Updates in the Management of Heart Failure

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LEARNING OBJECTIVES

1. Evaluate key recommendations and recent updates in the national guidelines in the treatment of heart failure (HF).
2. Analyze drug therapies according to the revised terminology and categories of HF.
3. Design practical strategies to optimize individualized guideline-directed medical therapies.

ABBREVIATIONS IN THIS CHAPTER

ARNI	Angiotensin receptor-neprilysin inhibitor
CKD	Chronic kidney disease
CV	Cardiovascular
GDMT	Guideline-directed medical therapy
ESKD	End-stage kidney disease
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
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro–brain natriuretic peptide
PDE5	Phosphodiesterase type 5
RAAS	Renin-angiotensin-aldosterone system
sGC	Sodium guanylate cyclase
SGLT2	Sodium-glucose cotransporter 2
T2DM	Type 2 diabetes mellitus

Table of other common abbreviations.

INTRODUCTION

Heart failure (HF) continues to be a major public health problem leading to substantial morbidity and mortality. It is projected that in the United States, over 1 million new individuals will develop HF in 2022, joining 6 million others with preexisting HF (Tsao 2022). In addition, HF mortality risk remains high (50% at 5 years), with frequent hospitalizations and rehospitalizations. Compared with the general population in the United States, evidence suggests that patients with HF across all age groups have a markedly reduced median survival (Shah 2017).

Despite current conventional treatment, the burden associated with HF remains high, necessitating the development of newer therapies. Several evidence-based therapies have been proven in randomized trials to reduce morbidity and mortality in patients with HF, specifically patients with HF with reduced ejection fraction (HFrEF). Treatments are evolving for patients with HF with mildly reduced EF (HFmrEF) and HF with preserved EF (HFpEF). Although there have been advances in the HF treatment, real-world registries show suboptimal implementation of guideline-directed medical therapy (GDMT).

Because of lack of standardization of HF definitions by different HF societies, a new universal definition was developed. Heart failure is now defined as a "a clinical syndrome caused by the inability of the heart to supply blood to meet tissue metabolic requirements." The new definition includes typical signs or symptoms of HF with evidence of functional or structural heart disease, corroborated by either elevated natriuretic peptide concentrations or objective evidence of cardiogenic pulmonary or systemic congestion (Bozkurt 2021).

Major HF Guideline Updates in 2022

The 2022 American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) guidelines replace those from 2013 and 2017 (focused update to 2013) and have significant updates to provide patient-centric and

evidence-based recommendations for clinicians (Heidenreich 2022).

The stages of HF have been modified with updated criteria to identify disease development and progression in patients with HF. Patients at risk of HF, but without symptoms, structural heart disease, or elevated biomarkers, are classified as having stage A HF (at risk of HF). Stage B HF, now known as "pre-HF," includes patients with evidence of structural heart disease, increased filling pressures, or elevated cardiac biomarkers, but without current or previous signs or symptoms of HF. Pre-HF terminology is easily understood by patients, thus raising the awareness for adherence, appropriate prevention, screening, and treatment strategies. In addition, part of the intent of these changes in terminology was to include language better understood by patients, payers, and non-cardiology providers. Primary prevention of HF through lifestyle modification, screening, and management of risk factors and comorbid conditions is recommended for those at risk (stage A) or those with pre-HF (stage B) (Table 1). Stage C HF is defined as patients with prior or current signs and/or symptoms of HF caused by structural and/or functional cardiac abnormality. Stage D includes patients with severe signs and/or symptoms of HF, those with recurrent hospitalizations despite receiving optimal GDMT, and those requiring advanced therapies (Heidenreich 2022).

The updated guidelines also revise the classification of HF by EF to include four distinct subtypes of HF. Heart failure with reduced ejection fraction includes patients with

BASELINE KNOWLEDGE STATEMENTS

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

- General knowledge of the pathophysiology of heart failure (HF)
- Guideline-directed medical therapy for HF with reduced ejection fraction
- Monitoring values for efficacy and safety of medical therapy

Table of common laboratory reference values

ADDITIONAL READINGS

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

- Sharma A, Verma S, Bhatt DL, et al. Optimizing foundational therapies in patients with HFrEF: how do we translate these findings into clinical care? JACC Basic Transl Sci 2022;7:504-17.
- Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol 2022;19:100-16.
- 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.
- Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022;79:e263-e421.

Table 1. ACC/AHA/HFSA Guideline-Recommended Treatment for Stage A and Stage B HF

High Risk of HF (Stage A) Primary Prevention	
Hypertension	Optimal BP control (COR 1)
T2D + CVD **or** High risk of CVD	SGLT2 inhibitor (COR 1)
CVD	Optimal management of CVD (COR 1)
Exposure to cardiotoxic agents	Multidisciplinary evaluation and management
Pre-HF (Stage B) Preventing Progression of HF	
LVEF ≤ 40%	ACEI (COR 1)
Recent MI + LVEF ≤ 40%	ARB if ACEI intolerance (COR 1)
LVEF ≤ 40%	β-Blocker (COR 1)
LVEF ≤ 30% > 1-yr survival > 40 days after MI	ICD (COR 1)
Recent or remote history of MI or ACS	Statin (COR 1)
Continue lifestyle modifications in Stage A and Stage B HF	

ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; BP = blood pressure; COR = class of recommendation; CVD = cardiovascular disease; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

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HF and a left ventricular EF (LVEF) of 40% or less. Patients with an LVEF of 50% or greater and evidence of elevated filling pressures are classified as having HFpEF. Patients with evidence of elevated filling pressures and an LVEF of 41%–49% are now classified as having HFmrEF. The fourth subtype of HF is classified as HF with improved EF (HFimpEF) and includes patients with previously diagnosed HFrEF who, on subsequent measurements, have an improvement in LVEF to greater than 40%.

Finally, the recent guideline updates now also include clinical trajectory terminologies for patients with stage C HF. Patients who experience resolution of their symptoms and myocardial structure and/or function are in remission rather than recovered. Heart failure in remission replaces recovered HF because improvement in systolic function does not mean HF has been cured.

Lack of improvement in symptoms is called persistent HF rather than stable HF, because even if the symptoms of HF have stabilized, optimization of therapies should continue to prevent further worsening of adverse outcomes (Figure 1). The guidelines also include specific cutoff points for brain natriuretic peptide (BNP) and N-terminal pro–BNP (NT-proBNP) in ambulatory and decompensated HF to support the diagnosis of HF. Signs and symptoms of HF have also been extended for clarity and include typical and atypical symptoms and specific examination findings (Heidenreich 2022).

In an era of increasing health care costs and expanding therapeutic options, the guidelines also include value-based statements for treatments. High value is defined as less than $60,000/quality-adjusted life-year gained or less. Low value is $180,000/quality-adjusted life-year gained or more. Tafamidis for cardiac amyloidosis is the only low-value therapy. Angiotensin receptor-neprilysin inhibitors (ARNIs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-blockers, mineralocorticoid receptor antagonists (MRAs), implantable cardioverter-defibrillators, and cardiac resynchronization therapies are classified as high value, whereas sodium-glucose cotransporter 2 (SGLT2) inhibitors and cardiac transplantation are classified as intermediate-value therapies.

Despite robust evidence, cardiac rehabilitation remains underused for HF in clinical practice. Cardiac rehabilitation leads to significant improvements in quality of life, functional capacity, exercise performance, and HF-related hospitalizations in patients with HF (Bracewell 2022). Cardiac rehabilitation is recommended by guidelines as safe and effective in all subtypes of HF and should be offered to all patients.

In summary, the intent of the revised language and classification scheme in the updated HF treatment guidelines is to facilitate patient engagement, improve communication, and empower clinicians to implement GDMT to improve outcomes in all stages and classifications of HF.

RECENTLY APPROVED TREATMENTS FOR PATIENTS WITH HF

Angiotensin Receptor-Neprilysin Inhibitors

Sacubitril/valsartan, which simultaneously blocks the renin-angiotensin-aldosterone system (RAAS) and neprilysin, was tested in the PARADIGM-HF trial (McMurray 2014). The primary composite end point of cardiovascular (CV) death or

Staging of HF	Classification by LVEF		New Trajectories in Stage C HF
• At risk for HF (Stage A) • Pre-HF (Stage B) • Symptomatic HF (Stage C) • Advanced HF (Stage D)	**Sub-Classification**	**LVEF**	• Persistent HF rather than "stable HF" • HF in remission rather than "recovered HF" • De Novo HF • Worsening HF • Symptom resolution
	HFrEF	≤40%	
	HFmrEF	41–49%	
	HFpEF	≥50%	
	HFimpEF	≤40% with later LVEF > 40%	

Figure 1. Reclassification of heart failure.

LVEF = left-ventricular ejection fraction, 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

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first HF hospitalization was reduced by 20% compared with enalapril in patients with HFrEF (HR 0.80; 95% CI, 0.73–0.87; p<0.001; number needed to treat [NNT] 21), establishing the role of ARNIs in this patient population (Solomon 2019).

