Heart Failure with Reduced Ejection Fraction

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LEARNING OBJECTIVES

1. Distinguish phenotypic, structural, and functional classifications of heart failure to assess the stage of illness and delay disease progression.
2. Justify the incorporation of recently approved pharmacologic therapies for heart failure with reduced ejection fraction (HFrEF) into evidence-based therapies consistent with the American College of Cardiology's 2021 Expert Consensus Decision Pathway.
3. Develop a pharmacologic treatment plan for HFrEF that optimizes the use of traditional guideline-directed medical therapy.
4. Evaluate the role of inotropic agents and advanced therapeutic modalities available for patients with stage D heart failure.
5. Assess the potential benefit of pharmacologic therapies with recently expanded indications and promise for treatment of heart failure with preserved ejection fraction.

ABBREVIATIONS IN THIS CHAPTER

ACC/AHA	American College of Cardiology/ American Heart Association
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
CKD	Chronic kidney disease
ECDP	Expert Consensus Decision Pathway
eGFR	Estimated glomerular filtration rate
GDMT	Guideline-directed medical therapy
HF	Heart failure
HFimpEF	Heart failure with improved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
HHF	Hospitalization for heart failure
JHFS	Japanese Heart Failure Society
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal fragment B-type natriuretic peptide

INTRODUCTION

Epidemiology and Public Health Burden of Heart Failure

Heart failure (HF) is a staggering public health burden in the United States, affecting individual patients, caregivers, clinicians, and health care systems across the country. Nearly 1 million new cases of HF are diagnosed each year, amounting to a national prevalence of about 6 million Americans aged 20 years or older (Virani 2021). Although contemporary health policy efforts aim to improve care efficiency and delay the progression of disease, the aging population is projected to drive a 46% increase in HF prevalence by 2030, which will affect more than 8 million adults, or 3.0% of the general population (Gerber 2015). Heart failure is evenly proportioned between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), with 53% of patients having impaired systolic function and the remaining 47% having preserved systolic function. However, gender and racial disparities persist in HF consistent with cardiovascular disease as a whole: Black men are more commonly hospitalized with HFrEF at 70% and white women at 59%; those two groups constitute the highest proportion of HFpEF hospitalizations (Virani 2021). Despite long-standing availability of lifesaving pharmacotherapies, there remains a pervasive underutilization of evidence-based HFrEF medications, whereas only limited disease-modifying treatment options are available for patients with HFpEF (Greene 2018). Consequently, the 5-year mortality rate of overall HF rivals most of the major malignancies—at 52.6%—whereas 1-year mortality reaches a strikingly high 29.6% (Gerber 2015).

RAAS	Renin-angiotensin-aldosterone system
SGLT2	Sodium-glucose cotransporter 2
T2DM	Type 2 diabetes mellitus

Table of other common abbreviations.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General understanding of the pathophysiologic derangements leading to heart failure
- Knowledge of the American College of Cardiology/American Heart Association staging system and the New York Heart Association functional classification of heart failure
- Familiarity with traditional pharmacologic therapies indicated for HFrEF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and mineralocorticoid receptor antagonists

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Maddox TM, Januzzi JL, Allen LA, et al. 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: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77:772-810.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-61.
- McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021;42:3599-726.
- Neu R, Leonard MA, Dehoorne ML, et al. Impact of pharmacist involvement in heart failure transition of care. Ann Pharmacother 2020;54:239-46.

In addition to alarming rates of morbidity and mortality, HF consistently ranks as the costliest condition in the United States, with expenditures totaling $30.7 billion—two-thirds of which is attributable to direct medical costs (Heidenreich 2013). Because of the 30-day rehospitalization rate of 18.2% among Medicare beneficiaries with HF, much of the cost burden disproportionately affects acute-care facilities (Virani 2021). The tremendous strain HF exerts on health care institutions across the country has influenced payment reform to incentivize improved coordination of HF care delivery at the system level. Though significant health policy advancements have been made during the past decade, little or no improvement in hospital readmission rates or 30-day mortality has yet been realized. It is therefore imperative that a standardized approach to the risk stratification, diagnosis, and staging of HF progression be adopted so as to more readily identify patients appropriate for implementation of disease-modifying pharmacotherapy and advanced therapeutic modalities.

Distinguishing Between the Different Definitions and Classifications of Heart Failure

Previous definitions of HF were highly ambiguous and inconsistent across varying platforms, with indiscriminate focus on hemodynamic parameters, pathophysiologic aspects, and other clinical diagnostic features. Patients, clinicians, and investigators facing an unclear picture of HF despite the growing epidemiologic burden of disease underscore the importance of an updated, standardized characterization of the illness. A recently proposed universal definition as set forth by the Heart Failure Society of America (HFSA), the Heart Failure Association of the European Society of Cardiology (HFA-ESC), and the Japanese Heart Failure Society (JHFS) describes HF as clinical syndrome with a specific constellation of symptoms and structural or functional cardiac abnormalities known to be associated with HF. Those cardinal symptoms include dyspnea, fluid retention or edema, fatigue, and intolerance of daily-life activities. The physical presentation of HF must be further corroborated by the presence of elevated biomarkers or objective evidence of cardiogenic congestion. More specifically, elevated B-type-natriuretic-peptide levels of 35 or more or 100 or more pg/mL or N-terminal fragment proBNP (NT-proBNP) of 125 or more or 300 or more pg/mL for the ambulatory or hospital setting, respectively, must be present alongside confirmatory signs of HF captured by means of diagnostic modalities such as chest radiography, echocardiography, or right heart catheterization (Bozkurt 2021). Notably, natriuretic peptide thresholds endorsed by the HFSA/HFA-ESC/JHFS for HF diagnosis—although consistent with clinical practice guidelines—may have lower specificities in patients with advanced age, atrial fibrillation, or chronic kidney disease (CKD).

Beyond an updated definition of disease, new categories of HF according to left ventricle ejection fraction (LVEF) were also recently developed (Table 1). Both HFrEF and HFpEF remain

Table 1. Universal Classification of HF According to LVEF

HFSA/HFA-ESC/ JHFS classification	LVEF
HFrEF	≤40%
HFmrEF	41% – 49%
HFpEF	≥50%
HFimpEF	Baseline ≤40%, a ≥10-point increase from baseline and a second measurement of >40%

HFimpEF = heart failure with improved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA/HFA-ESC/JHFS = Heart Failure Society of America/Heart Failure Association of the European Society of Cardiology/Japanese Heart Failure Society; LVEF = left ventricular ejection fraction.

Information from: Bozkurt B, Coats AJS, Tsutsui H, et al. 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. J Card Fail 2021; 27:P387-413.

defined as LVEF 40% or less and 50% or more, respectively. However, the dichotomy of LVEF above or below the traditional 40% threshold has been expanded to include HF with mildly reduced EF (HFmrEF), which distinguishes transitional patients with LVEFs of 41% – 49% and which represents an underinvestigated subgroup that comprises up to 20% of patients with HF (Bozkurt 2021). Previously referred to as having *midrange HF*, patients with HFmrEF overlap the characteristics of both HFrEF and HFpEF—but they may be more likely to benefit from neurohormonal antagonism than would patients with preserved EF. Although HFmrEF may indicate early signs of deteriorating systolic dysfunction, this classification can also reflect recovering EF—typically in the setting of adherence to disease-modifying therapy. Therefore, periodic echocardiography assessment is recommended as a way of monitoring trends in LVEF overtime and can meaningfully inform response to therapy. To more specifically define the phenomenon, a new category was created to characterize patients with HF who also have LVEFs from which they have indeed recovered. Heart failure with improved EF (HFimpEF) represents such patients with a positive trajectory phenotype. Patients with HFimpEF have baseline LVEFs of 40% or less, but they experience a 10-or-more-point increase in systolic function, with a subsequent measurement of more than 40% (Bozkurt 2021).

Proposed revisions to stages in the development and progression of HF also extend further than only an updated disease description and new LVEF categories. The original American College of Cardiology/American Heart Association (ACC/AHA) staging system that described HF was based entirely on symptoms and the unidirectional absence or presence of structural heart disease. Although it may be widely known among clinicians, the ACC/AHA platform does not incorporate the evolving role of biomarkers in disease progression, nor does it exhibit strong association with prognosis or quality of life. The recent HFSA/HFA-ESC/JHFS classification of HF revises the previous ACC/AHA staging system to address the prior approach's gaps and limitations and to enhance patient and public understanding and adoption (Bozkurt 2021). The revised HFSA/HFA-ESC/JHFS staging platform recognizes HF as a continuum of illness with corresponding clinical trajectories as patients move from at risk of HF to pre-HF or de novo HF to more-advanced disease. The New York Heart Association's (NYHA's) functional classification of HF offers a complementary understanding of a patient's ACC/AHA or HFSA/HFA-ESC/JHFS stage by describing symptomatic severity as it affects limitations on the activities of daily life (Table 2). Unlike the ACC/AHA staging system, the NYHA scale is a bidirectional functional assessment and exhibits strong correlation with mortality as well as health-related quality of life. Pharmacists should be become familiar with both HFSA/HFA-ESC/JHFS staging and NYHA classifications so as to become able to identify appropriate pharmacotherapy commensurate with illness severity to delay disease progression, reduce mortality risk, and improve quality of life.

HF UPDATES ACCORDING TO THE 2021 EXPERT CONSENSUS DECISION PATHWAY

Biomarker Considerations

In addition to providing practical guidance to integrate recently approved pharmacotherapeutic classes into the care of patients with HFrEF, recent recommendations also highlight the importance of the routine incorporation of biomarkers into clinical practice as well as management strategies for common comorbid conditions (Maddox 2021). The natriuretic peptide system is a central counterregulatory process directly compensatory to HF pathophysiology. In response to ventricular wall stretch caused by high intracardiac filling pressures, atrial natriuretic peptide and BNP get synthesized and then released from cardiac myocytes. These neurohormones promote diuresis, natriuresis, and vasodilation while also inhibiting both the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). B-type natriuretic peptide and its inactive proteolytic fragment, NT-proBNP, are the two most well-characterized biomarkers in HF. Specifically, clinical practice guidelines confer a Class I recommendation to measure serum BNP or NT-proBNP concentrations in order to establish or exclude a

Table 2. Comparison of Structural and Functional Classifications of HF Development and Progression

ACC/AHA HF Staging System		HFSA/HFA-ESC/JHFS Universal Definition and Classification of HF		NYHA Functional Classification	
Stage	**Description**	**Stage**	**Description**	**Class**	**Description**
A	Patients at high risk of developing HF but without structural heart disease (e.g., HTN, DM, CAD, metabolic syndrome)	At risk	Patients at risk of HF but without current or prior symptoms or signs of HF and without structural, biomarker, or genetic markers of heart disease (e.g., HTN, CVD, DM, obesity, known exposure to cardiotoxins, cardiomyopathy history)	No associated functional class	N/A
B	Patients with structural heart disease but no signs or symptoms of HF (prior MI, low EF, no symptoms)	Pre-HF	Patients without current or prior symptoms or signs of heart failure but having evidence of one of the following: structural heart disease (LVH, valvular heart disease, chamber enlargement, etc.), abnormal cardiac function (reduced LV or RV systolic function, increased filling pressures, etc.), elevated natriuretic peptide levels (or elevated cardiac troponin levels after cardiotoxin exposure)	No associated functional class	N/A
C	Patients with structural heart disease and current or previous symptoms (low EF, HF signs/symptoms)	HF	Patients with current or prior symptoms and/or signs of HF caused by structural and/or functional cardiac abnormalities	I	No limitations of physical activity
				II	Slight limitation of physical activity
				III	Marked limitation of physical activity
D	Patients with symptoms despite maximal medical therapy (end-stage HF)	Advanced HF	Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory to or intolerant of GDMT requiring advanced therapies	IV	Unable to carry on any physical activity without discomfort

CAD = coronary artery disease; CVD = cardiovascular disease; DM = diabetes mellitus; EF = ejection fraction; GDMT = guideline-directed medical therapy; HF = heart failure; HTN = hypertension; LV = left ventricle; LVH = left ventricular hypertrophy; MI = myocardial infarction; N/A = not applicable; NYHA = New York Heart Association; RV = right ventricle.

