated mortality benefit has been noted. More research and investment are needed to decrease the burden of HFpEF and to discover lifesaving treatments for this growing population.

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TAKEAWAY POINTS

- ▶ Heart failure (HF) is a growing problem that substantially affects the health and financial security of affected individuals.
- ▶ Due to its heterogenous etiologies, HF is a clinical syndrome with diverse symptomatic presentations.
- ▶ Treatment options are limited for patients with HF with a preserved ejection fraction (HFpEF)—left ventricular ejection fraction of at least 50%.
- ▶ Despite recent advances in the development of effective therapeutics for patients with HFpEF, substantial barriers to treatment remain, including therapeutic cost.
- ▶ More research and investment are needed to develop effective therapies for HFpEF and reduce its burden on the population and on health care systems.

Superficially, the phenotype of HFpEF neatly categorizes patients; however, HFpEF appears to be a heterogenous and multifaceted syndrome with numerous potential underlying etiologies.⁶ Hemodynamically, the syndrome of HFpEF manifests with elevated left ventricular filling pressures either at rest or with exertion, but these elevations may be the final common pathway for many diseases. The archetypal HFpEF disease remains cardiac amyloidosis, which likely has confounded the study of other types of HFpEF repeatedly; however, myocardial, vascular, metabolic, and other physiologic derangements likely participate in some types of patients with HFpEF.⁷ Thus, although LVEF offers a simple way of classifying this disease, substantially more specific and detailed elucidation of the subcategories of HF with LVEF of 50% or more are required for accurate characterization.

Epidemiology of HFpEF

The incidence of HF with reduced ejection fraction (HFrEF) has decreased, yet the incidence of HFpEF and its proportion of all HF continues to rise.⁸ It is estimated that currently over half of all patients with HF do not have a reduced LVEF.⁹

HFpEF more frequently occurs in patients with multiple comorbidities, and it has a higher prevalence in women and older patients.¹⁰ Among Black patients with HF, HFpEF appears to account for up to 70% of all HF and to be associated with worse outcomes.^{11,12}

Health Care Burden and Expenditures Related to HFpEF

HF—and HFpEF specifically—has a deep economic impact on health care systems. Health care costs related to HF in the United States are expected to exceed \$50 billion annually by 2030.¹⁰ Although designed as a quality improvement program, the Hospital Readmissions Reduction Program (HRRP) revealed a financial impact of HF that illustrates its burden on health systems. Implemented under the 2010 Patient Protection and Affordable Care Act, the HRRP is a mandatory, federal, pay-for-performance program to decrease 30-day hospital readmission rates; it financially penalizes hospitals with 30-day

readmission rates that are higher than expected.¹³ The HRRP came into effect on October 1, 2012; it penalizes close to 80% of hospitals and earns Medicare more than \$500 million annually.¹⁴

Along with health systems and the government, patients with HFpEF face a considerable financial burden. One report found that the rate of outpatient visits for this patient population was 3.6 visits per month. Of these patients, 27% were hospitalized within 30 days of their first urgent care HF visit; the mean total monthly health care cost per patient was \$7482. The total monthly medication cost was higher for patients with an LVEF of 50% or more than for those with a reduced LVEF (\$495 vs \$429, respectively).¹⁵

Compounding this financial burden, patients with HFpEF also have decreased quality and quantity of life. Although tremendous progress has been made in the treatment of HFrEF, there remains a paucity of therapies that decrease mortality and morbidity for patients with HFpEF. These patients have persistently diminished exercise tolerance and ability to perform physical activity.¹⁶ With the explosion of obesity and diabetes, HFpEF also affects younger patients, and an analysis of results from 3 clinical trials (RELAX [NCT00763867], NEAT-HFpEF [NCT02053493], INDIE-HFpEF [NCT02742129]) showed that patients with HFpEF who are young, who have obesity, and who have diabetes were more likely to score lower on quality of life (QOL) measures.¹⁷

Management Principles for HFpEF

Few effective therapies have been identified for patients with HFpEF, perhaps because this medical condition can occur in response to a wide variety of underlying etiologies. Further, unlike HFrEF, neurohormonal antagonists have not yet been shown to improve the multiple varieties of HFpEF.⁶ The heterogeneity exists in part because LVEF is a poor differentiator among the various flavors of HFpEF. Because of these issues and the symptom and diagnostic variability of HFpEF, clinicians should focus on diagnosing, treating, and preventing the etiologies known to cause this clinical syndrome.

A large proportion of the US population has high risk factors for HF; these include hypertension, obesity, diabetes, and atherosclerotic cardiovascular disease.^{1,4} Common causes of HFpEF include metabolic heart disease, valvular heart disease, and ischemic heart disease. Other causes may include cardiomyopathies that are stress induced, genetic, or peripartum. Infiltrative and inflammation-related diseases (eg, sarcoidosis) can also contribute, and amyloidosis should be appropriately evaluated and treated separately if present. Cardiotoxicity related to use of alcohol, stimulants (eg, cocaine, methamphetamine), and oncologic therapeutics can cause this clinical syndrome. Right ventricular dysfunction and pulmonary hypertension may lead to left-sided cardiomyopathy, but they more frequently are inappropriately labeled as HFpEF; careful vigilance is required to diagnose these patients and refer them to specialty centers.¹

Identification of the underlying etiologies is essential to patient management, because the most effective treatment is often determined by the etiology of presentation. Current guidelines recommend control of blood pressure in line with guideline-directed medical therapy for hypertension to decrease occurrence of HFpEF and encourage regular exercise and weight loss for patients with obesity.^{1,18} For those patients with HFpEF with underlying diseases, the ACC recommends coronary revascularization, valve replacement or repair, and medical ischemia management.¹⁸⁻²² Patients with HFpEF and obstructive sleep apnea may present with insomnia, daytime hypersomnolence, obesity, loud snoring, and witnessed apnea.²³ Treatment is directed toward weight loss via methods such as bariatric surgery and prescription of continuous positive airway pressure.²³ Arrhythmias such as atrial fibrillation can also exacerbate HFpEF symptoms, although HFpEF and increased left ventricular filling pressures also increase the risk of atrial fibrillation.¹