Although therapies that block the RAAS pathway have been successful in HFrEF, RAAS inhibition has not been as positive in patients with HFpEF. The PARAGON-HF was a randomized trial comparing sacubitril/valsartan with valsartan in 4822 patients with HF and an LVEF of 45% or more. In the PARAGON-HF, the primary composite outcome of total hospitalizations for HF and death from CV causes did not differ significantly between sacubitril/valsartan and valsartan alone in patients with an LVEF of 45% or more. Although the trial failed to show a significant difference between the two groups, there were suggestions of treatment heterogeneity showing a potential benefit in patients with an LVEF of 57% or lower and in women (Solomon 2019). Subgroup analyses showed a significant decrease in HF hospitalizations in subjects with an LVEF below the median 57% value. These results mirror the reduction in HF hospitalizations in post hoc analyses of trials conducted with candesartan and spironolactone in HFpEF (Yusuf 2003). A pooled analysis of the PARADIGM-HF and PARAGON-HF trials further suggests that the reductions in HF hospitalizations with sacubitril/valsartan vary by LVEF, and treatment benefits may extend to patients with HFmrEF (Solomon 2020). The AHA/ACC/HFSA guidelines now recommend sacubitril/valsartan in HFpEF to decrease hospitalizations, particularly among patients with an LVEF on the lower end of this spectrum (EF less than 50%). A recent pooled analysis of PARADIGM-HF and PARAGON-HF found that sacubitril/valsartan treatment resulted in a reduction in the composite renal outcome and slowed the decline in estimated glomerular filtration rate (eGFR) compared with RAAS inhibition alone, independent of baseline renal function (McCausland 2022).

Evidence from randomized clinical trials, meta-analyses, and observational studies indicates that sacubitril/valsartan is safe and well tolerated in patients with HFrEF and HFpEF, compared with an ACEI/ARB. In PARAGON-HF, compared with valsartan, sacubitril/valsartan had a higher incidence of hypotension (15.8% vs. 10.8%) and angioedema (0.6% vs. 0.2%) and a lower incidence of hyperkalemia (13.2% vs. 15.3%).

Because of the risk of life-threatening angioedema, a 36-hour washout period is required when changing from an ACEI to an ARNI. All patients should be counseled to monitor home blood pressure and transition slowly from sitting to a standing position if experiencing dizziness, lightheadedness, or presyncope. Although the incidence of hyperkalemia associated with ARNIs is low, serum potassium and eGFR should be monitored as appropriate. If symptomatic hypotension persists, dose reductions of sacubitril/valsartan should be considered. Dose reductions are preferred to discontinuation of sacubitril/valsartan because even low doses of ARNIs provide substantial clinical benefit (Mohebi 2022).

Sodium-Glucose Cotransporter 2 Inhibitors

Sodium-glucose cotransporters are a family of proteins responsible for all glucose reabsorption. Transporters include SGLT1, predominantly found in the gut lumen, and SGLT2, in the proximal tubule. Sodium-glucose cotransporter 1 is responsible for 10% of tubular glucose reabsorption and SGLT2 is responsible for 90%.

Selective inhibitors of SGLT2 were originally developed for type 2 diabetes mellitus(T2DM) to reduce renal glucose reabsorption, thus facilitating urinary glucose excretion. Early studies with SGLT2 inhibitors showed reductions in A1C, blood pressure, and body weight. The antihyperglycemic properties of SGLT2 inhibitors depend on eGFR – with decreasing effects in advanced chronic kidney disease (CKD) and low cardiac output states. Similarly, the antihyperglycemic effects of SGLT2 inhibitors are glucose-dependent with no augmented glucose excretion at normal or low blood glucose concentrations, limiting their ability to cause hypoglycemia.

The first CV outcomes trial with SGLT2 inhibitors was the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose (EMPA-REG OUTCOME), which investigated CV morbidity and mortality in patients with T2DM. This trial reported a significant reduction in the major adverse cardiac events composite end point of nonfatal stroke, nonfatal myocardial infarction (MI), or CV death with empagliflozin compared with placebo. In addition, there was a 38% relative risk reduction in CV death (HR 0.62; 95% CI, 0.49–0.77; p<0.001) and a 32% relative risk reduction in all-cause mortality (HR 0.68; 95% CI, 0.57–0.82; p<0.001) despite a nonsignificant difference in MI and stroke (Zinman 2015). The HF safety end points showed a dramatic reduction in HF hospitalizations and the composite of HF hospitalization or CV death, with relative risk reductions of 35% and 34%, respectively. These benefits were shown in patients with or without a previous diagnosis of HF at the baseline study visit. Subsequent trials with SGLT2 inhibitors also showed consistent benefits in HF, which appeared early on with a large reduction in HF hospitalizations. Most patients in these CV outcomes trials did not have a previous diagnosis of HF, thus suggesting that SGLT2 inhibitors prevented new-onset clinical HF and hospitalizations.

The mediation analysis of EMPA-REG OUTCOME concluded that the mortality reduction with SGLT2 inhibitors was not associated with changes in body weight, blood pressure, blood glucose concentrations, or renal function, suggesting a mechanism different from the traditional cardiometabolic effects (Inzucchi 2018). Several potential mechanisms have been investigated to explain the cardioprotective effects of SGLT2 inhibitors, including diuresis/natriuresis, blood pressure reduction, erythropoiesis, inflammation reduction, and inhibition of the sympathetic nervous system. Although the underlying mechanisms for CV benefits are debatable, the clinical benefit clearly exists.

Considering the consistent and clinically relevant reduction for HF end points achieved by SGLT2 inhibitors across several large CV outcomes trials, these agents were then specifically studied in patients with HF. Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) was the first randomized placebo-controlled trial of an SGLT2 inhibitor in patients with HFrEF with or without T2DM (McMurray 2019). DAPA-HF included 4744 patients with New York Heart Association functional class (NYHA FC) II–IV HF and an LVEF of 40% or less. Patients received dapagliflozin 10 mg daily or placebo as well as standard best-practice HF GDMT unless contraindicated. The primary outcome was a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death. Over a median of 18.2 months, the primary outcome occurred in 16.3% of patients in the dapagliflozin group and 21.2% in the placebo group (HR 0.74; 95% CI, 0.65–0.85; p<0.001).

Empagliflozin was also studied in patients with HFrEF in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction (EMPEROR-Reduced), a randomized placebo-controlled study that enrolled 3730 patients with class II–IV HF and an LVEF of 40% or less with or without T2DM (Packer 2020). Patients were assigned to empagliflozin 10 mg daily or placebo. The primary end point was a time-to-first-event analysis of the combined risk of CV death or first hospitalization for decompensated HF. After a median of 16 months, the primary outcome occurred in 19.4% of patients in the empagliflozin group and 24.7% in the placebo group (HR 0.75; 95% CI, 0.65–0.86; p<0.001). This was primarily driven by reduced rates of hospitalization for HF in the empagliflozin group with no significant difference in CV death. The rate of renal disease progression, as measured by eGFR slope over time, was significantly reduced in patients receiving empagliflozin compared with patients receiving placebo (-0.55 vs. -2.28 mL/minute/1.73 m^2 per year; absolute difference 1.73 mL/minute/1.73 m^2 per year; 95% CI, 1.10–2.37; p<0.001).

Additional analysis of these trials showed similar treatment effects for both primary and secondary end points in patients with or without diabetes and across a range of A1C values with empagliflozin and dapagliflozin (Anker 2021; Petrie 2020). In patients without diabetes at baseline, dapagliflozin delayed new-onset diabetes, likely related to delaying the progression of CV and renal dysfunction (Inzucchi 2021). Because neither trial was powered to assess effects on CV death or all-cause death, a meta-analysis was conducted to assess the effects of SGLT2 inhibitors on CV outcomes. The meta-analysis showed a 13% reduction in all-cause death and 26% reduction in CV death or HF hospitalization. A significant reduction of 38% in the risk of the composite renal end point (i.e., chronic dialysis, renal transplantation, or a 50% or greater sustained reduction of eGFR) was also observed. Even patients who were receiving target doses of GDMT had added benefits from the addition of SGLT2 inhibitors. In addition, these therapies are remarkably safe. All adverse effects (volume depletion, ketoacidosis) and rare complications (lower limb amputation, bone fracture) were balanced between the placebo and treatment arms (Zannad 2020).

In addition to lowering blood glucose, SGLT2 inhibitors are reported to reduce blood pressure,but only by 2–4 mm Hg compared with placebo. Of interest, in patients with a low systolic blood pressure (SBP less than 110 mm Hg) before adding an SGLT2 inhibitor, the blood pressure–lowering effects are negligible. This is important because many patients with HF tend to have low blood pressure, and SGLT2 inhibitors can safely be used in this patient population (Serenelli 2020b). In HFrEF, both empagliflozin and dapagliflozin meaningfully improved quality of life and functional status as measured by the Kansas City Cardiomyopathy Questionnaire – total system score (KCCQ-TSS) from baseline compared with placebo, with benefits appearing rapidly within days to weeks of initiation (Butler 2021).