Information from: Bozkurt B, Coats AJS, Tsutsui H, et al. 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. J Card Fail 2021;27:P387-413.

clinical diagnosis of HF, evaluate illness severity, and elucidate overall prognosis (Yancy 2017). Elevated natriuretic peptide concentrations in an ambulatory patient with HFrEF, for example, may be suggestive of an imminent risk of decompensation requiring intravenous diuretics and further escalation of care—particularly if levels are acutely increased from baseline.

Not only do natriuretic peptide levels play a prominent role in HF diagnosis and staging, but they also inform prognosis, determine risk stratification, and have more recently been applied to assess responsiveness to guideline-directed medical therapy (GDMT). This is because BNP and NT-proBNP concentrations typically get decreased by evidence-based pharmacotherapy proportional to their magnitude of clinical benefit. Conversely, patients with HFrEF whose natriuretic peptide levels fail to improve despite adherence to GDMT may be considered nonresponders, implying poor prognosis and advanced illness. In the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in HF trial, patients with HFrEF who achieved goal NT-proBNP levels of less than

1,000 pg/mL were associated with significant reverse ventricular remodeling, improved LVEF, and fewer adverse events after 1 year —independent of management strategy (Daubert 2019). Moreover, the Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure Study demonstrated that both the rapidity and robustness of NT-proBNP reductions after angiotensin- receptor–neprilysin-inhibitor (ARNI) initiation were associated with corresponding improvements in reverse remodeling as well as the odds of HF hospitalization or death (Januzzi 2020). Consequently, routine monitoring of natriuretic peptide concentrations serves as a useful risk assessment and treatment responsiveness tool. However, specific natriuretic-peptide-level targets as treatment goals are not currently endorsed by guidelines (Maddox 2021).

When using biomarkers to aid in clinical decision-making around intensification of GDMT, careful consideration must be given to assay interpretation for patients prescribed sacubitril/valsartan. Mechanistically—because of its inhibitory effect on neprilysin, a neutral endopeptidase responsible for BNP degradation—the sacubitril component of ARNI may cause concentrations of BNP to moderately increase and thereby further delay a return to baseline levels. And because NT-proBNP is not a substrate for neprilysin, however, it may be preferable to BNP as a monitoring parameter in the context of ARNI treatment (Maddox 2021). Pharmacists engaged in biomarker monitoring in the acute- or ambulatory-care context should inform HF-treatment providers of this unique interaction and then guide interpretation as needed.

Comorbidity Management in HF

Although HF is the leading individual cause of hospitalization in the United States, the presence of either cardiovascular or noncardiac comorbidities significantly increases the risk of further complications (Virani 2021). Multiple Class I and III antiarrhythmics used for control of atrial and ventricular arrhythmias, for example, are contraindicated in HF because of their negative inotropic or proarrhythmic effects. In addition, widely prescribed oral hypoglycemics for type 2 diabetes mellitus (T2DM)—such as thiazolidinediones often cause edema, which can precipitate HF symptoms. Even OTC medications such as NSAIDs or nasal decongestants like phenylephrine and pseudoephedrine can worsen HF (Pagell 2016). Guideline-directed medical therapy for HFrEF now also necessitates the use of four concomitant medication classes—all of which lower blood pressure. Therefore, prudent prescribing for patients with HF and comorbid conditions must be exercised so as to prevent polypharmacy and avoid medication-related adverse events.

Iron Deficiency

Iron deficiency—characterized by a ferritin of less than 100 ng/mL or 100–300 ng/mL with transferrin saturation of less than 20%—is estimated to affect approximately half of all patients with HFrEFs. The condition is independently associated with poor prognosis, reduced quality of life, and diminished exercise capacity irrespective of concomitant anemia (von Haehling 2019). Impaired oxygen delivery to tissue in patients with anemia precipitates neurohormonal and hemodynamic derangements that may overlap and exacerbate symptoms of HF like fatigue and dyspnea. Although screening for reversible causes of anemia is essential in a routine baseline evaluation for HF, the etiology is often complex and multifactorial. Functional iron deficiency caused by inflammation in the setting of chronic illness is not well understood, but it is important to know that lower ferritin thresholds for diagnosis apply to individuals without chronic conditions. Decreased dietary iron intake and reduced ferrous absorption in the edematous gut wall are likely contributory, but more-complex mechanisms related to iron sequestration have also been identified. It is important to correct iron deficiency in patients with HF, and therefore, pharmacists must carefully consider the iron formulation, route of administration, and dosing regimen.

Enteral iron preparations are poorly absorbed, often cause many unpleasant GI side effects, and require up to 6 months to replenish iron stores. The IRON-5 and IRONOUT-HF studies investigated the impact of ferrous sulfate and iron polysaccharide, respectively, but failed to demonstrate any functional impact on peak oxygen consumption in patients with iron-deficient HFrEF (von Haehling 2019). Intravenous iron avoids many of the drawbacks associated with oral supplementation and appears to hold more promising clinical benefit. Short-term exposure with parenteral ferric carboxymaltose in the FAIR-HF and CONFIRM-HF trials improved NYHA class performance and 6-minute walk-test performance. Ferric carboxymaltose was associated with a lower HF hospitalization risk in CONFIRM-HF, but the study was underpowered for assessment of clinical end points. Still, the 2017 ACC/AHA/HFSA guideline preferentially endorsed intravenous iron replacement in NYHA class II to IV HF with concomitant deficiency (Yancy 2017). Subsequently, the Randomised, Double-Blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Patients Admitted for Acute Heart Failure (AFFIRM-AHF) study demonstrated a 26% relative risk reduction in total HF hospitalizations with ferric carboxymaltose compared with placebo (217 [48.9%] vs. 294 [53.5%]; HR 0.74; 95% CI, 0.58–0.94, p=0.013) when initiated before discharge in clinically stabilized patients with iron-deficient acute HF with LVEFs of less than 50% after 1 year of follow-up (Ponikowski 2020). It is notable that ferric carboxymaltose was dosed at 500–2000 mg based on body weight and hemoglobin; patients who were persistently deficient received additional doses at weeks 6, 12, and 24 if needed. The ongoing FAIR-HF2, HEART-FID, and IRONMAN trials are expected to further inform the role of parenteral iron repletion

on clinical end points for patients with iron-deficient HF (clinicaltrials.gov).

Chronic Kidney Disease

The heart and kidney maintain saltwater homeostasis and regulate blood pressure by way of interdependent neurohormonal mechanisms that are critical to the function of either organ alone. Cardiorenal disease is, unsurprisingly, a prevalent manifestation of comorbid illness among patients with HF, because approximately half also suffer from CKD and vice versa (Virani 2021). Not only does CKD worsen an already poor prognosis of HF, but also mortality increases proportionally to the degree of coexistent renal insufficiency. It is important to note that randomized control trials establishing lifesaving pharmacotherapy for HFrEF have consistently excluded patients with severe renal dysfunction. Furthermore, this complex but common cohort is less likely to be prescribed GDMT compared with patients without kidney disease (Hein 2019). Many of the guideline-recommended medications for HF may affect kidney function, often necessitating renal dose adjustments and close monitoring. For example, RAAS inhibitors can potentiate the risk of hyperkalemia or precipitate acute kidney injury. Consequently, initial ARNI dosing should be reduced to 24/25 mg twice daily if estimated glomerular filtration rate (eGFR) is less than 30 mL/minute/1.73 m^2, whereas mineralocorticoid receptor antagonists (MRAs) are not recommended for use unless eGFR is more than 30 mL/minute/1.73 m^2 and serum potassium is less than 5 mEq/L (Yancy 2017).

Hyperkalemia is a well-established adverse medication reaction to RAAS inhibition that worsens with kidney disease and acts as a common barrier to the initiation or uptitration of GDMT (Maddox 2021). Beyond diet modifications to reduce potassium intake, novel potassium-binding resins such as patiromer sorbitex calcium and sodium zirconium cyclosilicate are now indicated for management of acute and chronic hyperkalemia. Adjunctive use of patiromer is associated with improved MRA utilization in patients with chronic HF and histories of hyperkalemia, but the impact on other RAAS inhibitors is not yet known (Pitt 2011). The ongoing DIAMOND, LIFT, and OPERA-HF trials should serve to (1) further define the roles of newer-generation potassium-binding resins to more broadly prevent hyperkalemia while enabling GDMT optimization and (2) clarify any potential benefit in HF outcomes (clinicaltrials.gov). Consideration of those agents in treating comorbid HF and CKD should include attention to binding interactions with other concurrent medications, GI discomforts, magnesium derangements with patiromer, and edema caused by increased sodium load with sodium zirconium cyclosilicate (Hein 2019). Until the role of novel potassium binders in HF is better understood, individualized selection of specific GDMT agents that may confer lower comparable levels of hyperkalemia or acute renal insufficiency risk such as ARNI or a sodium-glucose cotransporter 2 (SGLT2) inhibitor may be warranted (Riello 2021). Finerenone, a novel nonsteroidal MRA, has also demonstrated cardiorenal benefits, with a low incidence of hyperkalemia-related treatment discontinuation (1.2%–2.3%) in diabetic kidney disease studies FIDELIO-DKD and FIGARO-DKD (Pitt 2021; Bakris 2020). Recently, finerenone received regulatory approval to reduce the risk of sustained eGFR decline, end-stage renal disease, cardiovascular death, nonfatal myocardial infarction, and HF hospitalization in patients with comorbid CKD. The potential benefit of finerenone is being investigated in HFpEF as well by way of active enrollment of patients in the ongoing FINEARTS-HF trial (clinicaltrials.gov).

It is important that SGLT2 inhibitors be considered contraindicated in severe renal impairment per the prescribing label—but for a lack of A1C-lowering efficacy in diabetes management not explicitly because of safety concerns or relationship to nondiabetic indications. The SGLT2 inhibitors have been safely studied in patients with eGFRs as low as 20 mL/minute/1.73 m^2 for HF or CKD and have received corresponding label updates. For example, dapagliflozin recently received expanded regulatory approval to reduce the risk of kidney function decline, kidney failure, cardiovascular death, and hospitalization for HF on the basis of the DAPA-CKD trial (Heerspink 2020). In this study of patients with eGFRs of 25–75 mL/minute/1.73 m^2 and urinary albumin-to-creatinine ratios of 200–5000, dapagliflozin improved cardiorenal outcomes, including all-cause mortality independent of diabetes status after a median 2.4 years of follow-up compared with placebo. The ongoing EMPA-Kidney trial is anticipated to corroborate those beneficial effects with empagliflozin in patients with broader ranges of renal impairment inclusive of eGFR 20–90 mL/minute/1.73 m^2 (clinicaltrials.gov).

Diabetes

Among the most commonly encountered comorbidities for patients with HF, T2DM requires a strategic multidisciplinary approach to optimal management of both conditions simultaneously. Uncontrolled hyperglycemia typically leads to ischemic HF through atherosclerotic or hypertensive mechanisms but can also precipitate a diabetic cardiomyopathy that often manifests as diastolic dysfunction and, eventually, HFpEF (Jia 2018). Consequently, the presence of T2DM increases the risk of developing incident HF more than twofold among the general population; also, poor glycemic control significantly increases HF hospitalization risk and decreases overall survival among patients with established disease (Dunlay 2019).

Despite the substantial risk of cardiovascular complications in patients with T2DM, many commonly prescribed glucose-lowering agents have failed to consistently demonstrate improvements in macrovascular outcomes. And several antihyperglycemics have even demonstrated safety concerns related to HF. Thiazolidinediones as a class are known to carry an FDA boxed warning with regard to causing or exacerbating HF, and dipeptidyl peptidase 4 (DPP4) inhibitors alogliptin

and saxagliptin received regulatory precautions for increased HF hospitalization risk. Other conventional oral hypoglycemics like sulfonylureas and glinides have (1) only limited prospective evidence to support their safety in the treatment of HF and (2) mixed findings in observational studies (Dunlay 2019). In consideration of the more-consistent cardiorenal benefits demonstrated by SGLT2 inhibitors and glucagonlike peptide 1 (GLP-1) receptor agonists across multiple robust cardiovascular outcome trials, the most-recent American Diabetes Association guidelines recommend preferential use of these agents for patients who have T2DM with established atherosclerotic cardiovascular disease (ASCVD) or multiple cardiac risk factors (ADA 2020). Additional preference should be given to SGLT2 inhibitors specifically proven to reduce the risk of worsening HF and cardiovascular death in patients with diabetic HF—particularly those with HFrEF (Das 2020).