Evidence-Based Therapies

Until recently, few medications or devices have demonstrated improvement in mortality or morbidity for patients with HFpEF (**Table**).²⁴⁻³⁶ Fortunately, several recent successes in pharmaceutical development have overcome the results of multiple prior programs that were unable to show treatment effectiveness in the setting of HF with an LVEF of 50% or more (**Figure**).^{24-26,32} Diuretic use has not been supported by the results of clinical trials in the setting of HFpEF, but it remains a central part of the standard of care due to near-universal associations of patient exacerbation with intravascular or extravascular volume overload. Regardless of the etiology, patients with HFpEF often present with fluid retention. To relieve congestion, clinicians typically opt for a loop diuretic—intravenously in the acute inpatient setting and orally in the outpatient setting. Increasingly, ambulatory diuretic infusion clinics are used to assuage the hospital burden of HF and keep patients in the ambulatory setting as much as possible.³⁷

In the TRANSFORM-HF trial (NCT03296813), investigators compared the treatment strategy of torsemide versus furosemide for patients with HFrEF or HFpEF who were hospitalized.³⁸ Dosing was left to the discretion of the treating physicians. With a median follow-up of 17.4 months, there was no difference in all-cause mortality between patients who received torsemide versus those who received furosemide (HR, 1.02; 95% CI, 0.89-1.18).³⁹ The finding was present in patients with HF, regardless of whether their LVEF was reduced or preserved. For those patients whose disease is refractory to loop diuretic therapy alone, concomitant metolazone or chlorothiazide use may be considered to augment diuresis.

Outside of a case of acute decompensation, use of few medications and devices appear beneficial in improving outcomes for patients with HFpEF. These classes include the sodium-glucose cotransporter 2 inhibitors (SGLT2is), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor–neprilysin inhibitors (ARNIs) and pulmonary artery (PA) pressure monitoring.

Empagliflozin

In the EMPEROR-Preserved trial (NCT03057951), use of the SGLT2i empagliflozin demonstrated improvement on the primary composite end point of cardiovascular death and HF hospitalization for patients with HF and an LVEF of more than 40% (HR, 0.79; 95% CI, 0.69-0.90).²⁴ Most of the treatment effect was due to a reduction in hospitalizations in the treated group (from 6.0 to 4.3 hospitalizations/100 patient-years). Of the enrolled patients, 67% had an LVEF of at least 50%; in those patients, there also appeared to be benefit in terms of the primary end point, although the treatment effect appeared to diminish at progressively higher values of baseline LVEF.²

The EMPEROR-Preserved data led to an expansion of the empagliflozin label to not restrict use to patients with HF and a “reduced ejection fraction.”²⁴⁰ For those patients, the addition of empagliflozin appeared to be a meaningful advance in care to reduce morbidity and improve QOL. In addition, the EMPULSE trial (NCT04157751) enrolled 169 patients with an LVEF of more than 40%.⁴¹ These patients appeared to have similar benefit in terms of the composite win ratio end point of time to death, HF event frequency, time to event, and QOL score measured by the Kansas City Cardiomyopathy Questionnaire as patients enrolled with lower LVEF values.⁴²

Dapagliflozin

Results of the DELIVER trial (NCT03619213) showed that use of another SGLT2i, dapagliflozin, decreased the risk of worsening HF (defined as an urgent visit or unplanned hospitalization for HF) and cardiovascular death in patients with an LVEF of more than 40% (HR, 0.82; 95% CI, 0.73-0.92).²⁵ Dapagliflozin also reduced the risk of worsening HF and cardiovascular death for patients with an LVEF of 60% or more (HR 0.78; 95% CI, 0.62-0.98), which was similar to that of patients with an LVEF below 60% (HR 0.83; 95% CI, 0.73-0.95).

Sotagliflozin

In the SOLOIST-WHF trial (NCT03521934) of patients with type 2 diabetes (T2D), sotagliflozin therapy reduced the rate of the primary end point of cardiovascular death and hospitalization or urgent visits for HF for patients with diabetes mellitus and recent worsening of HF without limitation by LVEF²⁶; however, the trial was terminated early by the sponsor.⁴³ Similarly, results from the SCORED trial (NCT03315143) of patients with T2D and chronic kidney disease (ie, estimated glomerular filtration rate [eGFR] 25-60 mL/min/1.73 m² regardless of albuminuria status), and cardiovascular risk factors showed that sotagliflozin therapy significantly reduced the primary end point of cardiovascular death and hospitalization or urgent visits for HF.⁴⁴ These data and the consistent results of a meta-analysis suggested that the beneficial effect for patients with HFpEF may be a class effect for the SGLT2is.⁴⁵ As of May 2023 the SGLT2is empagliflozin, dapagliflozin, and sotagliflozin have received regulatory approval for HF regardless of ejection fraction.^{40,46,47}

The evidentiary support for SGLT2 inhibitors is sufficiently strong that the ACC recent consensus statement suggests that an SGLT2 inhibitor should be considered at the time of HFpEF diagnosis, except in patients with certain comorbidities (orthostatic hypotension, eGFR < 20-25 mL/min/1.73 m², very frequent yeast infections, or a history of severe genitourinary infections, including Fournier gangrene).⁴⁸

Sacubitril-Valsartan

In the PARAGON-HF trial (NCT01920711), patients with HF and an LVEF of at least 45% who received sacubitril-valsartan did not have significantly decreased rates of cardiovascular death or total HF hospital admissions when compared with findings in patients who received valsartan, based on the initial event adjudication (rate ratio, 0.87; 95% CI, 0.75-1.01).³² However, more total events were adjudicated by site investigators compared with those reviewed by the central adjudicators; further, when the data were analyzed