Recently, SGLT2 inhibitors were explored in HFpEF treatment. The benefit of SGLT2 inhibitors in HFpEF initially came from the subgroup analysis of early CV outcomes trials in T2DM. These preliminary findings led to the EMPEROR-Preserved trial, which evaluated the efficacy and safety of empagliflozin in HFpEF. The primary composite end point of CV death or HF hospitalizations occurred in 13.8% of patients in the empagliflozin group and 17.1% in the placebo group (HR 0.79; 95% CI, 0.69–0.90; p<0.001). The results appeared early, lasted throughout the trial, and were driven by a reduction in hospitalizations. The prespecified secondary end point of total number of HF hospitalizations was also significantly decreased by 27% compared with placebo. There was no difference in the primary end point in patients with or without diabetes and no interaction with sex or eGFR (less than 60 mL/minute/1.73 m^2 or 60 mL/minute/1.73 m^2 or greater). In addition, the effects were positive across the spectrum of LVEF, with largest benefit among participants with HFmrEF. The rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group (-1.25 vs. -2.62 mL/minute/1.73 m^2 per year; absolute difference 1.36 mL/minute/1.73 m^2 per year; 95% CI, 1.06–1.66; p<0.001). The secondary composite renal outcome (time to first occurrence of chronic dialysis, renal transplantation, a sustained reduction of at least 40% in eGFR, or a sustained decrease in eGFR of more than 10 or 15 mL/minute/1.73 m^2 from baseline) was nonsignificant (Anker 2021).

Empagliflozin reduced the risk of major HF outcomes across the range of baseline KCCQ-TSS scores and improved health-related quality of life in HFpEF (Butler 2022b). Overall rates of adverse effects and serious adverse effects were lower with empagliflozin than with placebo. The risks of genital infections and hypotension were higher in the empagliflozin group. There was no difference between the treatment groups with respect to frequency of hypoglycemia or ketoacidosis (Anker 2021).

The DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) compared the safety and efficacy of dapagliflozin with placebo in HFpEF and HFmrEF (Solomon 2022). DELIVER was the largest clinical trial to date of patients with HF with an EF above 40% (n=6263) and enrolled patients with or without T2DM. One distinguishing factor from the EMPEROR-Preserved trial was the inclusion of patients who previously had an LVEF of 40% or less that subsequently improved to greater than 40% before randomization. Compared with EMPEROR-Preserved, DELIVER reported a higher percentage of background MRA use (37% vs. 42.8%, respectively). Over a median follow-up of 2.3 years, the primary outcome (composite of CV death or worsening HF) occurred in 16.4% of patients in the dapagliflozin group compared with 19.5% in the placebo group (HR 0.82; 95% CI, 0.73–0.92; p<0.001; NNT 32). When examining the individual components of the primary outcome, a 21% reduction in worsening HF and 12% nonsignificant reduction in CV death was observed. These findings were consistent across prespecified subgroups, including those with HFimpEF. Dapagliflozin also improved symptom burden as measured by KCCQ-TSS (Cunningham 2022). In addition, dapagliflozin had benefits in patients with an LVEF of 60% or greater (Solomon 2022). A subset of patients (10%) with a recent hospitalization had treatment effects for the primary end point similar to the overall study population (Cunningham 2022). Adverse effects were similar among groups. A prespecified analysis of DELIVER showed a sustained improvement in NYHA FC over time (Ostrominski 2022). It is estimated than an average 65-year-old person would gain 2–2.5 additional years free of CV death or worsening hospitalization if treated with dapagliflozin (Vaduganathan 2022). These data further support SGLT2 inhibitors as the foundational therapy in HFpEF, regardless of care setting or EF.

In summary, SGLT2 inhibitors represent a new central pillar to reduce CV mortality and hospitalizations in patients with established HFrEF. The SGLT2 inhibitors can safely be initiated during or after hospitalization for HF, with limited monitoring needed. Because SGLT2 inhibitor therapies do not require a stepwise dose titration, they can easily be integrated into multidrug regimens to rapidly stabilize disease progression, prevent hospitalizations, and preserve kidney function.

To successfully implement SGLT2 inhibitors in clinical practice, patient education is critical. Some patients experience an excessive diuretic response when SGLT2 inhibitors are initiated. The concomitant effects on diuresis can be a concern, especially when an SGLT2 inhibitor is prescribed in combination with an ARNI and/or a loop diuretic, which may necessitate dose adjustments of the loop diuretic depending on the patient's volume status at the time of initiation. Patients should be counseled to monitor blood pressure and weight at home, particularly in the first week of SGLT2 inhibitor therapy, and any diuretic medication doses may need to be adjusted for patients who experience orthostasis or excessive volume loss. Patients should be advised to hold SGLT2 inhibitors if their oral intake of food and water is reduced because of an acute illness. Because of their glucosuric effect, SGLT2 inhibitors may increase the risk of genital mycotic infections and UTIs. Most genital mycotic infections can be managed with topical antifungals and proper genital hygiene. Typically, SGLT2 inhibitors do not increase the risk of UTIs; however, studies have not included patients at high risk of UTIs, such as those with an indwelling urinary catheter, recurrent UTIs, or neurogenic bladder. Even though the absolute risk of diabetic ketoacidosis (DKA) is low with SGLT2 inhibitors, very low-carbohydrate and ketogenic diets can increase the risk of DKA. Hypoglycemia is uncommon; however, risk is increased with concomitant use of sulfonylureas or insulin. Dose adjustments or discontinuation of the sulfonylurea or reduction in the total daily insulin dose may be required to reduce the risk of hypoglycemia in certain patients (Jhalani 2022).

Soluble Guanylate Cyclase Stimulators (Vericiguat)

Despite receiving optimal GDMT, some patients continue to develop worsening HF symptoms and are often hospitalized. These patients may benefit from additional therapies beyond the standard combination with an ACEI, ARB, or ARNI; a β-blocker; an MRA; and an SGLT2 inhibitor. One of these additional therapies is vericiguat. In HF, the production of cyclic guanosine monophosphate (cGMP) is diminished because of oxidative stress and endothelial dysfunction. Increased concentrations of cGMP decrease intracellular free calcium, resulting in vascular smooth muscle cell relaxation. Vericiguat directly stimulates soluble guanylate cyclase (sGC), which increases the availability of intracellular cGMP by targeting the nitric oxide–sGC-cGMP pathway in an independent, synergetic manner with nitric oxide. This improves endothelial function, decreases fibrosis, and reduces LV remodeling (Kang 2022).

The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial (Armstrong 2020) evaluated the efficacy and safety of vericiguat in patients at high risk with worsening HFrEF receiving background GDMT. The VICTORIA trial enrolled 5050 patients with NYHA FC II–IV HF with an LVEF of 45% or less and with elevated natriuretic peptide concentrations (BNP 300 pg/mL or greater or NT-proBNP 1000 pg/mL or greater). In addition, patients were required to have evidence of worsening HF, defined as HF hospitalization within 3–6 months or 3 months before randomization, or intravenous diuretic therapy (without hospitalization) in the preceding 3 months. Patients were excluded if they were taking long-acting nitrates or phosphodiesterase type 5 (PDE5) inhibitors or had an SBP less than 100 mm Hg. The primary outcome of the trial was a composite of CV death or first hospitalization for HF. About two-thirds of the patients had an HF hospitalization within 3 months of randomization. Median NT-proBNP concentrations were 2816

pg/mL, and 85.7% of patients had an LVEF of 40% or less. Of the participants, 60% were receiving triple therapy with an ACEI, ARB, or ARNI; β-blocker; and MRA. Vericiguat was initiated at a dose of 2.5 mg daily and titrated to a target dose of 10 mg daily within a few weeks. The median dose achieved in the trial was 9.2 mg, and around 90% of patients were receiving the target dose of 10 mg daily. Compared with placebo, vericiguat reduced the primary composite outcome of CV death or HF hospitalization, with a relative risk reduction of 10% and an absolute event-rate reduction of 4.2 events/100 patient-years. A subgroup analysis showed that patients in the highest quartile of the NT-proBNP subgroup (NT-proBNP concentration greater than 5314 pg/mL) had no benefit from vericiguat compared with placebo (Ezekowitz 2020). These findings raise the possibility that there is a level of severity of HF (manifest by extremely high concentrations of natriuretic peptides) beyond which the ability of vericiguat to favorably affect outcomes is diminished. Of importance, only a few patients in this trial received SGLT2 inhibitors, and only 15% of patients were taking an ARNI.

Overall, serious adverse effects were similar between groups, though syncope, symptomatic hypotension, and anemia were higher with vericiguat than with placebo. Patients should be counseled to monitor blood pressure after initiation of vericiguat. Certain medications, such as PDE5 inhibitors and other sGC stimulators, also target the cGMP pathway and can increase cGMP concentrations. Vericiguat is contraindicated in patients with concomitant use of PDE5 inhibitors (sildenafil, vardenafil, or tadalafil), long-acting nitrates, and riociguat because of increased risk of hypotension.

CLINICAL GUIDELINES IN DRUG THERAPY MANAGEMENT

Updated 2022 ACC/AHA/HFSA Recommendations of HF Drug Therapy for Patients

Heart Failure with Reduced Ejection Fraction

The four pillars of medication classes for HFrEF treatment are SGLT2 inhibitors, β-blockers, MRAs, and RAAS inhibitors (ARNI, ACEI or ARB), all of which have a class 1 recommendation. These medication classes should be considered in all patients without contraindications to their use. Diuretics continue to be recommended for patients with evidence of fluid retention. The combination of hydralazine and isosorbide dinitrate should be considered in patients with contraindications to or intolerance of ACEI/ARB/ARNI therapy or as an add-on therapy in self-identified African American populations with NYHA FC III and IV symptomatic HFrEF despite therapy with ACEIs/ARBs/ARNIs, β-blockers, MRAs, and SGLT2 inhibitors to further reduce morbidity and mortality.