Several GLP-1 receptor agonists have demonstrated reductions in major adverse cardiovascular events among patients with T2DM and established ASCVD or multiple high-risk features. In the 9340-patient LEADER trial, liraglutide significantly reduced the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, and stroke compared with placebo after 3.8 years of median follow-up (Marso 2016a). Both of the smaller, SUSTAIN-6 and PIONEER 6 trials comparing injectable and oral semaglutide with placebo, respectively, were underpowered to determine superiority; however, each formulation was associated with similar reductions in the primary three-point composite end point (Husain 2019; Marso 2016b). Neither exenatide nor lixisenatide in the EXSCEL and ELIXA trials, respectively, demonstrated statistically significant reductions in cardiovascular outcomes compared with placebo. Weekly injections of dulaglutide compared with placebo in 9901 patients with T2DM predominantly at high cardiovascular risk improved the risk of cardiovascular death, nonfatal myocardial infarction, and stroke in the REWIND trial (Gerstein 2019). Notably, REWIND was the only GLP-1 receptor agonist cardiovascular safety study thus far to prespecify urgent HF visits as a secondary outcome—though no differences versus placebo were found. The benefit of most GLP-1 agonists appears to be driven by a reduction in cardiovascular death; a discernible impact on HF events has yet to be observed for GLP-1 agonists in patients who have T2DM and various cardiovascular-risk profiles. The limited evidence for GLP-1 receptor agonists in patients with HF but without diabetes has been largely neutral, with one notable exception. The FIGHT trial—which evaluated liraglutide compared with placebo in 300 recently decompensated patients with HF irrespective of T2DM diagnosis—did not determine any benefit for a variety HF-related outcomes and functional status; however, a nonsignificant trend toward a numerically increased risk of death or HF hospitalization was identified (HR 1.30; 95% CI, 0.92–1.83, p=0.14) throughout the 6-month study duration (Margulies 2016). And that risk was higher (HR 1.54; 95% CI, 0.97–2.46, p=0.07) among patients with HFrEF and T2DM. And because GLP-1 agonists exhibit positive chronotropic effects that consistently increase heart rate by 5–10 beats/minute, precaution should be taken when used in patients with diabetes and HFrEF—particularly patients who may not be optimally prescribed β-blocker therapy.

The first antihyperglycemic-medication class to demonstrate cardiorenal benefits among patients with T2DM at high cardiovascular risk consisted of the SGLT2 inhibitors. The EMPA-REG OUTCOME trial randomized 7020 patients with T2DM and established ASCVD to empagliflozin or placebo, evaluating three-point major adverse cardiovascular events as the primary composite end point. After a median follow-up period of 3.1 years, empagliflozin lowered the risk of the primary outcome by a striking 38%; HF hospitalizations by 35%; and all-cause mortality by 32% (Zinman 2015). The subsequent, CANVAS clinical trial program integrated results of canagliflozin across two placebo-controlled studies inclusive of 10,142 patients, with about 65% having prior ASCVD and with the remainder at only high cardiovascular risk (Neal 2017). The larger proportion of patients under primary prevention likely contributed to the achievement of a significant reduction in the same three-point composite end point of empagliflozin but not the individual component of cardiovascular death alone. Further, the CANVAS trial was complicated by a signal for increased risk of lower-limb amputations—particularly of the toe or metatarsal in patients with advanced diabetes who were not otherwise observed in other canagliflozin studies to date (Perkovic 2019). The largest SGLT2-inhibitor cardiovascular safety study—DECLARE-TIMI 58—enrolled the smallest proportion of patients with T2DM, established ASCVD at 40.6%, and, consequently, did not demonstrate improvement in the same three-point composite outcome (Wiviott 2018). However, given the consistent reduction in HHF demonstrated by prior SGLT2-inhibitor trials, the study oversight committee amended the protocol to incorporate an additional primary end point of cardiovascular death or hospitalization for HF. Compared with placebo, dapagliflozin significantly reduced the right of this composite end point (4.9% vs. 5.8%; HR 0.83; 95% CI, 0.73–0.95; p=0.005)—predominantly because of a reduction in HF hospitalizations. Despite an enrollment of 8246 patients with diabetes and established ASCVD, ertugliflozin did not improve the risk of major adverse cardiovascular events compared with placebo in the VERTIS-CV trial (Cannon 2020). In alignment with prior SGLT2-inhibitor trials, only HF hospitalizations were significantly reduced with ertugliflozin. A dual SGLT1 and SGLT2 receptor antagonist—sotagliflozin—is currently being considered for regulatory approval. In SCORED—a recent, 10,584-patient cardiovascular outcomes study of patients with comorbid T2DM and CKD and with or without albuminuria—sotagliflozin significantly reduced its amended coprimary composite end point of cardiovascular death, HF hospitalizations, and urgent HF visits (HR 0.74; 95% CI, 0.63–0.88; p<0.001) (Bhatt 2021a).

In the subsequent, SOLOWIST-WHF trial, which enrolled 1222 patients with T2DM and recent hospitalizations for worsening HF, sotagliflozin also produced the same primary composite outcome (51.0% vs. 76.3%; HR 0.67; 95% CI, 0.52–0.85; p<0.001) compared with placebo (Bhatt 2021). Early terminations of the trials—caused by loss of sponsor funding and the advent of the COVID-19 pandemic—may have encumbered the ability to detect differences in individual components of the primary outcome. However, a pooled analysis of both studies suggests the benefits of sotagliflozin may apply to patients with diabetes and HF irrespective of LVEF, including HFmrEF and HFpEF (Bhatt 2021b).

New Evidence-Based Medications for HFrEF

SGLT2 Inhibitors

The use of SGLT2 inhibitors for cardiovascular-risk reduction in patients with T2DM has been part of consensus practice for the past few years, but their emerging role as the fourth pillar of HFrEF GDMT has been demonstrated only recently (Maddox 2021). By promoting glucosuria through a blockade of sodium and glucose reabsorption in the proximal tubule of the nephron, SGLT2 inhibitors lower glucose. Their mechanism for cardiorenal protection is not well understood but appears to be multifactorial and related principally to (1) hemoconcentration, (2) osmotic diuresis and natriuresis, (3) arterial pressure and stiffness reduction, and (4) efficient myocardial ketone metabolism—all of them independent of hyperglycemia (Zelniker 2020).

The first landmark randomized, controlled trial to establish the benefit of SGLT2 inhibitors beyond T2DM investigated the role of dapagliflozin in patients with HFrEF. In the DAPA-HF study, dapagliflozin reduced the risk of the primary composite end point of worsening HF or cardiovascular death compared with placebo in 4744 patients with HFrEF and with or without diabetes (16.3% vs. 21.2%; HR 0.74; 95% CI, 0.65–0.85) after 18.2 months of median follow-up (McMurray 2019). Unlike the previous, DECLARE-TIMI 58 study, dapagliflozin also significantly reduced the risk of key secondary end points, including cardiovascular death (9.5% vs. 11.5%; HR 0.82; 95% CI, 0.69–0.98) and all-cause mortality (11.6% vs. 13.9%; HR 0.83; 95% CI, 0.71–0.97). Based on the landmark findings from the DAPA-HF study, dapagliflozin received expanded regulatory approval to reduce the risk of death or HF hospitalization among patients with HFrEF irrespective of the presence or absence of T2DM. The EMPEROR-Reduced trial corroborated the benefits of SGLT2 inhibitors in patients with HFrEF and diabetes and patients with HFrEF but without diabetes alike. In the study, empagliflozin significantly reduced the primary composite outcome of HF hospitalization or cardiovascular death (19.4% vs. 24.7%; HR 0.75; 95% CI, 0.65–0.86) among 3730 patients with HFrEF compared with placebo after a median 16 months (Packer 2020). This benefit appeared to be largely influenced by the effect on HF hospitalizations, as neither cardiovascular death (10% vs. 10.8%; HR, 0.92; 95% CI, 0.75-1.12) nor overall mortality (10.1% vs. 10.7%; HR, 0.92; 95% CI, 0.62-1.19) achieved statistically significant differences. An ensuing meta-analysis of both pivotal trials, however, did indeed suggest the benefits of dapagliflozin and empagliflozin consistently improved a host of cardiorenal outcomes in HFrEF patients independent of T2DM (Zannad 2020).

The immense benefit of SGLT2 inhibitors in patients with or without diabetes is anticipated to rapidly increase overall prescribing rates, warranting practical considerations for routine incorporation into the HF armamentarium. It is important to note that the doses of dapagliflozin and empagliflozin studied for HFrEF were the same, 10-mg once-daily regimen. Dosing of empagliflozin should be increased to 25 mg only if additional glucose lowering is desired—for example, in uncontrolled comorbid T2DM. Hemoglobin A1C reduction is unlikely to occur in advanced kidney disease, but cardiorenal benefits appear to be maintained if eGFR is 25 or more or 20 or more mL/minute/1.73 m^2 with dapagliflozin and empagliflozin, respectively. Nondiabetic patients—and even diabetic patients not concomitantly prescribed a sulfonylurea or insulin therapy—rarely experience hypoglycemic events from an SGLT2 inhibitor alone. To avoid ketosis, however, (1) SGLT2 inhibitors should be held 3 days before major surgery in patients with T2DM and (2) confirmed modifiable risk factors for ketoacidosis should be resolved before reinitiating. In addition, fluctuating clinical features such as renal function, volume status, and nutritional intake should be evaluated before routine inpatient continuation of chronic therapy or new initiation in hospitalized patients across therapeutic indications. Dose reductions of concurrent loop diuretic therapy may be warranted over time for patients prescribed an SGLT2 inhibitor—especially if blood pressure is tenuous or indicative of intravascular volume contraction. Although genital mycotic infections are the most common adverse reactions to SGLT2 inhibitors—occurring predominantly in women and uncircumcised males—proper personal hygiene may mitigate risk. If treatment is required, topical or systemic antifungal therapy typically alleviates discomfort. Urinary tract infections occur less often but may be more likely to occur in patients with histories of pyelonephritis, kidney stones, ureteral stenting, or indwelling urinary catheters.

sGC Modulators

The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway regulates vasodilation and myocardial demand via smooth muscle relaxation. In HF, inadequate cardiac output and decreased NO bioavailability result in compensatory vasoconstriction and reduced cGMP generation. Organic nitrate supplementation activates NO-sGC-cGMP but is limited by tachyphylaxis and may contribute to oxidative stress. Novel oral sGC activators stimulate cGMP synthesis, enhance sGC sensitivity to NO, and promote vasodilation independent of NO or heme.

Vericiguat is the first sGC activator approved to reduce the risk of cardiovascular death, hospitalization for heart failure (HHF), and outpatient intravenous diuretics in symptomatic patients with chronic HF and LVEFs of less than 45%. Despite recent regulatory approval, vericiguat initially disappointed in the phase II, dose-finding Soluble Guanylate Cyclase Stimulation in Heart Failure with Reduced Ejection Fraction (SOCRATES-REDUCED) trial (Gheorghiade 2015). The SOCRATES-REDUCED trial randomized 456 clinically stable patients with chronic heart failure recently hospitalized for HF and with LVEFs of less than 45% to either placebo or one of four oral vericiguat doses ranging from 1.25 to 10 mg daily for 12 weeks. Although vericiguat was well tolerated, the primary end point of change in NT-proBNP was no different from that of placebo. The phase III Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial, however, achieved its primary composite end point of cardiovascular death or first HHF (Armstrong 2020). In the VICTORIA study, 5050 patients with NYHA II–IV HF and LVEFs of less than 45% on optimal medical therapy were randomized to receive vericiguat to a target 10 mg or placebo. Driven primarily by a reduction in HHF, vericiguat modestly reduced the risk of the primary outcome (37.9% vs. 40.9%; HR 0.90; 95% CI, 0.83–0.98; p=0.02) after a median 10.8 months of follow-up. Neither symptomatic hypotension nor syncope occurs more often with vericiguat.