TABLE. Therapeutics for Management of HFpEF²⁴⁻³⁶

Therapeutic	Clinical trial(s)	LVEF range	Mortality effect	Hospitalization effect	HRQOL effect (KCCQ score)	ACC/AHA/HFSA 2022 guideline recommendations	Cost/QALY	Cost/30 tablets ³⁶
Empagliflozin	EMPEROR-Preserved (NCT03057951) ²⁴	> 40%	Neutral	Beneficial	Beneficial	2a	> \$60,000	\$500-\$700
Dapagliflozin	DELIVER (NCT03619213) ²⁵	> 40%	Neutral	Beneficial	Beneficial	None ^a	> \$60,000 ^b	\$500-\$600
Sotagliflozin	SOLOIST-WHF (NCT03521934) ²⁶	N/A	Beneficial	Beneficial	Beneficial	None ^a	Unknown	Unknown
ARB	CHARM-Preserved (NCT00634712), ²⁷ I-PRESERVE (NCT00095238) ²⁸	> 40%	Neutral	Neutral	Beneficial	2b	< \$60,000 ^c	\$10-\$30
MRA	TOPCAT (NCT00094302) ^{29,30}	≥ 45%	Neutral	Neutral	Beneficial	2b	< \$60,000 ^b	\$3-\$12
ARNI	PARAMOUNT-HF (NCT00887588), ³¹ PARAGON-HF (NCT01920711) ^{32,33}	≥ 45%	Beneficial	Beneficial	Beneficial	2b	< \$60,000 ^b	\$600-\$700
CardioMEMS	CHAMPION (NCT00531661) ³⁴	N/A ^d	Neutral	Beneficial	Beneficial	2b	< \$60,000	N/A
Tafamidis	ATTR-ACT (NCT01994889) ³⁵	N/A ^d	Beneficial	Beneficial	Beneficial	1 ^e	> \$180,000	\$19,000-\$24,000/ 12 dose packs

ACC, American College of Cardiology; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFSA, Heart Failure Society of America; HRQOL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; N/A, not applicable; QALY, quality-adjusted life years.

^aData from the DELIVER and SOLOIST-WHF trials were not available in time to be included in the 2022 guideline.

^bStudied in patients with HFpEF only.

^cPatients with type 2 diabetes who had been hospitalized with signs and symptoms of heart failure.

^dPatients stratified by New York Heart Association class and not EF.

^eFor patients with cardiac amyloidosis.

by either the principal investigator adjudicated events or when the trial was readjudicated in a blinded fashion, there was a beneficial effect of sacubitril-valsartan on the primary end point (rate ratio, 0.83 [95% CI, 0.73-0.95] and 0.86 [95% CI, 0.75-1.00], respectively).^{32,33,49-51} Similar to results noted with use of empagliflozin, the benefit of sacubitril-valsartan was primarily on HF hospitalizations,⁵² and there was a decrement in treatment effectiveness at higher levels of LVEF. For this indication, the prescribing information for sacubitril-valsartan includes that “benefits are most clearly evident in patients with LVEF below normal,” referring to the diminishing treatment effect with respect to higher LVEF.⁵²

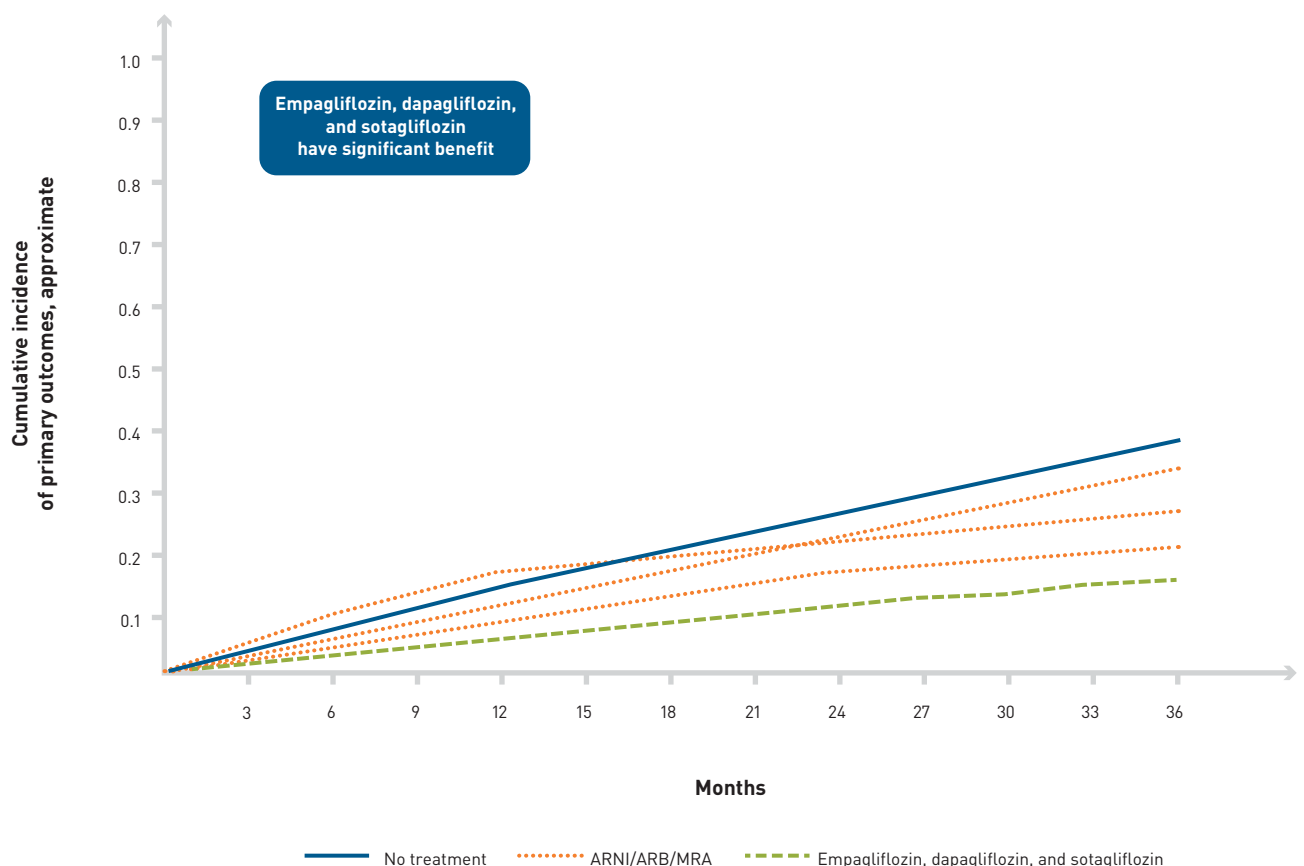
Use of renin-angiotensin-aldosterone system inhibitors, apart from sacubitril-valsartan, has not produced a statistically significant reduction in mortality or hospitalization for patients with HFpEF. In the CHARM-Preserved trial, the decrease in cardiovascular death or HF hospitalization in patients with an LVEF of more than 40% and who received candesartan did not achieve statistical significance