Additional pharmacologic therapies beyond the standard HF GDMT can be considered in certain patient populations depending on patient-specific risk factors, patient preference, and clinician input. These agents include ivabradine, vericiguat, and digoxin. Ivabradine can be considered in patients with NYHA FC II and III who are in sinus rhythm with a heart rate of 70 beats/minute or greater at rest and already taking maximum tolerated doses of β-blockers to further reduce hospitalizations for HF. In patients with symptomatic HFrEF despite GDMT (or who cannot tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF. In selected high-risk patients who are already receiving GDMT, vericiguat can be considered to reduce HF hospitalization and CV death (Heidenreich 2022). Vericiguat was FDA approved in 2021 as the newest addition for treating HFrEF. The 2021 European Society of Cardiology guidelines and the updated AHA/ACC/HFSA HF guidelines recommend consideration of vericiguat in symptomatic patients with HFrEF who have had worsening HF despite treatment with GDMT, to reduce the risk of CV mortality or HF hospitalization (class 2b recommendation) (Figure 2).

Quadruple therapy is the newly proposed standard of care in the treatment of patients with HFrEF consisting of an ACEI, ARB, or ARNI (with an ARNI preferred); a β-blocker; an MRA; and an SGLT2 inhibitor. This combination of GDMT is supported by a recent systematic network meta-analysis showing that quadruple therapy was most effective at reducing all-cause mortality and confirming an incremental benefit of combination GDMT on morbidity and mortality. The composite outcome of CV death or first hospitalization for HF was also reduced. It was estimated that a 70-year-old patient with HFrEF would gain 5 years of life expectancy if treated with quadruple therapy (Tromp 2022).

A 2021 update to the American College of Cardiology's Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment recommends a "layered approach," which consists of adding GDMT on the basis of pivotal trials in which patients were receiving proven foundational therapies before a newer disease-modifying agent was added (Maddox 2021). Titration of GDMT is recommended within 3–6 months either to target dose or to maximally tolerated dose. This conventional approach has been challenged because it assumes that GDMT is only effective when titrated to target doses; however, benefits are achieved even at low doses. Newer trials have clearly shown that patients who were not receiving optimal baseline therapies such as MRAs or ARNIs still had benefits. In addition, if clinicians follow the traditional sequencing scheme, it can take several months to titrate all medications to optimal dosing. Each drug class has been shown to reduce morbidity and/or mortality within 30 days, so delaying therapy places the patient at greater risk of CV events (McMurray 2021).

As a result, some clinicians have proposed simultaneous initiation and rapid titration of comprehensive disease-modifying treatments – namely ARNI, SGLT2 inhibitors, β-blockers, and MRAs – to drive maximum benefits for patients (Greene 2021). The guidelines also state to consider patient-specific factors when implementing therapy sequentially or

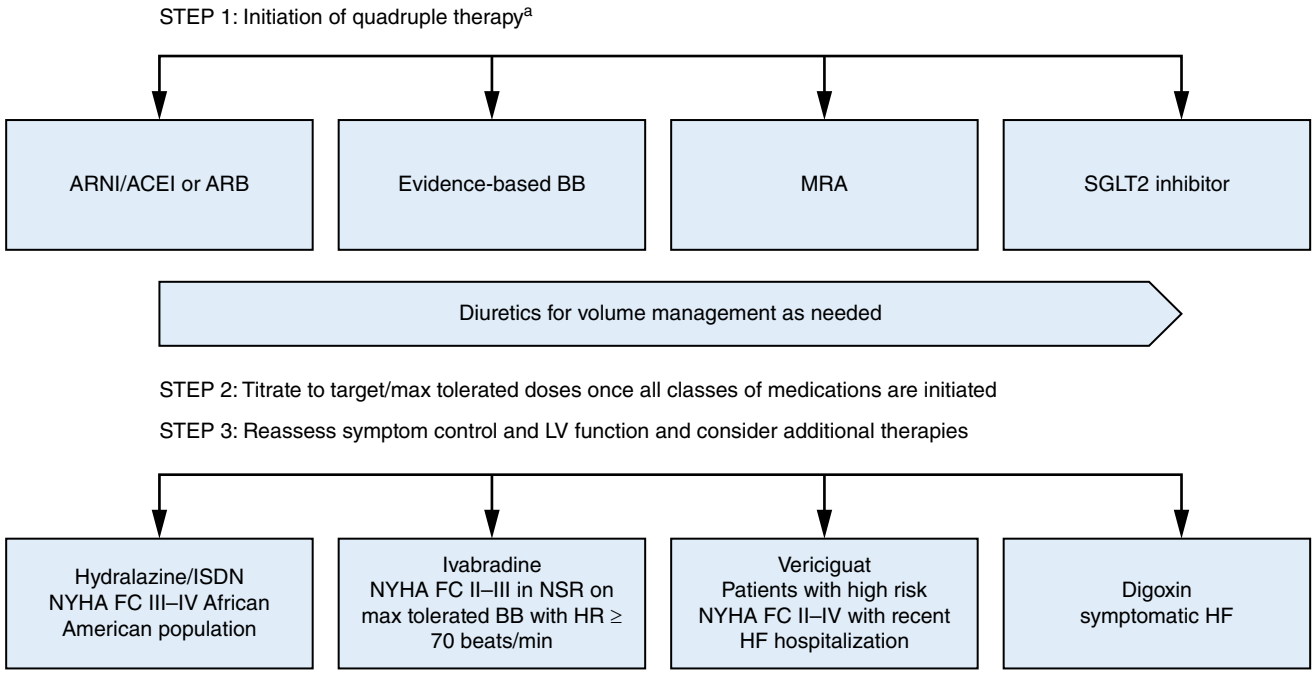

Figure 2. Management of heart failure with reduced ejection fraction (stage C).

[a]Medications can be started simultaneously at initial (low) doses; alternatively, therapy may be started sequentially with sequence guided by patient-specific factors (without need to achieve target doses before initiating next medication).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = β-blocker; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; ISDN = isosorbide dinitrate; LV = left ventricular; MRA = mineralocorticoid receptor antagonist; NSR = normal sinus rhythm; NYHA FC = New York Heart Association functional class; SGLT2 inhibitor = sodium-glucose cotransporter 2 inhibitor.

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simultaneously. In addition, it is not necessary to achieve target dosing before initiating the next medication because doses can be increased to target, as tolerated (Table 2).

Heart Failure with Mildly Reduced Ejection Fraction

Around one-fourth of patients with HF have HFmrEF, defined as an LVEF of 41%–49%. Currently, there are no therapies based on randomized controlled trials to treat this subset of HF. Evidence from post hoc and subgroup analyses of randomized controlled trials suggests that therapies that are effective in patients with HFrEF are also effective in patients with HFmrEF. In patients with HFmrEF, initial consideration should be given to a RAAS inhibitor (ARNI, ACEI, ARB), evidence-based β-blocker (e.g., metoprolol succinate, carvedilol, bisoprolol), and MRA (class of recommendation 2b). In addition, SGLT2 inhibitors now have a class 2a recommendation in this patient population and are beneficial in decreasing HF hospitalizations and CV mortality. Finally, diuretic therapy remains appropriate for symptom management in patients with fluid overload (Heidenreich 2022) (Figure 3).

Heart Failure with Preserved Ejection Fraction

Typically, individuals with HFpEF are older and more often are female than those with HFrEF and HFmrEF. These patients present with many comorbidities and risk factors that have been associated with increased morbidity and mortality. Therefore, adequate management of risk factors and comorbidities such as CKD, diabetes, hypertension, and obesity can improve patient prognosis and remains the treatment mainstay for this subset of HF. Evidence is limited that pharmacologic therapy, diet, or other therapies reduce the risk of mortality in patients with HFpEF.

Fluid overload may rapidly lead to signs and symptoms of congestion in patients with HFpEF. Thus, loop diuretics remain an essential part of HFpEF management. Hypertension should be treated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent

Table 2. Doses for Guideline-Directed Medical Therapy for Heart Failure Management

Drug Class	Drug	Initial Dose	Target Dose	Monitoring	Adverse Effects	Special Considerations
ACEIs	Captopril	6.25 mg TID	50 mg TID	BP, K, SCr	Hyperkalemia, hypotension, angioedema, cough	ACEI/ARB can result in an acute transient reduction in eGFR; an increase in SCr concentration by up to 30% from baseline is considered acceptable
	Enalapril	2.5 mg BID	10–20 mg BID			
	Lisinopril	2.5–5 mg daily	20–40 mg daily			
	Ramipril	1.25–2.5 mg daily	10 mg daily			
	Trandolapril	1 mg daily	4 mg daily			
ARBs	Candesartan	4–8 mg daily	32 mg daily	BP, K, SCr	Hyperkalemia, hypotension, angioedema	
	Losartan	25–50 mg daily	100–150 mg daily			
	Valsartan	20–40 mg BID	160 mg BID			
ARNI	Sacubitril/ valsartan	24/26–49/51 mg BID	97/103 mg BID	BP, K, eGFR	Hyperkalemia, hypotension, angioedema	Allow a 36-hr washout period when changing from an ACEI to an ARNI eGFR < 30 mL/minute/ 1.73 m^2: Starting dose 24/26 mg BID
β-Blockers	Bisoprolol	1.25 mg daily	10 mg daily	BP, HR, volume status	Bradycardia, dizziness, hypotension	Initiate therapy when patient is euvolemic
	Carvedilol	3.125 mg BID	25 mg BID for weight < 85 kg 50 mg BID for weight ≥ 85 kg			
	Metoprolol succinate	12.5–25 mg daily	200 mg daily			
Digoxin		0.125–0.25 mg daily	N/A	HR, eGFR, digoxin concentrations	Digoxin toxicity:Nausea, visual disturbances, bradycardia, confusion	Target serum digoxin concentration is 0.5–0.9 ng/mL
I_f channel inhibitors	Ivabradine	2.5–5 mg BID	7.5 mg BID	BP, HR	Bradycardia, hypotension, phosphenes	Contraindicated in patients with persistent atrial fibrillation, bradycardia, hypotension

(*continued*)

morbidity. Atrial fibrillation is highly prevalent in patients with HFpEF and should be treated accordingly to improve patient symptoms. Patients who develop HFpEF after being diagnosed with atrial fibrillation have worse outcomes, as shown by the post hoc analysis of the TOPCAT trial. Atrial fibrillation was independently associated with an increased risk of CV events (CV mortality, aborted cardiac arrest, or HF hospitalization) (Cikes 2018).