In light of guideline preference for ARNI and the addition of SGLT2 inhibitors to GDMT, vericiguat's place in therapy should be reserved for patients with advanced HFrEF and recent decompensation despite optimal therapy for whom an additional branded medication does not cause undue financial burden. Further benefit may also be derived in patients with low circulating biomarker levels, including cGMP, NO, and BNP, although this precision-medicine approach to vericiguat therapy requires further elucidation to support routine consideration. Because of the exclusion of patients prescribed long-acting nitrates and NO donors from the VICTORIA trial, however, it is unclear how the combination of vasodilatory therapies would be tolerated or would affect clinical outcomes (Armstrong 2020). Therefore, the traditional, vasodilatory combination of isosorbide dinitrate and hydralazine still remains strongly preferred to vericiguat for African American patients with HFrEF as a compulsory add-on to GDMT (Maddox 2021).

OPTIMIZING GDMT

For decades, the original, evidence-based pillars of GDMT for HFrEF have included RAAS inhibitors and sympathetic nervous system antagonists from three primary pharmacologic categories: angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), β-blockers, and MRA. Despite long-standing availability, widespread affordability, and robust evidence to support the strongest possible guideline recommendations for use in all patients with stage C HFrEF, less than 25% of eligible patients are prescribed all three medication classes in contemporary practice (Greene 2018). Furthermore, a dismal 1% of those patients are simultaneously titrated to target doses proven to extend survival in pivotal clinical trials (Table 3).

Table 3. Evidence-Based Dosing Guidance for HFrEF Medications

	Starting Dose	Target Dose	Mean Total Daily Dose Achieved in Clinical Trials
ACEI (Class I; LOE A)			
Captopril	6.25 mg TID	50 mg TID	122.7 mg
Enalapril	2.5 mg BID	10–20 mg BID	16.6 mg
Lisinopril	2.5–5 mg	20–40 mg	32.5–35 mg
Ramipril	1.25–2.5 mg	10 mg	7.7 mg
Trandolapril	0.5–1 mg	4 mg	2.5 mg
ARB (Class I; LOE A)			
Candesartan	4–8 mg	32 mg	24 mg
Losartan	50 mg	150 mg	129 mg
Valsartan	40 mg BID	160 mg BID	254 mg
ARNI (Class I; LOE B)			
Sacubitril/Valsartan	24/26–49/51 mg	97/103 mg BID	375 mg[a]

(*continued*)

Table 3. Evidence-Based Dosing Guidance for HFrEF Medications (*continued*)

	Starting Dose	Target Dose	Mean Total Daily Dose Achieved in Clinical Trials
β-Blockers (Class I; LOE A)			
Bisoprolol	1.25 mg	10 mg	8.6 mg
Carvedilol	3.125 mg BID	25 mg BID for weight <85 kg 50 mg BID for weight ≥85 kg	37 mg
Carvedilol CR	10 mg	80 mg	Not studied
Metoprolol succinate	12.5–25 mg	200 mg	159 mg
MRA (Class I; LOE A)			
Eplerenone	25 mg QD	50 mg	42.6 mg
Spironolactone	12.5–25 mg	25-50 mg	26 mg
sGC Modulators[b]			
Vericiguat	2.5 mg QD	10 mg	8.9 mg
SGLT2 Inhibitor[b]			
Dapagliflozin	10 mg	10 mg	Not reported
Empagliflozin	10 mg	10 mg	Not reported
Vasodilators (Class I; LOE A)			
Hydralazine	25 mg TID	75 mg TID	Not studied
Isosorbide dinitrate	20 mg TID	40 mg TID	Not studied
Fixed-dose combination hydralazine/ isosorbide dinitrate[c]	20/37.5 mg TID	40/75 mg TID	90 mg/175 mg
If Channel Inhibitor (Class IIA; LOE B)			
Ivabradine	2.5–5 mg BID	Titrate to HR 50–60 bpm Maximum dose 7.5 mg BID	13 mg

[a]Total daily dose of both individual sacubitril/valsartan components described in the PARADIGM-HF trial.

[b]Both sGC modulators and SGLT2I became recently approved for HFrEF, but only SGLT2Is are endorsed in updated Expert Consensus Decision Pathways as GDMTs.

[c]The ACC/AHA/HFSA guideline considers either the fixed-dose combination or the separate combination of isosorbide dinitrate and hydralazine appropriate for GDMT for HFrEF in self-described Black patients, but it is important to note that these recommendations do not include isosorbide mononitrate.

ACC = American College of Cardiology; ACEI = angiotensin-converting-enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BID = twice daily; bpm = beats per minute; GDMT = guideline-directed medical therapy; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; HR = heart rate; LOE = level of evidence; MRA = mineralocorticoid receptor antagonist; QD = once daily; sGC = soluble guanylate cyclase; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

Information from: Maddox TM, Januzzi JL, Allen LA, et al. 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: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77:772-810.

Because ARNI preference and SGLT2 inhibitor incorporation into GDMT became endorsed only more recently by guidelines and expert consensus statements, adoption of these newer therapies represents an immediately impactful quality improvement opportunity. For example, just 2% of patients with HFrEF and comorbid T2DM are currently treated with SGLT2 inhibitors—with prescribing rates for patients without diabetes presumably even lower (Vaduganathan 2020). Plus, positioning SGLT2 inhibitors as the fourth pillar of GDMT for HFrEF management may reduce cumulative mortality risk by 73%, thereby preventing one death for every 3.9 patients treated over 2 years (Bassi 2020). All four disease-modifying therapeutic classes have early, incremental, and additive benefits when used as quadruple therapy,

yet they remain woefully underutilized at present for a multitude of reasons.

Barriers to optimal medication titration are indeed multifaceted but most often include patient-specific factors such as abnormal kidney function, hyperkalemia, hypotension, pill burden, or out-of-pocket expenses—particularly in the incorporation of more-recently-approved therapies such as ARNI and SGLT2 inhibitors (Maddox 2021). Provider- and health-system-related impediments to the implementation of established GDMT may also play a role. Clinical inertia, siloed care, poor interprovider communication, and lack of familiarity with highly complex HF regimens are among the chief contributing nonpatient factors. Therefore, routine integration of pharmacists into collaborative, multidisciplinary-care pathways dedicated to HF management are critical to optimizing GDMT and promoting medication adherence.

Sequence of Initiation and Titration

The fundamental principle of HF care is to prioritize the use of GDMT to derive the greatest potential benefit. For all patients with HFrEF, this now includes quadruple therapy with ARNI, evidence-based β-blockers, MRA, and SGLT2 inhibitors (Maddox 2021). In addition, the combination of hydralazine and isosorbide dinitrate is also first-line therapy for all self-identified African Americans, and ivabradine may be considered second-line for select HFrEF patients in sinus rhythm (Figure 1).

Conventional sequencing of GDMT was cumbersome and protracted, typically requiring at least 6 months to reach target doses while also necessitating a trial period of ACEI or ARB before transitioning to ARNI (Yancy 2017). Although more-recent guideline recommendations endorse preference for ARNI initiation in de novo HFrEF, transitioning stable patients on ACEIs or ARBs is still a commonly encountered clinical scenario. Patients on equivalent ACEIs that total a daily dose of more than 10 mg of enalapril can begin sacubitril/valsartan 49/51 mg twice daily after a 36-hour washout period. The same dose of sacubitril/valsartan is also recommended for patients on an equivalent total daily dose of more than 160 mg of valsartan. Patients on fewer ACEI/ARB equivalents and who have eGFRs of less than 30 mL/minute/1.73 m^2 are recommended for initiation with sacubitril/valsartan 24/26 mg twice daily.

Within 1 or 2 weeks of initiation, GDMT begins to reduce the risk of cardiovascular death, HHF, and urgent HF visits, and based on that, treatment should begin immediately in stable patients (Packer 2021). Deferring optimal medical therapy reduces the likelihood of ever initiating GDMT and therefore may also result in preventable harm. Opportunities to initiate and uptitrate GDMT in the hospital setting or during the vulnerable, postdischarge period should not be missed. Furthermore, because target doses of each medication are associated with the best possible outcomes, titration to these dosing thresholds should be attempted until reached or maximally tolerated. Subtarget dosing still confers a magnitude of benefit—precluding the need to achieve target doses before initiating other disease-modifying therapy. Previous intolerance should not obviate future titration attempts in the absence of contraindications. Furthermore, tolerability may be improved by initiating GDMT at lower starting doses or by staggering individual agents—particularly ARNI and β-blockers (Greene 2021). Simultaneous initiation of MRA and SGLT2 inhibitors, however, requires no or minimal titration and rarely precipitates adverse effects.

Recent guidelines endorse ARNI initiation to be concurrent with β-blocker therapy, followed by adding MRA and SGLT2 inhibitors 2–4 weeks later (Maddox 2021). With continual potassium, creatinine, and vital sign monitoring, doses of each medication can be increased on a biweekly basis until goal or maximal tolerated dose is achieved. More-intensive approaches to GDMT optimization support synchronized initiation of all four foundational therapies at once, completing titration to target doses as soon as 3 weeks (Greene 2021). Alternative sequencing strategies propose simultaneous initiation of β-blockers and SGLT2 inhibitors first, followed by ARNI and MRA within 4 weeks thereafter (McMurray 2021). Uniquely, uptitration to target doses with this model occurs only after quadruple therapy has been established. A thorough understanding of medication-specific factors—including mechanism of action, common adverse effects, and routine monitoring parameters—is key to successful titration of GDMT to target dosing (Table 4). Irrespective of the particular pathway chosen, an individualized approach that prioritizes both the timely initiation and the optimization of GDMT must also coincide with close clinical assessment and consideration of patient-specific barriers to medication titration.

INOTROPIC THERAPY

The term *inotropic therapy* refers broadly to pharmacologic treatments that improve cardiac contractility. Although clinically useful for acute treatment of cardiogenic shock with low cardiac output, inotropes are associated with adverse outcomes when used for chronic HF. Despite a multitude of attempts, short-term improvements in hemodynamics or surrogate measures of cardiac performance with inotropic agents have not translated into longer-term morbidity benefits and have even increased mortality (Ahmad 2019). However, initial investigation of inotropic therapy was conducted before incorporation of β-blockers and cardiac resynchronization therapy or implantable cardioverter-defibrillator devices (CRT/ICD) into routine practice. Given the growing population of patients with end-stage HF, the high cost of ventricular-assist devices, and the organ shortage facing cardiac transplantation, interest in the development of novel and safe inotropes possessing unique mechanisms of action has been reinvigorated after a substantial hiatus.

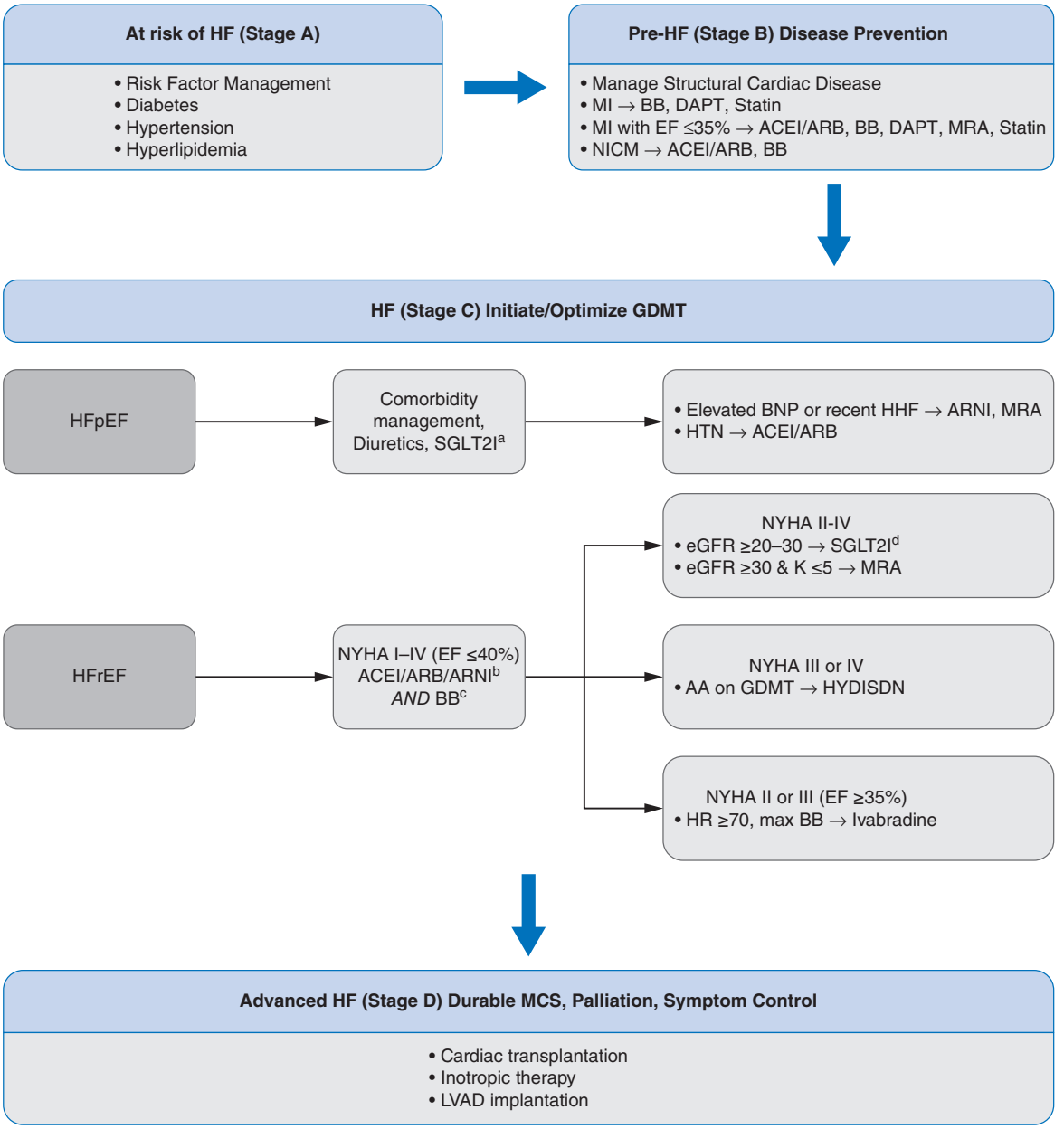

Figure 1. Treatment algorithm for HF.