(unadjusted HR, 0.89; 95% CI, 0.77-1.03).²⁷ In the I-PRESERVE trial (NCT00095238), patients with LVEF of at least 45% who received irbesartan did not have significantly decreased rates of mortality or hospitalization when compared with the placebo group (HR, 0.95; 95% CI, 0.86-1.05).²⁸

Spironolactone

Although the mineralocorticoid antagonist spironolactone did not achieve a regulatory indication for HF with a higher LVEF, it is often used by clinicians for these patients.⁵³ Results of the TOPCAT trial (NCT00094302) did not show a statistically significant reduction in composite primary end point of cardiovascular death, cardiac arrest, or HF hospitalization for patients with HF and a LVEF of at least 45% (HR 0.89; 95% CI, 0.77-1.04).³⁰ However, there were multiple regional irregularities found in the trial conduct, including enrollment of patients with very low event rates, unclear diagnoses of HF, and blood testing demonstrating an absence of spironolactone

FIGURE. Benefit of Current Guideline-Directed Medical Therapy in Patients With HFpEF^{24-26,32}



ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist.

metabolites in patients intended to be taking the drug.⁵⁴ In that light, post hoc analysis suggested efficacy in enrollees from the Americas (HR, 0.82; 95% CI, 0.69-0.98).⁵⁵ Similar to therapy with empagliflozin and sacubitril-valsartan, use of spironolactone appeared primarily to reduce the risk of hospitalization for HF, which seemed to be greatest for patients with a lower LVEF.

Pharmacotherapy Across the Range of Ejection Fraction

The diminishing therapeutic benefit noted among patients with a higher LVEF appears to be similar in the EMPEROR-Preserved, PARAGON-HF, and TOPCAT results and does not appear unique to empagliflozin, sacubitril-valsartan, or spironolactone.⁵⁰ A similar decrement in effectiveness for patients with HF and higher LVEF is apparent for most of the pharmacotherapies that have demonstrated a beneficial treatment effect for this population. Although the point estimate for effectiveness for dapagliflozin in patients with a higher LVEF from DELIVER is consistent with lower values of LVEF, and the statistical test for heterogeneity supports a benefit, at higher values of LVEF the confidence intervals are wide and cross no-benefit and the heterogeneity test is statistically weak, meaning that the evidence for effectiveness at elevated LVEF is substantially weaker than at lower LVEF.⁵⁶ The diminishing effectiveness of these pharmacotherapies at higher ranges of LVEF in patients with HF may be due to the multiple comingled pathophysiologies in these patients, many of whom may not respond to these therapies.⁵³ The trials of HF with higher LVEFs enrolled patients who could have had cardiac amyloidosis; it is likely that a proportion of patients did, as they were not systematically screened for this comorbidity, which may be unresponsive to the therapies tested above and may be better treated with more targeted therapies, as discussed below.⁷

PA Pressure Monitoring

The CardioMEMS HF System (Abbott) is a permanently implantable, battery-free, pressure-sensitive capacitor that is placed percutaneously in the left PA to measure PA pressure. Patients can communicate these measurements electronically, typically on a daily basis, to clinicians with their at-home portable communication units. Changes in PA pressure can then be appropriately treated by adjustment of diuretic or vasodilator dose or with other medical or device therapy.⁵⁷ The CHAMPION trial (NCT00531661) results showed a significant decrease in HF-related hospitalizations after 6 months for patients with HF without LVEF exclusion who received a PA pressure sensor compared with those who did not.³⁴ A post hoc analysis of patients with an LVEF of at least 50% showed a reduction in hospitalization that was similar to that seen in the overall trial.⁵⁸ The GUIDE-HF trial (NCT03387813) expanded the evidence for patients with New York Heart Association class II to IV symptoms, although this was substantially

impacted by the COVID-19 pandemic. Based on the overall data, the CardioMEMS system has regulatory approval for wireless measurement of PA pressure and heart rate for patients with HF, irrespective of LVEF.⁵⁹

Tafamidis for Cardiac Amyloidosis

Cardiac amyloidosis should be specifically evaluated as a cause of HFpEF, as it responds to targeted amyloid therapies that are distinct from the HF management discussed above. Amyloidosis is a restrictive cardiomyopathy caused most often by deposition of either immunoglobulin light chains or transthyretin. Amyloidosis is often present in undifferentiated patients with HF and an LVEF of at least 50%. Results of the ATTR-ACT trial (NCT01994889) showed that use of tafamidis, a transthyretin stabilizer, reduced all-cause mortality and cardiovascular-related hospitalizations and improved functional capacity and QOL when compared with placebo.³⁵