Historically, the focus has been less on providing therapeutic interventions for HFpEF and more on addressing

Table 2. Doses for Guideline-Directed Medical Therapy for Heart Failure Management (*continued*)

Drug Class	Drug	Initial Dose	Target Dose	Monitoring	Adverse Effects	Special Considerations
MRAs	Eplerenone Spironolactone	25 mg daily 12.5–25 mg daily	50 mg daily 25–50 mg daily	K, SCr, eGFR	Gynecomastia, (spironolactone), hyperkalemia	Monitor electrolytes (especially potassium) and renal function in **2–3 days** and 7 days after initiation/titration; then check monthly for 3 mo and every 3 mo afterward Adjust doses on the basis of potassium concentrations and renal function (See Table 3)
sGC modulators	Vericiguat	2.5 mg daily	10 mg daily	BP, CBC	Anemia, hypotension	Contraindicated with concomitant use of other sGC stimulators, long-acting nitrates, and PDE5 inhibitors
SGLT2 inhibitors	Dapagliflozin Empagliflozin	10 mg daily 10 mg daily	10 mg daily 10 mg daily	eGFR, BP, glucose, volume status	Genital mycotic infections, hypoglycemia, ketoacidosis, UTIs	Contraindicated in type 1 diabetes Ensure eGFR ≥ 30 mL/min/1.73 m^2 for dapagliflozin and eGFR ≥ 20 mL/min/1.73 m^2 for empagliflozin SGLT2 inhibitors can result in an acute transient reduction in GFR; an increase in SCr concentration by up to 30% from baseline is considered acceptable
Vasodilators	Hydralazine Isosorbide dinitrate	25 mg TID 20 mg TID	75–100 mg TID 40 mg TID	BP	Dizziness, headache, hypotension	Isosorbide dinitrate is contraindicated with concomitant use of sGC stimulators and PDE5 inhibitors

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BID = twice daily; BP = blood pressure; eGFR = estimated glomerular filtration rate; HR = heart rate; (If) = funny current; K = potassium; MRA = mineralocorticoid receptor antagonist; N/A = not applicable; PDE5 = phosphodiesterase type 5; Scr = serum creatinine; sGC = soluble guanylate cyclase; SGLT2 = sodium-glucose cotransporter 2; TID = three times daily; UTI = urinary tract infection.

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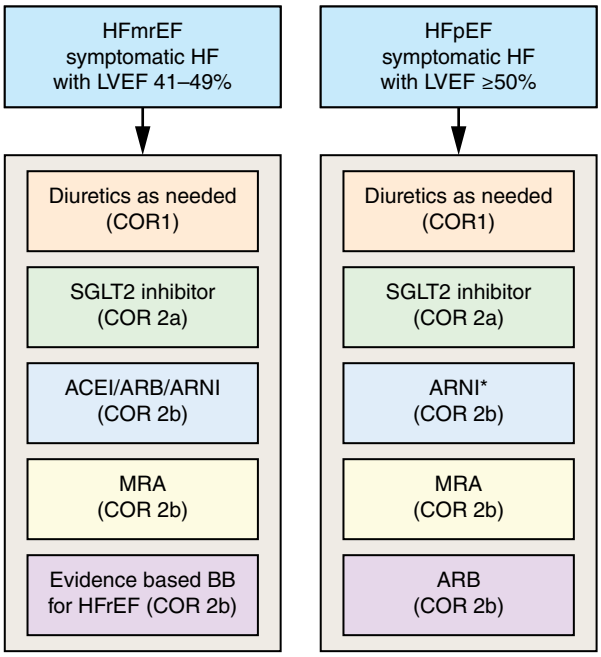
comorbidities. Although specific interventions for HFpEF are available, they offer no mortality benefits. For HFpEF, an MRA and/or an ARNI/ARB may be considered to decrease hospitalizations, particularly among patients with an LVEF less than 50% (class 2b recommendation). In addition, SGLT2 inhibitors are becoming the standard of care both from a symptomatic perspective and for decreasing HF hospitalizations and CV mortality and now have a class 2a recommendation for use in HFpEF (Heidenreich 2022) (see Figure 3).



*Greater benefit in patients with LVEF closer to 50%.

Figure 3. Treatment recommendations for patients with HFmrEF and HFpEF.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = β-blocker; COR = class of recommendation; HFrEF = heart failure with reduced ejection fraction; HFmrEF = HF with mildly reduced EF; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter 2.

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Heart Failure with Improved Ejection Fraction

A distinct subset of patients have HFimpEF, which is defined as patients previously with an LVEF of 40% or less with improvement in LVEF to greater than 40% with or without GDMT. Although GDMT leads to reverse remodeling and improvement in HF symptoms, in most patients, functional and structural abnormalities do not fully recover, and patients' HF conditions can relapse after GDMT is discontinued. This is supported by the results of the TRED-HF trial (Halliday 2019), which showed that discontinuation of pharmacologic HF therapy in patients with recovered dilated cardiomyopathy (LVEF greater than 50%) resulted in relapse of HF in around 40% of cases. This suggests improvement in function represents "remission" rather than "permanent recovery" for many patients. The guidelines recommend continuing and/or optimizing GDMT in patients with HFimpEF regardless of the presence or absence of symptoms. Notable exceptions to this recommendation may include patients who recover from peripartum cardiomyopathy, fulminant myocarditis, or stress cardiomyopathy.

PATIENT-CENTERED APPROACH FOR OPTIMIZING GDMT

Despite treatment advances, many eligible patients are not receiving one or more evidence-based guideline-recommended HF therapies. There are gaps, variations, and disparities in the use of GDMT, leading to preventable mortality and morbidity. Real-world registries indicate that medications with class 1 recommendations are still not prescribed (Maddox 2020). Contemporary evidence in primary care and cardiology practice also suggests limited attempts to titrate disease-modifying therapies. Among eligible patients for all classes of medications, only 1% were simultaneously receiving target doses (Greene 2018). Reasons identified for underuse of GDMT in HFrEF include therapeutic inertia; concerns about tolerability, access, cost, and value; and lack of systems to implement therapies. In addition, a typical patient with HF is older and frail, has several comorbid conditions, and may lack social, financial, and/or caregiver support. The presence of several chronic diseases increases symptom burden, contributes to progression of disease and hospitalizations, and greatly affects HF treatment and the ability to optimize GDMT. On average, patients with HF receive 10 or more medications, many of which are non-HF medications that can affect adherence to and tolerability of HF GDMT (Unlu 2020). Patients at high risk present with multiorgan system involvement, lower SBP, worsening renal function, hyperkalemia, and medication intolerance, adding another layer of complexity.

Patient factors such as hemodynamic profile (blood pressure, heart rate, congestion) and kidney function may limit implementation of medical therapy. Recent HF guidelines together with expert consensus decision pathways for HFrEF now provide a personalized approach for optimizing GDMT (Heidenreich 2022; Maddox 2021). One approach is to initiate all four foundational therapies (ARNI, SGLT2 inhibitor, β-blocker, and MRA) near-simultaneously at low doses in patients with newly diagnosed stage C HFrEF (Green 2021). This should occur within 1 week, and doses should be titrated to target or the maximally tolerated dose. An alternative approach is a three-step pathway, with a β-blocker and an SGLT2 inhibitor initiated concomitantly (step 1). The rationale for this approach is that the primary therapeutic goal in new-onset HF is to improve survival, and β-blockers have been shown to reduce sudden cardiac death in the early phase of HF. Early initiation of SGLT2 inhibitors improves renal function and potassium homeostasis, thus allowing

Patient Care Scenario

L.M. is a 64-year-old man with a medical history significant for HFrEF (LVEF 27%), T2DM (A1C 7.2%), hypertension, stage 3b CKD (baseline eGFR 38 mL/minute/1.73 m^2, K 5.2 mEq/L), dyslipidemia (LDL 55 mg/dL), and obesity (BMI 36.8 kg/m^2) who presents for a follow-up with the HF clinic. His home medications include sacubitril/valsartan 49/51 mg twice daily, metoprolol succinate 150 mg daily, torsemide 20 mg daily, rosuvastatin 20 mg daily, aspirin 81 mg daily, metformin 1000 mg daily, and glipizide extended release 20 mg daily. His blood pressure is 136/84 mm Hg and heart rate is 70 beats/minute. His physical examination reveals jugular venous pressure of 8 cm H_2O and 1+ bilateral pedal edema. What is best to recommend for this patient's HF regimen?