[a]Empagliflozin reduced the risk of cardiovascular death or HHF among patients with HFpEF.
[b]ARNI is preferred to ACEI or ARB as first-line therapy. Prior ACEI/ARB tolerance is not required.
[c]Evidence-based β-blockers include bisoprolol, carvedilol, and metoprolol succinate. Though also recommended, carvedilol CR was approved on the basis of pharmacokinetic equivalence.
[d]Empagliflozin if eGFR is 20–29 or more mL/minute/1.73 m^2. Either dapagliflozin or empagliflozin if eGFR is 30 or more mL/minute/1.73 m^2.
AA = African American; ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = β-blocker; CRT = cardiac resynchronization therapy; DAPT = dual antiplatelet therapy; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GDMT = guideline-directed medical therapy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HHF = hospitalization for heart failure; HR = heart rate; HTN = hypertension; HYD-ISDN = hydralazine-isosorbide dinitrate; ICD = implantable cardioverter-defibrillator; K = potassium; MCS = mechanical circulatory support; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; SGLT2I = sodium-glucose cotransporter 2 inhibitor.
Information from: Maddox TM, Januzzi JL, Allen LA, et al. 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: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77:772-810.

Table 4. HF Therapies: Mechanism of Action, Adverse Effects, and Monitoring

Drug Class	Mechanism of Action	Adverse Effects	Monitoring Parameters
ACEI	Inhibit ACE, reducing Ang I conversion to Ang II	• Acute kidney injury • Angioedema • Cough • Hyperkalemia • Hypotension	• BP • K • SCr
ARB	Antagonize Ang II type 1 receptor	• Acute kidney injury • Angioedema • Hyperkalemia • Hypotension	• BP • K • SCr
ARNI	Inhibit neprilysin, potentiating natriuretic peptide activity Antagonize Ang II type 1 receptor	• Acute kidney injury • Angioedema • Cough • Hyperkalemia • Hypotension	• BP • K • NT-proBNP • SCr
β-Blockers	Antagonize β-adrenergic receptor and potentially α-adrenergic activity	• Bradycardia • Dizziness • Hypotension	• BP • HR
Digoxin	Inhibit Na/K ATPase pump, increasing intracellular Na and Ca influx, improving impaired baroreceptor reflex and renal Na reabsorption, and inhibiting sympathetic activity	• Bradycardia • Confusion • Dizziness • Nausea • Visual disturbances • Vomiting	• BP • Digoxin level • HR
Hydralazine	Direct arteriole vasodilation	• Dizziness • Headache • Hypotension	• BP
If Channel Inhibitors	Selective sinoatrial node funny-channel-current-flow disruption	• Bradycardia • Hypotension • Phosphenes	• BP • HR
Isosorbide dinitrate	Increase cGMP concentration, relaxing vascular smooth muscle	• Dizziness • Headache • Hypotension	• BP
Loop Diuretics	Inhibit Na reabsorption in ascending loop of Henle	• Dizziness • Continual urination • Hypotension • Muscle cramps • Thirst	• BP • Urine output • Volume status • Weight
MRA	Antagonize mineralocorticoid receptor, blocking aldosterone	• Gynecomastia (spironolactone) • Hyperkalemia	• BP • K • SCr
sGC Modulators	Increase cGMP concentration, relaxing vascular smooth muscle	• Anemia • Hypotension	• BP • CBC
SGLT2I	Antagonize Na-glucose cotransporter in proximal tubule, reducing renal glucose reabsoprtion	• Acute kidney injury • Dyslipidemia • Genital mycotic infection • Hypoglycemia • Ketoacidosis • Urinary tract infection	• A1C • BP • Glucose • SCr • Volume status

(*continued*)

Table 4. HF Therapies: Mechanism of Action, Adverse Effects, and Monitoring (*continued*)

ACEI = angiotensin-converting enzyme inhibitor; Ang I = angiotensin I; Ang II = angiotensin II; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BP = blood pressure; Ca = calcium; CBC = complete blood count; HF = heart failure; HR = heart rate; K = potassium; MRA = mineralocorticoid receptor antagonist; Na = sodium; NT-proBNP = N terminal fragment B-type natriuretic peptide; SCr = serum creatinine; sGC = soluble guanylate cyclase; SGLT2I = sodium-glucose cotransporter-2 inhibitor.

Because of both lack of demonstrated benefit and potential for harm, the current role of conventional inotropic agents—chiefly dobutamine, and milrinone—is limited to patients with advanced HF refractory to GDMT for either palliation or as bridge therapy to mechanical circulatory support or cardiac transplant in eligible patients (Yancy 2013). Dobutamine—a β-agonist—and milrinone—a phosphodiesterase-3 inhibitor—directly improve cardiac contractility and provide varying degrees of vasodilation through activity in the peripheral vasculature. Dobutamine reduces systemic vascular resistance at lower doses but exerts a largely neutral impact on vascular tone at higher doses because of a counterbalance of α_1 and β_2 receptor affinity. Although milrinone provides more-balanced inodilation across the dosing spectrum, it is eliminated renally, and given its comparably longer half-life, it may accumulate in kidney injury. Milrinone does avoid direct adrenergic agonism, which may be advantageous for patients with HF-prescribed concomitant β-blocker therapy. Both agents are highly arrhythmogenic, however, which necessitates

Patient Care Scenario

A 56-year-old African American woman with a medical history significant for T2DM (A1C = 7.4% on metformin), CKD stage 3 (baseline SCr 1.3; eGFR 45 mL/minute/1.73 m²), and HFrEF (LVEF = 33%) was hospitalized for shortness of breath and fluid overload consistent with an acute decompensation requiring intravenous diuretics. During the hospital stay, her home losartan 100 mg daily was changed to sacubitril/valsartan 97/103 mg twice daily; home metoprolol succinate continued at 200 mg daily; and she was newly started on spironolactone 50 mg daily.

During a visit to the HF disease management clinic 2 weeks after discharge, she reports somewhat tolerating the new medication regimen aside from a few headaches, fatigue, and episodes of lightheadedness. A basic metabolic panel from the clinic is unremarkable. Her HR is 72 beats/minute, and blood pressure is 105/75 mm Hg. A repeat echocardiogram revealed her LVEF was remaining around baseline at 34%. What is best to recommend for this patient?

ANSWER

The sequencing of initiation and uptitration of GDMT for HFrEF is a common but complex clinical problem facing contemporary HF management. Before SGLT2 inhibitors' demonstrations of cardiovascular mortality and HHF benefit when added on to ACEI/ARB/ARNI, β-blocker, and MRA, the combination of hydralazine and isosorbide dinitrate would be indicated as part of GDMT for self-identified Black patients given the 43% relative reduction in mortality observed in the A-HeFT trial. Current guidance recommends African American patients with HFrEF be prescribed this combination after GDMT has been adjusted to target or maximally tolerated doses. This patient's GDMT regimen was titrated to goal during the hospital stay. Although her systolic blood pressure is only on the lower end of normal, she is already experiencing side effects likely attributed to low blood pressure. The combination of hydralazine and isosorbide dinitrate often causes headache and dizziness but reduces systolic and diastolic blood pressure by only 1.9 and 2.4 mm Hg, respectively; SGLT2 inhibitors reduce systolic blood pressure by about the same magnitude or less. Given her concomitant CKD and T2DM with an A1C above goal, there are compelling indications for initiation of an SGLT2 inhibitor such as dapagliflozin or empagliflozin to reduce the risk of cardiorenal complications and thereby preserve kidney function. To date, no heterogeneity by ethnicity or race has been identified in SGLT2 inhibitor studies. Prioritizing the initiation of both the combination of hydralazine and isosorbide dinitrate as well as the SGLT2 inhibitor studied in HF would be consistent with the 2021 ACC Expert Consensus Decision Pathway and should be individualized to the patient's comorbid conditions and tolerance for additional GDMT that may further lower blood pressure.

1. Maddox TM, Januzzi JL, Allen LA, et al. 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: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77:772-810.
2. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57.
3. Morris AA, Testani JM, Butler J. Sodium-glucose cotransporter-2 inhibitors in heart failure: racial differences and a potential for reducing disparities. Circulation 2021;143:2329-31.

careful monitoring and use of minimal effective doses to alleviate symptomatic congestion.

Palliative HF Care

Although successful implementation and titration of GDMT substantially improve survival, HF remains a debilitating and progressive disease with a poor overall prognosis. Therefore, palliative care is strongly recommended for all patients with advanced HF in order to improve quality of life (Yancy 2013). Despite those recommendations and robust evidence for improved patient-centered health outcomes, palliative care is a persistently underutilized service that is rarely offered to patients with HF (Diop 2017). A comprehensive palliative-care plan should be integrated early in HF management and include intensive symptomatic relief, detailed end-of-life preferences, and access to caregiver support. Even in advanced HF, GDMT may be useful to extend life and avoid hospitalization. Diuretic agents, however, are more critical to achieve immediately control of symptoms of congestion and should be continued through hospice to end of life (Maddox 2021). Home infusions of dobutamine or milrinone should also be considered for palliation to improve functional status, though patients with end-stage HF may become (1) inotrope dependent as their conditions worsen and (2) unable to wean without deterioration. As patients with HF transition toward comfort care, discontinuation of life-sustaining inotropes or neurohormonal antagonists may be prudent. These complex treatment decisions should be individualized to reflect a patient's wishes in concert with a palliative-care consultant.

Investigational Therapies

Omecamtiv Mecarbil

Omecamtiv mecarbil selectively activates cardiac myosin to promote conformational change of the physiologic, weakly bound myosin-ATP intermediate state to a stronger, actin-bound, force-producing state to stimulate myosin phosphate release. This mechanism is thought to enhance the duration and force of each systolic contraction without affecting myocardial energetics. Because omecamtiv acts directly on the sarcomere, it avoids certain potentially problematic calcium-related proarrhythmic effects observed with other inotropes like digoxin, dobutamine, milrinone, and levosimendan (Psotka 2019).

The Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial recently compared pharmacokinetically guided dosing of omecamtiv mecarbil with placebo in 8256 patients with symptomatic chronic HF and LVEFs of 35% or less (Teerlink 2021). After a median follow-up period of 21.8 months, the primary composite outcome of HHF, urgent HF visit, or cardiovascular death occurred significantly less often with omecamtiv (37.0% vs. 39.1%; HR 0.92; CI 0.86–0.99; p=0.03). It is important to note that that difference was driven by HHF and urgent-care visits; cardiovascular death alone was not affected (19.6% vs. 19.4%; HR 1.01; CI 0.92–1.11). Potentially related to increased contractility, patients with severely depressed LVEFs of 28% or less appeared to derive greater benefit than did patients with systolic dysfunctions of more than 28%. A modest quality-of-life improvement in the Kansas City Cardiomyopathy Questionnaire was also observed for patients recruited in the hospital but not in the ambulatory-care setting. Although NT-proBNP decreased by 10% at week 24, omecamtiv increased cardiac troponin levels 4 ng/L higher. Despite that finding, cardiac ischemic and ventricular arrhythmia events were similar to placebo.