Additional HF Management Modalities

Because patients with HFpEF frequently have multiple other comorbidities, recommended interventions include care given by multidisciplinary teams. This often includes arrhythmia specialists and staff who provide structured HF education and screening for mental illness, frailty, and health literacy.¹

Cost, Accessibility, and Implementation of Therapeutics

Although meaningful advances have been made in the development of effective therapeutics for patients with HF and an LVEF of at least 50%, barriers remain to delivering these evidence-based treatments. Therapeutic cost poses a substantial obstacle. Overall, prescription medication cost comprises the biggest portion of outpatient cardiovascular spending, and it is rising faster than is inflation.⁶⁰ However, the complex relationship between drug makers, insurers, pharmaceutical companies, and distributors conceals the prices of medications as it influences the accessibility of these medications to patients.^{60,61} Patient assistance can facilitate access to sacubitril-valsartan and empagliflozin for some patients with HFpEF; however, other individuals are limited by high insurance co-payments and co-insurance or other utilization management procedures (Table).²⁴⁻³⁶

Tafamidis exemplifies the barriers to effectively treating patients with newly developed therapeutics. At an annual cost of \$225,000, tafamidis is the most expensive cardiovascular drug ever launched in the United States. For tafamidis to be cost-effective, a 92.6% reduction in its price would be needed. Annual health care spending would increase by \$32.3 billion if all eligible patients with HF were treated with tafamidis. Current guidelines classify tafamidis as a drug with low economic value (> \$180,000/quality-adjusted life-years [QALYs] gained) due to its pricing.¹

The EMPA-REG OUTCOME trial (NCT01131676) demonstrated that empagliflozin reduces cardiovascular mortality in patients with T2D.⁶² Several post hoc analyses have evaluated the cost-effectiveness of empagliflozin and found that, compared with standard of care, empagliflozin is a cost-effective treatment option for patients with HF and T2D.⁶³⁻⁶⁵ Results of a US-based, post hoc analysis showed that empagliflozin therapy added 0.67 QALYs and \$17,322 per patient over a lifetime horizon for those patients, which is generally accepted to be cost-effective.⁶⁶ However, the cost-effectiveness of empagliflozin for patients with HFpEF is highly dependent on cost.⁶⁷ The cost of empagliflozin per QALY gained was \$437,442 based on the EMPEROR-Preserved results and the list price at the time of publication. Dapagliflozin cost-effectiveness presumably is similarly sensitive to the same analyses.

Based on the available clinical trial data, the CardioMEMS device reduction in hospitalizations appears to be of good economic value (< \$60,000/QALY gained). In patients similar to those in the CHAMPION trial cohort, the cost per QALY gained was \$47,768 in patients with HFpEF.⁶⁸

Given the cost and accessibility of HF therapies for patients with HFpEF, low-cost interventions could increase implementation of guideline-directed medical therapy. PROMPT-HF (NCT04514458) was a cluster-randomized, comparative effectiveness trial in which 100 clinicians managing patients with HFpEF were randomly assigned to receive an electronic health record (EHR) alert recommending guideline-directed medical therapy for HF or to provide usual care without an EHR best practice advisory alert. HF medical therapy prescriptions were significantly increased in the alert exposure group, and similar methodology could be used for the prescription of therapies for patients with HFpEF.⁶⁹

Conclusion and Future Directions

HFpEF remains a challenging pathology for physicians and patients because of the ongoing evolution of a standardized definition of the disease state, results of few randomized controlled trials showing therapeutic benefit, and no therapies having a clearly demonstrated mortality benefit. In addition, substantial treatment barriers and financial burdens exist for patients, payors, and health systems. Because the population of patients with HFpEF continues to grow and impact a greater proportion of patients in the US medical systems, comprehensive strategies are needed to improve care, prevent disease worsening, and develop new treatments. ■

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Defining a Path Toward Improved Heart Failure Care

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Introduction

Heart failure (HF) affects more than 6.5 million people in the United States alone, with approximately 550,000 new cases diagnosed annually.¹ Overall, spending for HF comprises 1% to 2% of the US total health care expenditure,² with hospitalizations accounting for a majority of the direct costs.^{2,3} In 2011, 3.3 million hospital readmissions occurred at an associated cost of \$41.3 billion, with the overall cost of HF projected to rise to \$69.8 billion by 2030.^{4,5}

Given the economic burden of HF, health care systems are striving to implement value-based payment (VBP) models instead of traditional fee-for-service (FFS) models. While FFS models involve volume-based payments, VBP models offer incentives to physicians and institutions for meeting certain care quality standards.⁶ In this way, VBP models aim to address the fragmented, low-quality health care associated with FFS models (Figure).⁷⁻¹¹ Thus, the goal of payment reform is to drive improvements in health care quality, positively influence treatment outcomes, and reduce costs for the HF patient population. To improve the quality of HF care and reduce costs, a path for improvement is needed that can incorporate additional patient data and metrics to define outcomes while implementing innovative new payment and care delivery models.

Improving Phenotyping by Incorporating New Measures

Traditionally, HF treatment has been based largely on determination of the left ventricular ejection fraction (LVEF).¹² For example, patients with HF with preserved EF (HFpEF) may be older and have more comorbidities than patients with HF with reduced EF (HFrEF).¹³ However, when compared with patients with HFpEF, those with HFrEF tend to have longer hospital stays and higher mean hospitalization costs (\$8858 vs \$10,286, respectively).¹³ However, this approach does not accurately capture the multifactorial causes of HF, and it may lead to worsened patient outcomes. Thus, a better approach to characterizing HF is needed as our understanding of the underlying pathophysiology improves.