Clinical practice guidelines recommend "foundational quadruple therapy": a combination of ACEI, ARB, or ARNI (ARNI preferred); an evidence-based β-blocker; an MRA; and an SGLT2 inhibitor. The patient is not currently taking target doses of an ARNI and β-blocker and is not receiving an MRA or SLGT2 inhibitor. The estimated cumulative effect of these four medication classes includes a 73% relative reduction in mortality over 2 years. Combined use of these therapies can improve life expectancy for the average 50-year-old patient with HFrEF by a median of 6 years compared with more conventional therapy of introducing one agent at a time and titrating it to a maximum tolerated dose before introducing a new therapy (Tromp 2022). The SGLT2 inhibitors reduce CV mortality and morbidity and improve patient-reported quality of life, with these benefits occurring within days to weeks of initiation. The SGLT2 inhibitors also substantially preserve renal function and reduce the risk of end-stage renal disease. This patient is at high risk of HF progression and decline in renal function. Thus, initiation of an SGLT2 inhibitor can be considered at this visit. The patient's potassium concentrations are mildly elevated and may require diligent monitoring. Given the patient's CKD and diabetes, he is at risk of hyperkalemia. Data from SGLT2 inhibitor trials suggest that combination therapy with an MRA reduces the risk of hyperkalemia (particularly severe hyperkalemia, defined as K greater than 6 mEq/L). Guidelines do not recommend MRA initiation if pretreatment K concentrations are greater than 5 mEq/L. Because the patient is slightly volume overloaded, titration of metoprolol succinate to the target dose can be delayed. Although increased use of loop diuretic therapy for decongestion could be considered, this might further worsen the patient's renal function. Because SGLT2 inhibitors have diuretic effects, clinicians may choose to reduce the diuretic dose upfront. However, preemptive dose reduction of loop diuretics, before initiating SGLT2 inhibitors, is not well defined, thereby confounding the need for loop diuretic dose adjustment when initiating an SGLT2 inhibitor. Furthermore, in DAPA-HF, an empiric dose reduction of diuretics was not required; instead, monitoring of congestion and weight and considering changes in 2–4 weeks after initiation were recommended. Empagliflozin or dapagliflozin 10 mg daily should be initiated, and eventually all GDMT should be optimized, as tolerated. Spironolactone should be considered once K is less than 5 mEq/L. In addition, this patient is taking glipizide, which is not a recommended first-line treatment for T2DM and increases the risk of hypoglycemia because of concomitant renal dysfunction. Consider consulting with endocrinology or primary care to help with management of diabetes.

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2. Bassi NS, Ziaeian B, Yancy CW, et al. Association of optimal implementation of sodium-glucose cotransporter 2 inhibitor therapy with outcome for patients with heart failure. JAMA Cardiol 2020;5:948-51.
3. Shen L, Kristensen SL, Bengtsson O, et al. Dapagliflozin in HFrEF patients treated with mineralocorticoid receptor antagonists: an analysis of DAPA-HF. JACC Heart Fail 2021;9:254-64.
4. Sharma A, Verma S, Bhatt DL, et al. Optimizing foundational therapies in patients with HFrEF. JACC Basic Transl Sci 2022;7:504-17.

safe initiation of an MRA. Another reason to add an SGLT2 inhibitor together with a β-blocker is to counteract the fluid retention that can be caused by β-blocker therapy. The next step (step 2) should be initiation of an ARNI (within 1–2 weeks) if the SBP is greater than 100 mm Hg and the patient has no signs or symptoms of hypotension. If renal function and electrolytes are within normal range, an MRA should be added (within 1–2 weeks of step 2). Ultimately, patient factors and drug coverage will dictate the sequencing (e.g., if the SBP is low, an MRA can be initiated before an ARNI). The goal is to achieve GDMT within 4 weeks in the absence of contraindications (McMurray 2021).

Chronic Kidney Disease

Renal dysfunction is common in patients with HF and associated with worse outcomes. When choosing a medication for HF treatment, it is important to consider renal function because many treatments can affect renal parameters. A modest decline in eGFR is expected after initiation of an ACEI/ARB/ARNI and an SGLT2 inhibitor, followed by stabilization of renal function over time. When initiating an ACEI/ARB/ARNI or SGLT2 inhibitor, it is important to consider whether the decline in renal function creates a risk that outweighs the benefit of the medication.

Reanalysis of data from the landmark SOLVD trial (Studies of Left Ventricular Dysfunction) showed that 16% of patients in the enalapril arm and 12% in the placebo arm had an increase in serum creatinine (Yusuf 2003). Patients in the placebo arm whose renal function declined had a greater increase in the primary end point of mortality and hospitalizations. The survival advantage of enalapril over placebo was more pronounced in patients with worsening kidney function than in patients without CKD. The PARADIGM-HF trial showed that patients with CKD had a higher risk of CV death or readmission for HF, but this risk decreased in patients with CKD who received an ARNI compared with patients who received enalapril. Similarly, a post hoc analysis of PARADIGM-HF (Damman 2018) and PARAGON-HF (McCausland 2020) showed that ARNIs led to a slower rate of decrease in eGFR and improved renal outcomes in patients with HFrEF and HFpEF. Another meta-analysis that compared RAAS inhibitors with ARNIs showed that ARNIs significantly increased the eGFR, suggesting renal and CV benefits in patients with HF and CKD (Kang 2020).

As previously discussed, SGLT2 inhibitors have been shown effective at slowing the progression of kidney disease in patients with or without CKD. The DAPA-CKD trial showed a renoprotective benefit of dapagliflozin in patients with an eGFR of 25–75 mL/minute/1.73 m^2 and a urinary albumin/creatinine ratio (UACR) of 200–5000 mg/g (Heerspink 2020). The primary outcome was a composite of a sustained decline in the eGFR of at least 50%, end-stage renal disease, or death from renal or CV causes. Over a median of 2.4 years, dapagliflozin significantly reduced the primary outcome event and the risk of composite renal events in patients with or without T2DM. Similar to RAAS inhibitors, SGLT2 inhibitors can cause an early mild to moderate reduction in eGFR (around 3–6 mL/minute/1.73 m^2) at the start of therapy, followed by significantly less decline over time. Recent publication of the Study of Heart Protection with Empagliflozin trial (EMPA-KIDNEY) had results similar to the DAPA-CKD trial in improving cardiorenal outcomes in patients with CKD, with or without diabetes. The primary composite end point of kidney disease progression (defined as end-stage kidney disease, a sustained decrease in eGFR to less than 10 mL/minute/1.73 m^2, a sustained decrease in eGFR of 40% or greater from baseline, or death from renal causes) or CV death was reduced by 28% (HR 0.72; 95% CI, 0.64–0.82; p<0.0001) with empagliflozin compared with placebo. Despite the initial decline in eGFR in the first 2 months of randomization, the annual rate of eGFR decline was slower in the empagliflozin arm by 0.75 mL/minute/1.73 m^2. The effect of empagliflozin across the prespecified subgroups (diabetes, eGFR, and UACR) was mostly consistent. There were no between-group differences in the incidence of serious adverse events. The evidence further supports the use of SGLT2 inhibitors to prevent CKD progression and enable the tolerability of GDMT in CKD (Herrington 2023).

Patients with stage 4 and 5 CKD were excluded in clinical trials, making it difficult to provide recommendations in severe renal dysfunction. An observational study of severe renal dysfunction showed that continuing an ACEI or ARB after the eGFR declined to less than 30 mL/minute/1.73 m^2 was associated with decreased major adverse cardiac events and no significant progression to end-stage kidney disease compared with discontinuation (Qiao 2020). However, ACEI or ARB continuation was associated with higher rates of hyperkalemia. This safety signal for continuation of RAAS inhibitor therapy in CKD is reassuring until the results of a multicenter randomized controlled trial of ACEI/ARB withdrawal in advanced renal disease (STOP-ACEi) are available (Bhandari 2016). Evidence is also very limited for ARNIs in patients with stage 4 or 5 CKD or end-stage kidney disease (ESKD). A real-world study showed 28% fewer CV deaths or HF hospitalizations in patients with stage 4 or 5 CKD treated with an ARNI than in those receiving standard HF treatment. This benefit was also seen in patients with an eGFR of less than 30 mL/minute/1.73 m^2 (Chang 2019).