Omecamtiv mecarbil awaits regulatory review, but its place in therapy within the expanding HFrEF treatment landscape deserves further clarification. Based on GALACTIC-HF, recently decompensated patients with poor systolic functions may stand to benefit the most. Omecamtiv may also be especially useful when hypotension or renal insufficiency limits the initiation or titration of GDMT as well as in patients with advanced or end-stage HF who may not be candidates for continuous inotrope infusions. Given that plasma concentration-guided dosing of omecamtiv mecarbil was used in clinical trials, it is likely that pharmacists will play a crucial role in its future use and monitoring.

ADVANCED THERAPEUTIC MODALITIES

CRT/ICD Devices

Ventricular arrhythmias are common complications of HF and are of concern. Arrhythmogenesis is often multifactorial because of increased sympathetic tone, underlying ischemic heart disease or myocardial scarring, conduction delays, electrolyte abnormalities, and drug-induced arrhythmias. Although GDMT may reverse cardiac remodeling and lower arrhythmia risk, up to half of all patients with HF still die from sudden cardiac death precipitated by a ventricular tachyarrhythmia (Virani 2021). Implantable cardiac devices consist of an electronic generator and lead wires, typically placed by way of a minimally invasive procedure in a cardiac catheterization or electrophysiology laboratory. Leads are inserted into a peripheral vein and guided toward the heart, one end attaching to the generator and the other terminating in cardiac tissue itself. The generator is powered by lithium batteries, which can last up to 10 years before requiring replacement, at which time the device must be accessed from a tunneled pocket under the skin of the chest well. Device pocket hematomas are rare but major risks of morbidity, necessitating cautious periprocedural anticoagulation management. Subcutaneous systems are alternatives to the traditional transvenous approach, featuring an entirely extracardiac implantation procedure that avoids many of the common perioperative complications of conventional devices.

Implantable cardioverter-defibrillators (ICDs) detect and terminate ventricular dysrhythmias by way of single- or dual-chamber defibrillator leads capable of electronic-shock delivery. A biventricular ICD, also known as a *cardiac resynchronization therapy* (CRT) device, consists of a right-ventricular defibrillator lead as well as an added, left-ventricular pacing lead. The CRT devices optimize the atrioventricular interval through the coronary sinus, thereby coordinating contraction between and within both ventricles. Implantation of either cardiac device has been shown to improve outcomes among patients with HFrEF for both primary and secondary arrhythmia prevention. Primary-prevention ICD placement should be considered for patients with HFrEF and persistently reduced LVEFs of 35% or less despite at least three optimally dosed GDMTs (see Figure 1). For this indication, ICD therapy reduced all-cause mortality by more than 50% during a 5-year study period compared with conventional medical therapy in patients with LVEFs of 30% or less, histories of myocardial infarction, and inducible ventricular tachyarrhythmia (Moss 1996). A subsequent study of 1232 similar patients recruited without requiring invasive electrophysiological testing found that defibrillator implantation reduced all-cause mortality by 31% after only 20 months of average follow-up (Moss 2002). Among NYHA Class II or III patients with LVEFs of 35% or less of either ischemic or nonischemic etiology, preventive ICD therapy reduced all-cause mortality by 23% compared with amiodarone after a median 45.5 months of follow-up (Bardy 2005). Cardiac resynchronization therapy should be considered in symptomatic patients with EFs of 35% or less in sinus rhythm with QRS durations of 120 msec or greater. Although CRT alone initially did not improve survival in 1520 patients with advanced HF and QRS intervals of at least 120 msec, the combination of CRT with a pacemaker-defibrillator did reduce the risk of death by 36% compared with optimal pharmacologic therapy (Bristow 2004). A subsequent CRT trial did, however, demonstrate improved survival as well as echocardiography findings, symptoms, and quality of life in 813 patients with advanced HF because of systolic dysfunction and cardiac dyssynchrony compared with standard pharmacologic therapy (Cleland 2005). Implantation of an implantable cardioverter-defibrillator for secondary prevention has also been shown to reduce mortality risk by 20%–30% and is indicated for survivors of sudden cardiac arrest or those with syncopes from or histories of presumed sustained ventricular arrhythmia. It is important to note that patients at NYHA stage IV have not been shown to benefit from ICD placement and should be considered only if awaiting heart transplantation. In addition, to avoid inappropriate shocks that may be inconsistent with goals of care, clinicians must also disable cardiac devices in patients with HF who are transitioning to hospice care.

Antiarrhythmic medications variably affect the defibrillation threshold of an ICD. *Defibrillation threshold* refers to the lowest amount of energy necessary to successfully defibrillate an arrhythmia with a view to restore normal sinus rhythm. Amiodarone, lidocaine, and nondihydropyridine calcium channel blockers can potentially raise the defibrillation threshold and thereby require higher voltage or risk defibrillation failure and subsequent shocks. Contrastingly, β-blockers as well as sotalol or dofetilide may lower the defibrillation threshold. These agents can also slow the rate of ventricular tachycardia to below rate-sensing cutoff programming, thereby misfiring an appropriate ICD shock opportunity (Lampert 2013). Amiodarone plus β-blockers appears to be more effective than sotalol to prevent device shocks—but at the expense of more-adverse pulmonary and thyroid events as well as bradycardia (Connolly 2006). Drug–device interactions represent an important component of CRT/ICD management, and pharmacists are uniquely qualified and well positioned to inform providers and patients so as to avoid adverse events and improve quality of life.

Remote Hemodynamic Monitoring

Development of remote patient monitoring accelerated because of the 2019 coronavirus pandemic, thereby leveraging the accessibility and convenience of electronic, telehealth, or mobile technology to manage and monitor disease outside traditional health care facilities. Remote patient monitoring debuted in the area of HF almost 3 decades ago, when a multidisciplinary telephonic monitoring and follow-up program reduced the rehospitalization rate by more than 50% (Rich 1995). However, subsequent large, prospective, multicenter investigations of more-advanced remote patient-monitoring interventions—including implantable cardiac electronic devices, thoracic bioimpedance or dielectric sensing systems, and wearable hemodynamic sensors—have failed to demonstrate any benefit and were not cost-effective (Dickinson 2018). One notable exception is the CardioMEMS implantable pulmonary artery pressure-monitoring system, which received FDA approval in 2014 based on an analysis of long-term ongoing follow-up from the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial. The CHAMPION trial was a prospective multicenter, single-blind study of 550 patients with NYHA III HF who had had recent HHFs in the past year and were randomized to receive wireless implantable pulmonary artery pressure monitors compared with usual care (Abraham 2011). After a mean of 15 months follow-up, the CardioMEMS device had reduced the primary end point of HHF by 37% (158 vs. 254; HR 0.763; 95% CI, 0.52–0.77; p<0.0001). Because HF decompensation is typically preceded by days to weeks of asymptomatic intracardiac and pulmonary artery pressure elevations, patients who were managed with hemodynamic data from the CardioMEMS device were more likely to have GDMT titration performed as well as to receive real-time diuretic dose adjustments before symptoms of congestion developed. Adverse event rates were consistent with those of right-heart catheterization

but better than other permanent implants such as CRT/ICD. Based largely on reductions in HHF, CardioMEMS was associated with a comprehensive health care cost reduction of $13,190 per year per patient implanted with the device (Desai 2017). A postapproval CardioMEMS single-arm observational study demonstrated even greater benefits in all-cause hospitalizations across HF subgroups, including patients with HFpEF (Shavelle 2020). A pre-COVID-19-pandemic analysis of the recent Haemodynamic-Guided Management of HF study suggested a possible benefit on mortality and total HF events based on hemodynamic-guided management through the CardioMEMS monitoring system (Lindenfeld 2021). Pharmacists participating in remote hemodynamic-monitoring programs may be able to optimize GDMT or guide diuretic dose titrations to prevent HHF and reduce total cost of care.

LVAD and Cardiac Transplantation

Patients with advanced HF refractory to GDMT should be considered for advanced therapeutic modalities such as definitive therapy, including durable mechanical circulatory support with left ventricular assist devices (LVADs) or referrals for orthotopic heart transplantation (see Figure 1). Cardiac transplantation is the only curative treatment for HF and has a median donor graft survival of more than 12 years. However, the paucity of suitable organ donors renders heart transplantation an epidemiologically insignificant therapeutic strategy when compared with the growing need of potential stage D recipients. Therefore, to extend life with improved functional status, the implantation of an LVAD may be useful as a bridge to transplantation or used as destination therapy in those not eligible for transplantation. End-of-life goals and individualized, patient-specific characteristics should be reviewed thoroughly in consideration of advanced therapeutic modalities. For example, pulmonary hypertension is a significant contraindication to transplantation but not for LVAD candidacy. Conversely, patients with severe right ventricular failure are suboptimal LVAD candidates but may experience better transplantation outcomes. Other LVAD precautions include history of recurrent infections, untreated aortic regurgitation, older age, and high frailty index. Anticoagulation with warfarin to an INR goal of 2–3 is currently recommended to prevent LVAD thrombosis for all available devices. Alternative anticoagulation strategies with newer-generation VADs that have magnetically suspended propulsion systems are currently under investigation, potentially obviating the need for anticoagulation altogether, which may significantly reduce complications if pump thrombosis risk can be minimized.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Despite accounting for approximately half of the overall HF population and conferring a comparably high mortality risk, HFpEF has historically lacked even a single evidence-based pharmacologic treatment option offering an observable impact on overall prognosis (Virani 2021). Traditionally characterized by a crude categorization of LVEF of 50% or more, HFpEF actually represents a heterogenous subpopulation of HF with a multitude of distinct pathophysiologic phenotypes inherently more complex than classification by diastolic dysfunction alone (Riello 2021). Impaired left ventricular relaxation is a common hallmark sign of HFpEF, but it may be caused by a host of interdependent factors such as cardiometabolic disease and systemic inflammation, obesity and epicardial adipose accumulation, myocardial ischemia and fibrosis, and arterial and vascular rigidity (Obokata 2020). Although active development of disease-modifying pharmacotherapy for HFpEF has remained unsuccessful for several decades, recent emerging research and regulatory expansion suggest that this area of tremendous need may soon establish more-definitive treatment—and with measurable benefit beyond symptomatic control and comorbidity management.

Angiotensin- Receptor–Neprilysin-Inhibitor

Given its landmark success in HFrEF and encouraging multifactorial impact on several compensatory neurohormonal pathways thought to be at least partially shared with HFpEF, patients, clinicians, and investigators were hopeful that ARNI may be among the first medications to show a clear and consistent benefit in HFpEF. The Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) study randomized 4796 symptomatic patients with LVEFs of 50% or more and elevated NT-proBNP to sacubitril/valsartan 97/103 mg twice daily or valsartan 160 mg twice daily (Solomon 2019). Although ARNI reduced the primary composite end point of cardiovascular death and HHF by 13%, it narrowly missed statistical significance after a median 35 months of follow-up (894 vs. 1009; HR 0.87; 95% CI, 0.75–1.01; p=0.059). The fragility index of this result required a net difference of only seven events to reach a p value of less than 0.05 (Solomon 2021). Furthermore, had urgent HF visits—which were collected prospectively and adjudicated independently—been incorporated into the primary composite outcome, as with other contemporary HFpEF trials, PARAGON-HF would have indeed achieved its end point (HR 0.86; 95% CI, 0.75–0.99; p=0.040). There was significant heterogeneity of the trial findings between two prespecified subgroups—including hypothesis-generating observations of more-favorable effects with ARNI in those with LVEFs of 45% to 57%. as well as in women compared with men. Notably, ARNI was also associated with an improvement in the exploratory renal composite outcome of death from kidney failure, end-stage renal disease, and an eGFR decrease of 50% or more from baseline (1.4% vs. 2.7%; HR 0.50; 95% CI, 0.33–0.77). It was important that fewer patients randomized to sacubitril/valsartan also discontinued the study drug and had SCr elevations of 2.0 or more mg/dL or any elevated

serum potassium but did experience more hypotension and angioedema.