In addition to biological considerations, other outcome metrics that include social determinants of health (SDOH) and patient-reported

ABSTRACT

Defining a path toward improved heart failure (HF) care is essential, as there is a clear need to improve HF treatment quality, outcomes, and value. This article reviews potential strategies to help improve the quality of HF clinical care and decrease costs.

To start, HF phenotyping may be useful in guiding patient treatment, as some phenotypes are associated with higher hospitalization costs and longer length of stay. Identifying and addressing social determinants of health that may be barriers to optimal health may improve management of HF and help to prevent disease progression. In addition, patient-reported outcomes can be useful for evaluating the effectiveness of treatment regimens and assessing which treatments lead to a genuine improvement in quality of life (QOL).

Recent innovations in payment reform have seen the implementation of value-based payment (VBP) models over the traditional fee-for-service (FFS) models. FFS models can lead to low-quality care focused on treating illness instead of supporting wellness initiatives. By contrast, VBP models aim to decrease excessive health care costs, thereby increasing incentives to hospitals that deliver high-quality patient care.

Further, novel care delivery approaches, such as hospital-at-home and other digital tools, can provide patients with lower-cost care and are associated with improved QOL, including reductions in hospital readmission.

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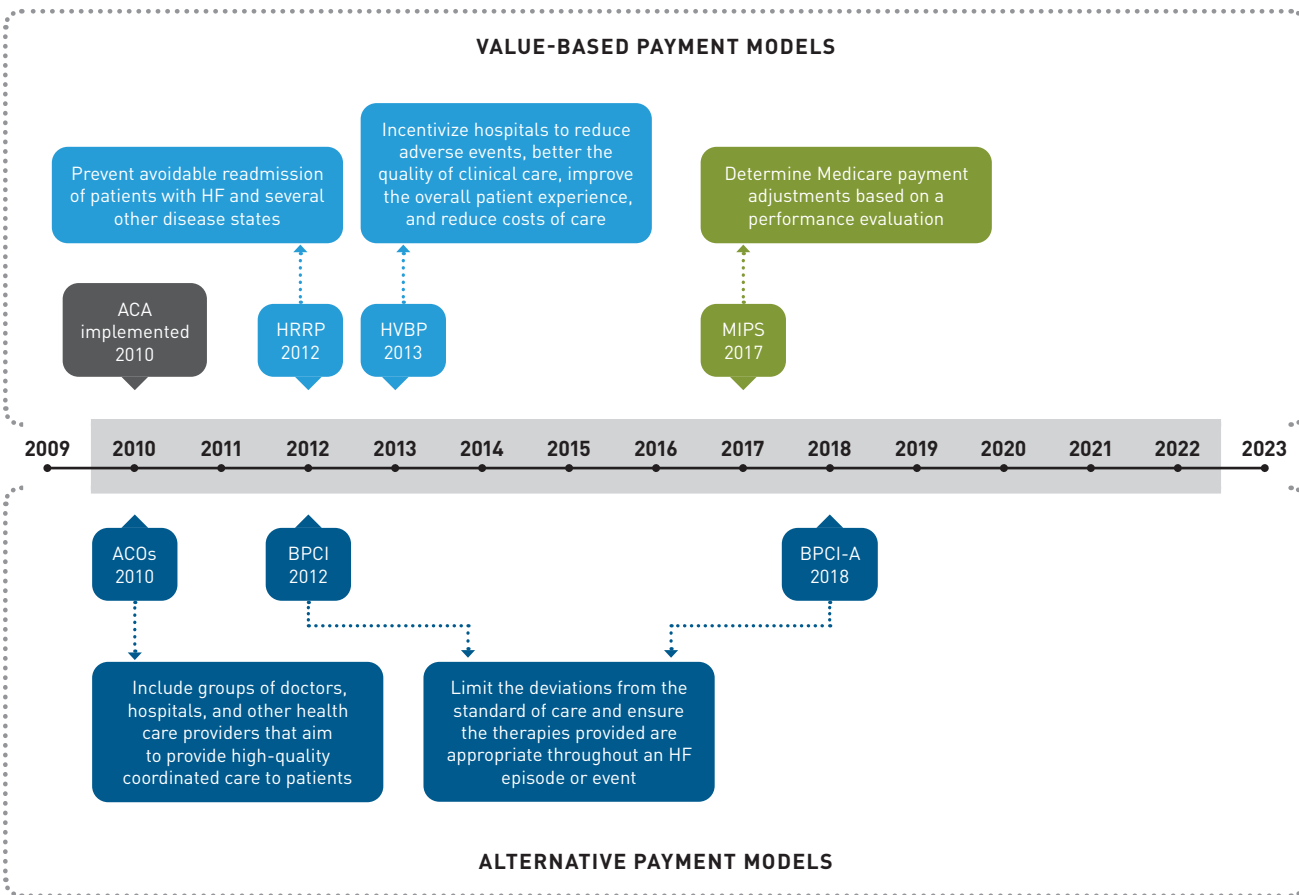
For author information and disclosures, see end of text.

A plain language summary of this article is available at
<https://www.ajmc.com/view/HF-NewTherapiesManagedCare-PLS>

TAKEAWAY POINTS

- The prevalence of heart failure (HF) continues to increase, and HF is associated with substantial morbidity and mortality and health care expenditure.
- Some phenotypes of HF are associated with higher hospitalization costs and longer length of stay.
- In the current health care system, the diagnosis of HF can place a significant economic burden on a patient, which can ultimately affect treatment outcomes.
- Social determinants of health can act as barriers to optimal health care by impacting management and disease progression.
- Evaluating patient-reported outcomes can give greater insight into the effectiveness of treatments and identify genuine improvements in patient quality of life.
- By improving phenotyping and incorporating novel metrics, new payment models could drive improvements in treatment outcomes for patients with HF.