Continuation of RAAS inhibitor therapy is generally considered safe when the SCr is less than 3 mg/dL. The initial increase in SCr upon medication initiation is usually not because of intrinsic kidney injury but because of a change in hemodynamics. A moderate, asymptomatic decline in renal function is not an indication to discontinue the RAAS inhibitor. However, a significant increase in serum creatinine (greater than 30% from baseline) should prompt a detailed clinical review to verify the cause and may require a temporary dose reduction or cessation of therapy (Clark 2019). The same approach may be reasonable for SGLT2 inhibitors. The goal is to prevent kidney failure and CV events and to avoid reacting to small changes in eGFR. In patients with moderate CKD (eGFR 30–59 mL/minute/1.73 m^2), no dose adjustment is required when initiating an ARNI; however, the dose should be reduced in patients with severe CKD (eGFR less than 30 mL/minute/1.73 m^2) (Maddox 2021). Because a reduction in diuretic needs was observed in the PARADIGM-HF and DAPA-HF trials, a careful assessment and adjustment of diuretic doses should be considered before and after initiation of an ARNI or SGLT2 inhibitor to avoid overdiuresis, which can potentially worsen renal function. Furthermore, because SGLT2 inhibitors decrease the risk of ESKD or sustained worsening of renal function, initiation of SGLT2 inhibitors can potentially improve the tolerability of other key medications such as MRAs and ARNIs.

Hypotension

In landmark clinical trials of HF, around 10%–15% of patients with HF had low SBP (less than 100–120 mm Hg). Hypotension is an SBP of 90 mm Hg or less (Cautela 2020). Hypotension can be asymptomatic or symptomatic with dizziness and syncope. In patients with HFrEF, a lower SBP is a marker of worse outcomes than higher blood pressure. In trials, clinical

judgment rather than a predefined blood pressure threshold was generally used to characterize hypotension. Earlier clinical trials with RAAS inhibitors showed that patients with more severe HF benefit the most from GDMT. In HFrEF, low blood pressure may be the result of hypovolemia secondary to diuretic use, low cardiac output, autonomic dysfunction, vasodilatory effects of certain HF medications, and non-HF medications that include, but are not limited to, calcium channel blockers, α-blockers, nitrates, centrally acting agents for psychiatric disorders or Parkinson disease, and PDE5 inhibitors (Cautela 2020).

In clinical trials, the blood pressure–lowering effects of β-blockers were modest, if at all, and usually less than placebo. Evidence suggests it is safe to initiate β-blockers before ACEIs in patients with a low SBP (Willenheimer 2005). In patients with a borderline baseline SBP, metoprolol succinate may be better than carvedilol because of a lack of vasodilatory properties.

In the PARADIGM—HF study, the risk of symptomatic hypotension was 14% with an ARNI (McMurray 2014). Only a small patient subset (2.7%) had an SBP less than 90 mm Hg associated with symptoms. Hypotension was managed by reducing the dose or temporarily discontinuing ARNI treatment, simply waiting for a spontaneous improvement, or changing concomitant treatments. Permanent treatment discontinuation was observed in only 2.2% of cases. Of note, patients with a lower blood pressure (usually receiving a low—dose ARNI) had benefit from an ARNI similar to patients with higher blood pressure. A titration trial that compared the tolerability of ARNIs with condensed titration (titration over 3 weeks) to conservative titration (titration over 6 weeks) found that more patients with lower SBP (100–110 mm Hg) achieved treatment success with conservative than with condensed titration (Senni 2016).

Blood pressure is not significantly affected by MRA therapies in clinical trials. A study showed that clinical benefits were sustained with MRA therapy even when baseline SBPs were low (Serenelli 2020a). Therefore, low SBP is not a reason to withhold MRA therapy in patients with HFrEF. The blood pressure–lowering effects of SGLT2 inhibitors are also negligible. The mean decrease in blood pressure with dapagliflozin was only -1.92 mm Hg, and the agent was well tolerated across the range of SBP (McMurray 2019). In EMPEROR-Reduced, there was no significant difference in SBP compared with placebo (mean decrease in SBP -2.4 mm Hg) (Parker 2020).

Even though clinical data support the use of therapies in lower SBP, evidence is not strong to support their use in SBP less than 100 mm Hg because most clinical trials excluded these patients. Guidance is insufficient on how to concomitantly add GDMT in patients with low blood pressure. In addition, achieving target doses of therapies may be challenging because of dose-related reductions in blood pressure. Some strategies can be considered to optimize GDMT when patients present with low blood pressure (Box 1).

Box 1. Management of Hypotension in Patients with HF

Asymptomatic Hypotension

- No action is required when SBP ≥ 100 mm Hg with negative orthostasis and no postural symptoms
- SBP < 90 mm Hg with negative orthostasis and no postural symptoms: Continue to monitor blood pressure and any symptoms of hypotension

Symptomatic Hypotension

- Adjust diuretic doses in the absence of congestion
- Avoid/discontinue non-HFrEF blood pressure–lowering medical therapies (e.g., α-blockers, calcium channel blockers, nitrates)
- Consider separate timing of medications that may cause hypotension
- Assess non-cardiovascular causes of hypotension
- Initiate and titrate GDMT slowly with close follow-up and monitoring
- Early initiation of SGLT2 inhibitor
- Check for orthostasis. Patients with postural hypotension should be set up with compression stockings
- Consider cardiac rehabilitation

GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = HF with reduced ejection fraction; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter 2.

Information from: Cautela J, Tartiere JM, Cohen-Solal A, et al. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. Eur J Heart Fail 2020;22:1357-65.

Hyperkalemia

Hyperkalemia is common in HF, with the risk increasing in the presence of comorbidities such as diabetes and CKD. The mainstay HF therapies that target the RAAS pathway can also lead to increases in potassium and thus hyperkalemia (Hunter 2019). The true incidence of hyperkalemia varies because of different cutoffs. This lack of an agreed-on definition for hyperkalemia creates challenges in how to manage elevated potassium concentrations in clinical practice. Major risk factors for hyperkalemia include advanced age, low eGFR, and the presence of several comorbidities. Heart failure outcomes are best when K concentrations are 4–5 mEq/L. The risk of CV mortality increases with K concentrations greater than 5 mEq/L, and at concentrations greater than 5.5 mEq/L, intervention is required.

The clinical consequences of hyperkalemia contribute to the under-prescription of HF GDMT. In the PARADIGM-HF study, patients with an eGFR less than 30 mL/minute/1.73 m^2 and baseline hyperkalemia (K greater than 5.4 mEq/L) were excluded before randomization (McMurray 2014). During the 4- to 8-week run-in phase, 29.4% of patients in the enalapril group and 22.5% in the ARNI group discontinued ACEI and ARNI therapy if they developed hyperkalemia. Thus, the concern for hyperkalemia seems reasonable, and elevated potassium concentrations should prompt clinicians to discontinue or taper therapy. An observational study showed

that many patients' disease-modifying therapies were discontinued or the doses reduced, even in mild hyperkalemia (5.1–5.4 mEq/L), and that, as a result, mortality increased (Epstein 2015).

Landmark trials of MRAs suggest that CV prevention is independent of the incidence of hyperkalemia or worsening renal function. Addition of an MRA is advantageous in maintaining potassium concentrations within normal range and protecting against hypokalemia. A secondary analysis of the RALES trial showed that mortality rates were higher in participants randomized to placebo than in those taking spironolactone at all potassium concentrations (Vardeny 2014). The treatment benefit was maintained at least until K concentrations were greater than 5.5 mEq/L with spironolactone. However, in patients with HF with impaired renal function, spironolactone use is associated with increased rates of hyperkalemia (greater than 5.5 mEq/L). Because of this, MRAs are the only RAAS inhibitor that have a contraindication if the pretreatment K concentration is greater than 5 mEq/L and/or eGFR is less than 30 mL/minute/1.73 m^2 (Maddox 2021).

Clinical trials with SGLT2 inhibitors have consistently shown a reduction in the risk of hyperkalemia. Sub analyses from the EMPEROR data set showed that empagliflozin significantly reduced hyperkalemia events regardless of background MRA use in both HFrEF and HFpEF (Ferreira 2022). Results were similar with dapagliflozin, showing a 50% reduction in the risk of moderate/severe hyperkalemia (K greater than 6 mEq/L) and a 36% reduction in hyperkalemia with MRA

Table 3. Recommended Dosing Strategies for MRAs According to Severity of Renal Function and Potassium Concentrations in HF

Initiation of MRA in HF

Serum K^+ (mEq/L)	eGFR (ml/min/1.73m^2)	Spironolactone	Eplerenone
≥ 5.0	At any eGFR	Do not initiate	Do not initiate
≤ 5.0	≥ 50	Initiate 12.5 mg – 25 mg once daily	Initiate 25 mg once daily
≤ 5.0	30 - 49	Initiate 12.5 mg once daily or every other day	Initiate 25 mg every other day

Titration and Maintenance of MRA in HF[a]

Serum K^+ (mEq/L)	Spironolactone	Eplerenone
< 4.0	If dose = 12.5 mg every other day → increase to 12.5 mg/day If dose = 12.5 mg/day → increase to 25 mg/day If dose = 25 mg every day → no adjustment recommended	If dose = 25 mg every other day → increase to 25 mg/day If dose = 25 mg/day → increase to 50 mg/day If dose = 50 mg/day → → no adjustment recommended
4.0 - 5.4	No adjustment recommended[b]	No adjustment recommended[b]
5.5 - 5.9	If dose = 12.5 mg/day → decrease to 12.5 mg every other day If dose = 25 mg/day → decrease to 12.5 mg day or 25 mg every other day If dose = 50 mg/day → decrease to 25 mg/day	If dose = 25 mg/day → decrease to 12.5 mg daily or 25 mg every other day If dose = 50 mg/day → decrease to 25 mg/day
≥ 6.0	Evaluate other reasons for elevated K^+ If high risk for hyperkalemia, stop MRA and reassess in 1 week or initiate K^+ binders and reintroduce MRA	
	If eGFR falls ≤30 ml/min/1.73 m^2, stop MRA and reassess in 1 week	

[a]Only when eGFR > 30 ml/min/1.73 m^2

[b]If maximal tolerated dose or target dose achieved

BP = blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; K+ = potassium; MRA = mineralocorticoid receptor antagonist

Information from: Ferreira JP, Butler J, Rossignol P, et al. Abnormalities of potassium in heart failure: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:2836-50. doi: 10.1016/j.jacc.2020.04.021; Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-e239. doi: 10.1016/j.jacc.2013.05.019

use (Shen 2021). The reduction in the risk of serious hyperkalemia with SGLT2 inhibitors can potentially increase the tolerability of RAAS inhibitor therapy in patients with CKD and HF.