In consideration of the totality of evidence—particularly across the spectrum of LVEF consistent with PARADIGM-HF—the FDA Cardiovascular and Renal Drugs Advisory Committee voted to approve an expanded ARNI indication "to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure," with no specific LVEF cutoff (Solomon 2021). Although the merits of the largely unprecedented regulatory decision to expand ARNI labeling to support use in HFpEF despite a neutral trial finding are contentious, it may be reasonable to consider sacubitril/valsartan for female patients with HFpEF as well as those with EFs of 57% or less who are at low risk of symptomatic hypotension.

Mineralocorticoid Receptor Activation

Mineralocorticoid receptor activation is associated with sodium retention, potassium loss, endothelial dysfunction, vascular inflammation, myocardial fibrosis, and hypotrophy central to the pathophysiology of HFrEF and is shared, at least in part, by HFpEF. Therefore, the use of MRA to manage diastolic dysfunction in HFpEF was once a promising therapeutic target that initially disappointed when studied rigorously. The Treatment of Preserved Cardiac Function with an Aldosterone Antagonist Trial (TOPCAT) was a large multicenter, double-blind, placebo-controlled trial that evaluated the effect of spironolactone on morbidity and mortality in 3445 patients with HFpEF (Pitt 2014). The primary composite end point of cardiovascular death, HHF, and resuscitated cardiac arrest was similar between treatment arms (18.6% vs. 20.4%; HR 0.89; 95% CI, 0.77–1.04; p=0.14) after a mean follow-up of 3.3 years, as were cardiovascular mortality and aborted cardiac arrest individually. Rates of HHF, however, were significantly lower with spironolactone (12.0% vs. 14.2%; HR 0.83; 95% CI, 0.69–0.99; p=0.04). Furthermore, hyperkalemia and renal failure were also more common in spironolactone-treated patients. Interestingly, a post hoc analysis of TOPCAT revealed significant geographic disparities with regard to the primary outcome between study sites in North America and South America (27.3% vs. 31.8%; HR 0.82; 95% CI, 0.69–0.98; p=0.26) compared with those in eastern Europe (9.3% vs. 8.4%; HR 1.10; 95% CI, 0.79–1.51; p=0.576) (Pfeffer 2015). About half of all patients enrolled in TOPCAT were recruited from Russia and Georgia, experiencing curiously low event rates consistent with a healthier study population not necessarily suffering from HFpEF. In addition to these regional biases, serum concentrations of the active spironolactone metabolite, canrenone, were undetectable in 30% of participants from Russia versus only 3% from the United States and Canada (de Denus 2017). These findings suggest, at a minimum, that lack of study drug adherence as well as other potential protocol violations may have occurred disproportionately outside the Americas. Current guidelines recommend consideration of an MRA for patients with HFpEF and LVEFs or more than 45%, elevated BNPs, and recent hospitalizations within the past year to reduce the risk of subsequent HHF (see Figure 1). Much like the recent ARNI label expansion, the same FDA Cardiovascular and Renal Drugs Advisory Committee also voted that the totality of evidence from TOPCAT was compelling enough to support a broader indication for spironolactone inclusive of at least patients with HFmrEF up to LVEFs of 55% – 57%. However, a formal label expansion request has yet to be submitted to the FDA for consideration.

Another recently approved MRA, finerenone, is currently being investigated in the ongoing FINEARTS-HF trial for a potential impact on the primary composite end point of cardiovascular death, HHF, or urgent HF visits in HFpEF (clinicaltrials.gov). About 5550 patients with LVEFs of 40% or more, NYHA II–IV symptoms, elevated NT-proBNPs, structural heart disease, and recent HF events will be randomized in either an ambulatory or an acute-care setting to receive finerenone 40 mg once daily or matching placebo. Should finerenone demonstrate an impact similar to that in the FIDELIO-DKD and FIGARO-DKD trials in the area of cardiorenal end points among patients with nondiabetic HFpEF, it may be the first MRA to definitively mitigate morbidity and mortality risk beyond HFrEF.

SGLT2 Inhibitors

Sodium-glucose cotransporter 2 inhibitors have consistently demonstrated cardiorenal outcome benefits among patients with HFrEF and patients with CKD independent of T2DM. Notably, several pivotal cardiovascular safety studies of patients with T2DM at high cardiovascular risk—such as EMPA-REG, CANVAS, and DECLARE-TIMI 58—did not distinguish comorbid HF subpopulations by ejection fraction. Cardiovascular outcome trials with pretrial ejection fraction information available like VERTIS CV, SCORED, and SOLOIST suggest a benefit of HHF among patients with comorbid T2DM and HFpEF but remain unproven in nondiabetic HFpEF. Given that diabetic cardiomyopathy can manifest as either systolic or diastolic function, independent trials were necessary to confirm the hypothesis-generating benefits of SGLT2 inhibitors for both HFrEF and HFpEF. Based on the landmark findings of DAPA-HF and EMPEROR-Reduced, dapagliflozin and empagliflozin are now considered part of quadruple GDMT for HFrEF; however, only empagliflozin has yet completed its HFpEF trial to date (Maddox 2021).

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure (EMPEROR-Preserved) trial randomized 5988 patients with LVEFs of more than 40%, NYHA II–IV symptoms for 3 months or more before enrollment, elevated NT-proBNPs, and either structural heart disease or recent HHF to empagliflozin 10 mg once daily or placebo for a median 26.2 months of treatment. Empagliflozin significantly reduced the risk of the primary composite end point of cardiovascular death or

HHF (13.8% vs. 17.1%; HR 0.79; 95% CI, 0.69–0.90; p<0.001), driven predominantly by a 29% lower risk of hospitalization (Anker 2021). Although there was a nonsignificant 9% lower risk of cardiovascular death with empagliflozin (HR 0.91; 95% CI, 0.76–1.09), overall mortality was neutral (HR 1.00; 95% CI, 0.87–1.15). It is important to note that those benefits were consistent among patients with or without diabetes; however, an attenuation appeared to be observed in patients with the highest ejection fractions (Anker 2021). Adverse events more commonly experienced with empagliflozin than with placebo included uncomplicated UTI and hypotension. Although the high rate of treatment discontinuation (23%) was similar between arms, that discontinuation may have notably minimized the effect size of empagliflozin on cardiovascular and all-cause mortalities (Drazner 2021). The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial is a similar international, randomized, placebo-controlled HFpEF study evaluating the impact of dapagliflozin 10 mg once daily on the primary composite end point of cardiovascular death, HHF, or urgent HF visits after about 39 months of follow-up (clinicaltrials.gov). To date, the DELIVER study has recruited 6263 ambulatory or hospitalized patients with LVEFs greater than 40%, evidence of structural heart disease, NYHA II–IV functional status for 6 weeks or more before enrollment, and elevated NT-proBNPs. It is anticipated that the results of both trials will establish SGLT2 inhibitors as constituting the first medication class to offer indisputable cardiovascular outcome benefits among patients with HFpEF.

CONCLUSION

Four classes of disease-modifying therapeutics proven to reduce cardiovascular mortality and prevent HF hospitalizations are now available for patients with HFrEF. The medications—ARNIs, β-blockers, MRAs, and, most recently, SGLT2 inhibitors—are all supported by robust clinical trial evidence as well as the strongest possible guideline recommendation compelling their use. Nonetheless, HF remains the costliest condition in the United States, with a 5-year mortality rate comparable to most of the major malignancies. One of the most critical reasons for that is the abysmal uptake of evidence-based pharmacotherapy across the country. Recent guidance on pathways for initiation, titration, and sequencing of GDMT as well as how to address barriers to medication optimization provides a framework for closing that gap in care.

The integration of pharmacists into multidisciplinary care teams dedicated to this endeavor represents a necessary step toward optimal GDMT implementation, promotes best possible patient outcomes, and ensures medication adherence. Furthermore, recent recognition of the increasing prevalence and heterogeneity of HFpEF, without any definitive therapies to mitigate its formidable morbidity and mortality, has reinvigorated clinical investigators and regulatory agencies alike to establish safe and effective therapies for this unmet need.

Practice Points

Clinical pharmacists must overcome many barriers in their optimizations of pharmacotherapies for patients with HF. As new strategies to better inform implementation of GDMT for HFrEF and promising therapeutics for HFpEF loom on the horizon, new guideline recommendations as well as expanded indications for existing medications continuously evolve contemporary practice:

- **The HFSA/HFA-ESC/JHFS recently proposed a universal definition of HF and updated standardized HF classifications and staging beyond LVEF and structural cardiac disease.**
- **Patients with HF should be routinely assessed and treated for common comorbidities such as iron deficiency, CKD, and T2DM to improve quality of life and reduce cardiorenal complications.**
- **Dapagliflozin and empagliflozin have recently been shown to improve cardiovascular death rates and HF hospitalizations—independent of diabetes status—among patients with HFrEF.**
- **Clinicians should ensure that patients with HFrEF are receiving quadruple therapy with a RAAS inhibitor—preferably, ARNI—in combination with a β-blocker, an MRA, and now also an SGLT2 inhibitor.**
- **GDMT for HFrEF should be titrated to maximally tolerated doses from randomized, controlled trials but not at the expense of initiating all four disease-modifying agents.**
- **Optimization of evidence-based therapy should occur every 2 weeks during hospitalization for HFrEF and when patients are outpatients so as to achieve GDMT within 3–6 months of diagnosis.**
- **Despite arguably neutral HFpEF trials, ARNI and spironolactone recently received regulatory support for expanded use in patients with LVEFs greater than 40%.**
- **SGLT2 inhibitors may represent the first medication class in HFpEF to definitively improve cardiovascular mortality and HF hospitalizations.**

Although ARNI and MRA recently received regulatory support for expanded indications in HFpEF, SGLT2 inhibitors have now become the only pharmacologic treatment options with clear potential to significantly improve cardiorenal outcomes for patients with HF, irrespective of ejection fraction or diabetes status. Given the pervasive underutilization of GDMT in patients with HFrEF, as new therapeutics emerge and prove beneficial for HFpEF, pharmacists must ensure the same latency to optimize that evidence-based treatment not also affect HFpEF.

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

Q.E., a 57-year-old white woman with a medical history significant for breast cancer, completed a 6-cycle regimen of chemotherapy including doxorubicin, docetaxel, and cyclophosphamide less than 1 week ago. She feels fatigued, which her oncologist attributes to the recent chemotherapy. Out of an abundance of caution, Q.E. is referred to a cardiologist who performs a laboratory assessment and ECHO that resulted in an NT-proBNP of 390 pg/mL [reference range <125 pg/mL] and a left ventricular ejection fraction (LVEF) of 58% and no identifiable abnormalities. Q.E. denies any symptoms of heart failure (HF) and reports being able to complete her normal activities of daily life without limitations.

1. Which one of the following best evaluates Q.E. with respect to the Heart Failure Society of America (HFSA), Heart Failure Association of the European Society of Cardiology (HFA-ESC), and the Japanese Heart Failure Society (JHFS) staging system and New York Heart Association (NYHA) functional classification?

   A. At risk for HF and NYHA Class I
   B. At risk for HF with no accompanying NYHA classification
   C. Pre-HF and NYHA Class I
   D. Pre-HF with no accompanying NYHA classification

2. During her annual follow-up visit to the cardiologist, Q.E. had a repeat ECHO and laboratory assessment that reported a LVEF of 38% and NT-proBNP of 1670 pg/mL [reference range <125 pg/mL]. Over the past month, she reports being unable to walk up a flight of stairs without assistance, frequent breaks due to dyspnea while brushing her teeth or collecting the mail, and requiring 2-3 pillows propped in a chair to sleep a few times per week. Which one of the following best categorizes Q.E. according to the HFSA/HFA-ESC/JHFS staging system and NYHA functional classification?

   A. HF and NYHA Class II
   B. HF and NYHA Class III
   C. Advanced HF and NYHA Class III
   D. Advanced HF and NYHA Class IV

3. Based on Q.E.'s presentation, laboratory, and ECHO findings, the cardiologist diagnoses her with HF and prescribes an ARNI and β-blocker that same visit. Q.E. is referred to a HF disease management clinic to optimize the rest of her guideline-directed medical therapy regimen and titrate to target dosing. After 6 months of consistent follow-up visits in the clinic, a repeat ECHO reports an LVEF of 49%. According to the HFSA/HFA-ESC/JHFS Updated Universal Definition of HF, which one of the following best evaluates Q.E.'s category of HF?