FIGURE. Value-Based Payment Models Address Inequalities in the Health Care System⁷⁻¹¹



ACA, Affordable Care Act; ACO, accountable care organizations; BPCI, bundled payments for care improvement; BPCI-A, bundled payments for care improvement-advanced; HF, heart failure; HRRP, Hospital Readmission Reduction Program; HVBP, Hospital Value-Based Purchasing; MIPS, Merit-Based Incentive Payment System.

outcomes (PROs) could help to improve phenotyping. SDOH are potential barriers (eg, poverty, underemployment, access to care) to receiving optimal health care. By identifying and addressing these social factors, underserved populations can receive appropriate health care to manage and, hopefully, prevent acute events in HF. Distinct from statistical or clinical effects of treatment, PROs could be used to assess whether treatments lead to an actual improvement in patient quality of life (QOL) and to help guide health care providers to personalize treatment as appropriate.

Social Determinants of Health

The complexity of treating HF creates an economic, emotional, and social burden for patients and caregivers.¹⁴ This burden can be further exacerbated by SDOH that can affect the accessibility of quality health care.¹⁵ Patients with HF may also be at risk for depression and more likely to have low socioeconomic status than are individuals without HF, and they may face food insecurity or stretches of unemployment.¹⁶⁻²⁰ Low socioeconomic status is associated with an increased prevalence of HF and an increased risk of death or hospitalization in patients with HF.^{16,18-20} In this way, SDOH impact on equity in health care, affecting the risk of HF and patients' capacity to manage HF and, consequently, their outcomes, QOL, and well-being.^{18,21}

By developing and supporting programs that address economic disparities, an opportunity exists to improve management of HF and prevent disease progression. Because of this wide-reaching potential impact on treatment outcomes, SDOH should be incorporated into assessments and used to inform the development of future payment programs to better assist underserved patient populations.

Patient-Reported Outcomes

In addition to objective clinical outcomes, an understanding of the patient perspective is paramount to evaluating the value and effectiveness of treatment regimens. PROs can provide data regarding symptom burden, functional limitations, and social and emotional well-being.²² These instruments are subjective, but they aim to quantify pain, functional status, or severity of disease as perceived by patients.

A prominent PRO used in patients with HF, the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12), measures physical limitations, symptoms, self-efficacy, knowledge, social interference, and overall QOL.²³ Use of the KCCQ-12 improves clinicians' accuracy in assessing health status and it leads patients to believe their clinicians better understand their symptoms.²⁴

Innovation in Payment Reform: Refining Value-Based Payment Models

Health care policy makers continue to strive to improve quality, reduce variation, and increase the efficiency of HF care, which translates to hospitals focusing on the quality of inpatient care and developing strategies to improve care transitions.¹⁴ Traditional

payment models are based on an FFS model, which can lead to fragmented, low-quality care focused on treating illness instead of supporting wellness initiatives.⁶ For this reason, Medicare and other payers are beginning to move away from these FFS payment models in favor of VBP models that aim to improve quality and outcomes while also reducing costs. VBP models offer increased incentives to hospitals and providers that deliver high-quality care to patients and implement strategies to address unwarranted variation.²⁵ The use of these VBP models is increasing—in 2018, VBP models accounted for 36% of all health care spending.⁶

Under the 2010 Patient Protection and Affordable Care Act, the Centers for Medicare & Medicaid Services (CMS) developed several VBP programs intended to improve patient care; these included the Hospital Readmission Reduction Program (HRRP) and the Hospital Value-Based Purchasing (HVBP) Program.²⁶

The HRRP was intended to reduce the number of patients readmitted after discharge. Beginning in 2010, the HRRP has imposed financial penalties on hospitals with high 30-day readmission rates among patients with HF; identifying the reasons why hospitals are underperforming is crucial to decrease penalties and improve quality of care. In 2019, the HRRP began using an adjusted model to compare hospitals that serve Medicare patients; this decreased penalties by 14%.²⁶ This updated model spreads the distribution of penalties more evenly across hospitals by including SDOH in the algorithm.²⁷ One limitation is that HRRP measures readmissions; however, deaths are not included in the program's metrics.²⁸

The HVBP program, a complementary program to the HRRP, provides acute care hospitals with incentive payments based on broader domains, such as patient experience, outcomes, safety, and efficiency of inpatient care for Medicare and Medicaid patients.⁹ This program was intended to reduce adverse events and reduce the overall costs of care.⁹ A limitation of the HVBP program is that it does not account for socioeconomic factors. However, results of studies assessing mortality and hospital readmissions within the HVBP program indicated no significant improvements among patients with acute myocardial infarction, HF, or pneumonia; evidence to support the effectiveness of the HVBP program is generally lacking.²⁹⁻³²

The Bundled Payments for Care Improvement Advanced model launched in 2018 is a voluntary alternative payment model, with HF one of the main clinical episodes included. Each clinical episode is covered from the inpatient stay to 90 days after discharge. FFS payments are issued for individual health care services during the episode and are subsequently compared against a predetermined target price. This program incentivizes high quality inpatient and outpatient care and the efficiency of care following hospital discharge.³³

Barriers to Model Efficiency

Several barriers need to be addressed for health care providers and hospitals to accept VBP models. According to results of a

survey of Medicaid managed care organizations, the main barrier to implementing VBP models is provider willingness to adopt alternative payment models.³⁴ Further, models should be tailored to address the needs of rural populations with limited access to cardiologists.⁶ If VBP models are patient- and culture-centric, they can potentially reduce health inequalities by providing additional support to disadvantaged patient populations.⁶ However, more evidence is needed to demonstrate that VBP models can improve treatment outcomes and reduce costs regardless of socioeconomic status.³⁵