   A. HF with reduced ejection fraction (HFrEF)
   B. HF with mildly reduced ejection fraction (HFmrEF)
   C. HF with improved ejection fraction (HFimpEF)
   D. HF with preserved ejection fraction (HFpEF)

4. About 4 months ago, a 68-year-old white man was hospitalized for an anterior wall myocardial infarction complicated by left ventricular systolic dysfunction. At discharge, he was prescribed the following medications: aspirin 81 mg daily, atorvastatin 80 mg daily, carvedilol 12.5 mg twice daily, sacubitril/valsartan 49/51 mg twice daily, spironolactone 25 mg daily, and ticagrelor 90 mg twice daily. During a post-discharge follow-up visit today, the patient's LVEF as measured via ECHO has improved from 25% to 32% since the last hospital assessment. His laboratory results are within normal limits. He is euvolemic, normotensive, and reports only slight limitations of physical activity. Which one of the following is best to recommend for this patient?

   A. Increase carvedilol to 25 mg twice daily.
   B. Increase spironolactone to 50 mg daily.
   C. Start empagliflozin 10 mg daily.
   D. Increase sacubitril/valsartan to 97/103 mg twice daily.

5. A 55-year-old white man (weight 214 lb) is admitted to the hospital with acutely decompensated HF requiring inotropic support. Echocardiogram shows LVEF 42%, moderate functional mitral regurgitation, and dilated left ventricle. The patient's medical history is significant for hyperlipidemia and idiopathic dilated cardiomyopathy. His condition stabilizes and he is resumed on his home regimen of bumetanide 2 mg daily, carvedilol 12.5 mg twice daily, eplerenone 25 mg daily, lisinopril 20 mg daily, and rosuvastatin 10 mg daily. A basic metabolic panel is unrevealing aside from a Hgb of 11.2 g/dL. The patient is clinically stable other than complaints of feeling fatigued and inability to participate in physical therapy. He exhibits no clinical signs of bleeding, so the medical resident begins to work up the cause of his anemia. Iron studies return with a serum ferritin 115 ng/mL and transferrin saturation 18% [reference range 20%-50%]. Which one of the following is best to recommend to correct this patient's iron-deficiency anemia?

   A. Ferric carboxymaltose 500 mg IV once
   B. Ferrous sulfate 200 mg Monday, Wednesday, Friday for 3 months
   C. Iron dextran 1,000 mg IV once
   D. Iron sucrose 200 mg IV every other day for 5 doses

Questions 6 and 7 pertain to the following case.

I.M. is a 56-year-old white man with a medical history significant for uncontrolled diabetes and hypertension. He denies taking any medications and has been lost to follow-up with his primary care provider. I.M. presents to the ED with difficulty breathing due in the setting of volume overload with 8 kg weight gain in the past week. His laboratory results are unremarkable except Na: 130 mEq/L, K 4.9 mEq/L, SCr 2.5 mg/dL (baseline 1.1 mg/dL), and NT-proBNP 11,000 pg/mL [reference range >300 pg/mL]. Cardiology is consulted and an ECHO is performed, revealing severely impaired systolic function with an LVEF of 22%. I.M.'s vital signs are blood pressure of 149/88 mm Hg, HR 98 beats/minute, respiratory rate of 24 breaths/minute, and oxygen saturation of 97% on room air. I.M. is admitted to the telemetry floor for management.

6. The admitting resident is undecided about which medication to start first for I.M.'s acute heart failure management. Which one of the following is best to recommend for I.M.?

   A. Eplerenone
   B. Furosemide
   C. Metoprolol succinate
   D. Sacubitril/valsartan

7. After being stabilized, I.M. is initiated on the following medication regimen: eplerenone 25 mg daily, furosemide 40 mg daily, metoprolol succinate 100 mg daily, and sacubitril/valsartan 49/51 mg twice daily. His vital signs have improved to 124/82 mm Hg, heart rate 62 beats/minute, respiratory rate 19 breaths/minute, and oxygen saturation 99% on room air. A repeat laboratory assessment is unrevealing except for a SCr of 1.4 mg/dL. Which one of the following is best to recommend to optimize I.M.'s guideline-directed medical therapy?

   A. Add dapagliflozin 10 mg daily.
   B. Increase eplerenone to 50 mg daily.
   C. Increase metoprolol succinate to 150 mg daily.
   D. Increase sacubitril/valsartan to 97/103 mg twice daily.

Questions 8 and 9 pertain to the following case.

J.T. is a 72-year-old white man with a medical history significant for diabetes (A1C 6.8%), CKD stage 4 (baseline SCr 1.3 mg/dL) and HFrEF (LVEF 34%). His home drugs include aspirin 81 mg daily, carvedilol 25 mg twice daily, dapagliflozin 10 mg daily, furosemide 20 mg daily, losartan 100 mg daily, metformin 1,000 mg twice daily, rosuvastatin 20 mg daily, and spironolactone 25 mg daily. J.T. is clinically stable but appears overly dry on examination and has had a limited appetite and complains of thirst. His laboratory results within normal limits except for an eGFR 22 mL/min/1.73 m^2.

8. During a visit with J.T.'s primary care provider, dapagliflozin and furosemide were both discontinued due to concerns for his renal function. Which one of the following is best to recommend for J.T.?

   A. Continue without dapagliflozin.
   B. Initiate empagliflozin at 10 mg daily.
   C. Initiate empagliflozin at 25 mg daily.
   D. Reinitiate dapagliflozin at 5 mg daily.

9. Three months later, J.T. is following-up in the HF disease management clinic. He is euvolemic with an eGFR 30 mL/min/1.73 m^2 and reports adherence to all previous medications including an SGLT2 inhibitor. Which one of the following is best to recommend regarding optimization of J.T.'s guideline-directed medical therapy?

   A. Increase losartan to 150 mg daily.
   B. Switch losartan to sacubitril/valsartan 49/51 mg twice daily with a 36-hour washout.
   C. Switch losartan to sacubitril/valsartan 49/51 mg twice daily without a 36-hour washout.
   D. Increase spironolactone to 50 mg daily.

10. A 47-year-old African American man (weight 176 lb) with no medical insurance has a medical history significant for drug and alcohol use disorder, hypertension, and HFrEF (LVEF 31%). He endorses good adherence to his medications and has been stable on a previous regimen of carvedilol 25 mg twice daily, furosemide 20 mg daily, lisinopril 40 mg daily, and spironolactone 50 mg daily. On the patient's last visit to the HF disease management clinic, however, he was switched from lisinopril to sacubitril/valsartan 49/51 mg twice daily. Although he has been tolerating ARNI well, he is about to run out of his 30-day free supply provided by a manufacturer coupon and expresses concerns that he lacks prescription insurance and cannot afford subsequent refills. The cardiologist transitions him back to lisinopril after a 36-hour washout period. Which one of the following is best to recommend to optimize this patient's guideline-directed medical therapy?

    A. Reinitiate sacubitril-valsartan at 97/103 mg twice daily.
    B. Initiate dapagliflozin 10 mg daily.
    C. Initiate isosorbide dinitrate 20 mg and hydralazine 37.5 mg three times daily.
    D. Increase lisinopril to 80 mg daily.

11. A 72-year-old white man (weight 168 lb) has a medical history significant for advanced HF (LVEF 21%) with LVAD implantation 2 years prior. He is referred to the palliative care service to discuss goals of care. His home drugs include bumetanide 4 mg daily, carvedilol 25 mg twice daily, dapagliflozin 10 mg daily, eplerenone 50 mg daily, ivabradine 7.5 mg twice daily, sacubitril/valsartan 97/103 mg twice daily, and warfarin 6 mg daily. Despite this regimen, the patient is unable to perform any physical activities without significant discomfort and is

predominantly bed bound. He does not wish to undergo surgery and wants to "live comfortably" to see his grandchildren graduate high school in 6 months. Which one of the following is best to recommend for this patient?

A. Start digoxin 125 mcg daily, goal 0.5-0.9 ng/mL.
B. Initiate home infusion of dobutamine 7.5 mcg/kg/min.
C. Initiate home infusion of milrinone 0.125 mcg/kg/min.
D. Discontinue GDMT and transition to hospice.

12. A 57-year-old white man (weight 215 lb) with a medical history significant for HFpEF (LVEF 55%; NYHA Class III), well-controlled hypertension, and CKD stage 3 (baseline SCr 1.2 mg/dL; eGFR 57 mL/min/1.73 m^2) arrives to the HF diuretic clinic with symptoms of congestion for the first time in the last year. The nurse practitioner in the clinic administers intravenous bumetanide 4 mg then performs a medication reconciliation, noting pertinent home drugs to include amlodipine 10 mg daily, bumetanide 2 mg daily as needed, ferrous sulfate 325 mg every other day, losartan 50 mg daily, multivitamin with B-complex, and rosuvastatin 20 mg daily. Which one of the following is best to recommend to optimize this patient's HF regimen?

    A. Increase bumetanide 4 mg daily.
    B. Start spironolactone 25 mg daily.
    C. Start empagliflozin 10 mg daily.
    D. Switch losartan to sacubitril/valsartan 24/26 mg twice daily.

13. A 61-year-old African American woman (weight 159 lb) was newly diagnosed with HFmrEF (LVEF 44%) after a hospitalization for myocardial infarction. Her medical history includes diabetes (A1C = 7.0%). The patient's home drugs include aspirin 81 mg daily, clopidogrel 75 mg daily, empagliflozin 10 mg daily, furosemide 20 mg daily as needed, metformin 1000 mg twice daily, metoprolol succinate 100 mg daily, rosuvastatin 20 mg daily, and sacubitril/valsartan 97/103 mg twice daily. Pertinent laboratory results include K 4.0 mEq/L, SCr 1.1 mg/dL, and eGFR 65 mL/min/1.73 m^2. The patient complains of increased swelling in her feet and legs with a 4-lb weight gain over the last few days which she self-medicated with furosemide. She reports more limitations with physical activity than normal lately. She can no longer walk the length of the local track without losing her breath and sleeps in a chair upright once per week. Which one of the following is best to recommend for this patient?

    A. Increase empagliflozin to 25 mg daily.
    B. Start isosorbide dinitrate 20 mg and hydralazine 37.5 mg three times daily.
    C. Start spironolactone 25 mg daily.
    D. Start vericiguat 2.5 mg daily.

Questions 14 and 15 pertain to the following case.

C.H. is a 68-year-old white woman (weight 148 lb) with newly diagnosed with HFpEF (LVEF 54%) and a medical history significant for hypertension and diabetes (A1C 7.4%). Her current medication regimen includes atorvastatin 40 mg daily, chlorthalidone 12.5 mg daily, furosemide 20 mg daily as needed, and metformin 1000 mg twice daily. C.H.'s blood pressure is 128/84 mm Hg and heart rate 65 beats/minute. A laboratory assessment for today's visit includes pertinent results of NT-proBNP 750 pg/mL [reference range >125 pg/mL], K 4.5 mEq/L, SCr 1.2, and eGFR 61 mL/min/1.73 m^2.

14. Which one of the following is best to recommend to manage C.H.'s comorbidities?

    A. Start empagliflozin 10 mg daily.
    B. Start liraglutide 0.6 mg subcutaneous daily.
    C. Start sitagliptin 25 mg daily.
    D. Increase chlorthalidone to 25 mg daily.

15. Three months later, C.H. returns for a follow-up appointment. Since her last appointment, she has been hospitalized for acute decompensated HF and required intravenous diuretics. Her vital signs during today's visit are blood pressure 141/88 mm Hg, heart rate 75 beats/minute, and pertinent laboratory results of NT-proBNP is 1220 pg/mL [reference range >125 pg/mL], K 4.9 mEq/L, SCr 1.5, and eGFR 29 mL/min/1.73 m^2. Which one of the following is best to recommend for C.H.'s HFpEF?

    A. Start irbesartan 150 mg daily.
    B. Start nebivolol 5 mg daily.
    C. Start sacubitril/valsartan 24/26 mg twice daily.
    D. Start spironolactone 25 mg daily.