Several risk assessment models that evaluate the performance of hospitals use administrative claims data, but these may not accurately capture the differences in disease severity and other geographic, social, and economic factors that can vary between hospitals.³⁵ For example, the HRRP has penalized hospitals that serve high-risk populations, even though poor performance was likely due to the challenges in treating disadvantaged populations.³⁶

A further challenge is that current payment models for cardiovascular conditions are mainly based on short-term episodes. This approach does not accommodate patients with HF who often need long-term care to prevent subsequent acute events. Thus, given the complexity of HF, a hybrid model that considers both long- and short-term complications would be more appropriate. This model could provide support during an episode and assist in preventing disease progression. Readmission rates in HF may be attenuated if current payment models, such as the HRRP, included additional factors from longitudinal payment models focused on specialized care.⁶ In addition, models that include specific population demographics and SDOH may more accurately assess hospital performance, as both social factors and health status affect treatment outcomes and health care costs.³⁷

As a practical example, new classes of guideline-directed medical therapy (GDMT), including sodium-glucose cotransporter 2 inhibitors (SGLT2is) and angiotensin receptor-neprilysin inhibitors (ARNIs), will be key tools to incorporate into VBP models to ensure their success. Extensive literature demonstrates that the use of both SGLT2is and ARNIs in HF improves survival, decreases hospitalizations, and leads to improvements in PROs.^{38,39} These agents may incur higher initial costs, but VBPs provide a direct incentive for quality and efficiency that can facilitate improved clinical outcomes and reduce total costs over time. Thus, there is strong evidence to support the use of new medications under new payment models. Further efforts to tailor VBP models to HF could meaningfully influence treatment outcomes and reduce overall costs.

Novel Care Delivery Approaches

Hospital at Home

To reduce readmissions in HF, hospital-at-home (HAH) interventions can provide tailored patient care at a lower cost by using nurse-led

multidisciplinary teams in a patient's home environment. Patients with HF who received at-home care, including telephone support from physicians, reported lower depression levels, improved QOL, and longer time to readmission than did patients who received hospital-based care.^{40,41} HAH interventions can be used to educate and provide support to patients in managing HF.

The challenges that patients experience following hospital discharge for HF can be used to inform HAH interventions.⁴² For instance, some patients are unable to afford required medications and need guidance in accessing discount medication programs. Furthermore, patients may need support in HF disease management overall.⁴² To date, most HAH interventions have occurred in small groups of patients, and larger studies are warranted to assess feasibility in real-world settings.

Digital Tools

Novel innovations can foster improved quality of care and accessibility to health care services. PROMPT-HF (NCT04514458) is a recent pragmatic clinical trial that tested the effectiveness of a targeted electronic health record (EHR)-based alert system on improving the percentage of HF patients on GDMT.⁴³ More specifically, providers were randomly assigned to receive an alert with patient characteristics and individualized GDMT recommendations vs no alert or usual care. After 30 days, higher rates of GDMT were prescribed following the alerts than what is typically observed in standard care. On the other hand, a similar EHR-based study provided clinicians with the patient's risk of 1-year mortality during HF admissions to assess decisions about initiation or intensity of treatment, but this information did not affect hospitalizations, mortality, or clinical decision-making.⁴⁴ Thus, additional studies of EHR-based tools focused on indicated treatments could be used to improve treatment decisions and overall outcomes. Other digital tools in development are described in the [Table](#).^{45,46}

Conclusion

HF is a growing concern that requires a multidisciplinary approach to managing the disease.⁴⁷ While incumbent FFS models are based on volume, better payment models, such as VBP, have the potential to promote better short- and long-term outcomes in patients with HF by incentivizing improvements in health care.⁶ Further, incorporating SDOH into PROs could help to make the models more accurate in evaluating and managing HF in underserved populations.²³

Continued payment reform is needed to improve treatment outcomes and reduce costs in HF and to improve health equity within the context of SDOH. By improving phenotyping and incorporating metrics that account for SDOH and PROs, new VBP models could drive improvements in treatment outcomes for patients with HF. New technologies and care delivery models could have far-reaching impacts on the current health care system. ■

TABLE. Emerging Digital Tools^{45,46}

App/Service	Company	Description
Health Navigator	Amazon	An online service that helps employees get fast access to health care at their convenience and at their preferred location; it includes a tool that matches symptoms with possible diagnoses. ⁴⁵
Texttract	Amazon	A HIPAA-compliant machine learning service that automatically extracts text and data from insurance claims and medical charts without clinician intervention and allows for a quicker processing time for insurance claims. ⁴⁵
Health Care App	Apple	Personal health information (eg, medication records, laboratory results, and other vital information) from a third-party app that allows downloading by patients to their iPhones. ⁴⁶ Apple has collaborated with the US Department of Veterans Affairs to give millions of veterans access to their records through this app. ⁴⁵
Apple Watch	Apple	Users can volunteer to provide health-related data collected from the watch to further research in heart health, hearing, woman's health, and mobility. ⁴⁵
Predictive analytics platform	Google	This predictive analytics platform aggregates data from electronic health records to be able to predict adverse events; currently in development. ⁴⁵
Partnership between Mayo Clinic and Google	Google/Mayo Clinic	Google has entered a 10-year partnership with the Mayo Clinic and will use artificial intelligence machine learning to advance remote diagnosis, improve the ability to conduct research, and optimize treatment precision and patient outcomes. ^{45,46}
Partnership between Highmark Health, Verily, and Google Cloud	Google Cloud/Highmark Health/Verily	Highmark Health is launching a 6-year collaboration with Verily to build on its tech partnership with Google Cloud. Highmark will add the digital care tools for managing chronic conditions, including HF, to its Living Health model for patients and clinicians. ⁴⁶

App, application; HF, heart failure; HIPAA, Health Insurance Portability and Accountability Act.

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