Hyperkalemia can be life threatening with K concentrations greater than 6 mEq/L. Potassium concentrations of 5.2–5.4 mEq/L likely indicate a risk of high comorbidity burden. Before discontinuing GDMT, careful evaluation is required to address causes of hyperkalemia. For MRA therapy, renal function evaluation and potassium concentrations should dictate dose adjustments (Table 3). Typical treatment approaches have also included removal of foods that increase serum potassium. However, dietary restrictions to maintain normal potassium concentrations can be challenging for patients and may not be best to facilitate titration of medication therapy (Box 2).

Two novel potassium binders, patiromer and sodium zirconium cyclosilicate, have been approved for the treatment of hyperkalemia (Sarwar 2016). Patiromer and sodium zirconium cyclosilicate are considered enabling agents to optimize GDMT in chronic hyperkalemia. Clinical trials have shown that potassium binders are very effective in treating hyperkalemia and well tolerated and that drug-drug interactions are manageable (Anker 2015; Buysse 2012). Results from the DIAMOND trial showed the efficacy of patiromer in reducing serum potassium concentrations and hyperkalemia events among patients with HFrEF with a history of hyperkalemia while also allowing 85% of participants to receive optimal doses of RAAS inhibitors (Butler 2022a). A consensus statement by cardiologists and nephrologists provides detailed practical guidance on how to manage hyperkalemia with different potassium cutoff values, when to use potassium binders and how to choose between the available agents, and a timeline for monitoring (Ferreira 2020).

Practice Points

Despite the high risk of morbidity and mortality in HFrEF, real-world data suggest that most patients with no clinical contraindications to GDMT are not treated optimally. Clinical practice guidelines emphasize the importance of early and rapid initiation of GDMT. Recognizing that many barriers to GDMT initiation and optimization exist, clinicians should strive to introduce the four pillars of therapy as recommended by 2022 HF guidelines. Guidelines propose a new set of recommendations and expand treatments for a broad range of LVEF values according to contemporary evidence.

- **A universal definition of HF strives to increase uniformity, whereas the redefinition of HF stages emphasizes prevention and provides different categories of HF according to LVEF.**
- **New drug therapies now include SGLT2 inhibitors, which incrementally improve the HF prognosis beyond foundational neurohormonal therapies.**
- **Quadruple therapy (a combination of ACEs/ARBs/ARNI [ARNI preferred], evidence-based β-blockers, MRAs, and SGLT2 inhibitors) is the new standard for HFrEF and is associated with the greatest improvement in clinical outcomes.**
- **The optimal approach is to use each GDMT shown to decrease morbidity and mortality in combination and to titrate to maximally tolerated doses without delay.**
- **Simultaneous or sequential strategies can be used to initiate or titrate GDMT according to patient-specific factors (blood pressure, kidney function, and electrolytes).**
- **In patients with an LVEF lower than normal, including those with HFmrEF and HFpEF, addition of an ARNI, ACEI, or ARB and an SGLT2 inhibitor is beneficial.**
- **It is recommended to continue GDMT in patients with HFimpEF, including those who are asymptomatic, to prevent relapse of HF and LV dysfunction.**

Box 2. Assessment and Management of Hyperkalemia

- Assess other medications that may increase potassium
  - Potassium supplements
  - Salt substitutes
  - Cyclosporine, tacrolimus, NSAIDs, trimethoprim, etc.
- Assess for acute increase in potassium vs. chronically elevated potassium
- Assess changes in renal function
- Identify source of laboratory errors (e.g., hemolysis)

Management strategies

- Substitute ACEIs/ARBs with ARNI (if clinically appropriate)
- Educate patients and provide a list of foods high in potassium content
- Use potassium binders as clinically indicated

ARNI = angiotensin receptor neprilysin inhibitor; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; NSAID = non-steroidal anti-inflammatory drug.

Information from: Ferreira JP, Butler J, Rossignol P, et al. Abnormalities of potassium in heart failure: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:2836-50.

CONCLUSION

Because HF can easily decompensate, the updated guidelines emphasize the importance of early and rapid titration of GDMT in patients with HFrEF. When appropriate, all attempts should be made to initiate quadruple therapy. Patient-specific parameters should be considered when optimizing therapy for patients with HF because they have unique needs and reserves. Offending agents that can affect HF care should be avoided and removed to decrease pill burden, improve adherence, and avoid adverse effects. The frequency of follow-up and laboratory data should also be patient-specific because some patients will require closer follow-up than others. Costs of newer therapies should be considered because of restricted coverage and out-of-pocket expenses. A multidisciplinary approach to management of HF has clearly shown

an improvement in clinical outcomes. The pharmacist's role as a liaison between patients and other health care providers is essential for effective implementation and optimization of HF medication therapies. Pharmacist-led ambulatory HF clinics provide collaborative medication management and patient education sessions, help navigate prior authorizations, and provide financial assistance to decrease the cost of medications.

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Self-Assessment Questions

1. A 69-year-old man with heart failure with reduced ejection fraction (HFrEF) (left ventricular ejection fraction [LVEF] 25%) and New York Heart Association functional class (NYHA FC) III symptoms presents to the HF disease management clinic for a follow-up. The patient has recurrent pulmonary congestion and has had two hospitalizations for HF within the previous 6 months. His home medications include sacubitril/valsartan 97/103 mg twice daily, carvedilol 25 mg twice daily, spironolactone 25 mg daily, dapagliflozin 10 mg daily, and furosemide 40 mg daily. His current symptoms include shortness of breath with activity, bilateral lower extremity 1+ pitting edema, and basal crackles on lung examination. The patient's vital signs include blood pressure 130/60 mm Hg and heart rate 68 beats/minute. Laboratory values are K 4.0 mEq/L, SCr 1.0 mg/dL, and NT-proBNP 890 pg/mL. Which one of the following is the next best step to decrease his risk of HF hospitalization and improve clinical outcomes?

   A. Reduce the furosemide dose.
   B. Initiate ivabradine 5 mg twice daily.
   C. He is receiving optimal guideline-directed medical therapy (GDMT); no additional therapy is needed.
   D. Initiate vericiguat 2.5 mg daily.

2. A 54-year-old woman (weight 85 kg) with HFrEF (LVEF 40%) was initiated on dapagliflozin 2 weeks ago. Her current medications include furosemide 40 mg twice daily and carvedilol 12.5 mg twice daily. She reports shortness of breath with activity and two-pillow orthopnea that has not improved since her last clinic visit. Her physical examination reveals lower extremity 1+ pitting edema with no jugular venous distension. Her SCr has increased to 1.32 mg/dL from 1.1 mg/dL (after initiation of dapagliflozin); K is 4.0 mEq/L, Na is 139 mEq/L, and eGFR is 40 mL/minute/1.72 m^2. Her vital signs today include blood pressure 130/65 mm Hg and heart rate 70 beats/minute. Her weight is stable. Which one of the following is best to recommend for this patient?

   A. Dapagliflozin should be discontinued temporarily and reinitiated after renal function improves.
   B. Dapagliflozin should be continued with monitoring of eGFR and daily weights.
   C. The patient should be changed to empagliflozin, given its cardiorenal benefits.
   D. Furosemide dose should be decreased because her renal function has declined.

3. Which one of the following patients is the best candidate for initiation of vericiguat?

   A. A 55-year-old man who was recently hospitalized for HF exacerbation, with NYHA FC II symptoms (LVEF 50%), blood pressure 120/75 mm Hg, and NT-proBNP 1000 pg/mL
   B. A 45-year-old woman with two HF hospitalizations in the past 6 months, with NYHA FC III symptoms (LVEF 35%), blood pressure 137/80 mm Hg, and NT-proBNP 600 pg/mL and receiving optimal quadruple therapy and taking sildenafil.
   C. A.65-year-old woman with two HF hospitalizations in the past 6 months, with NYHA FC III symptoms (LVEF 20%), blood pressure 130/80 mm Hg, and NT-proBNP 1000 pg/mL and receiving optimal quadruple therapy.
   D. An 85-year-old man with NYHA FC IV symptoms (LVEF 40%) with blood pressure 98/80 mm Hg and NT-proBNP 12,000 pg/mL and receiving maximum tolerated doses of quadruple therapy

4. A 57-year-old woman (weight 68 kg) returns for a follow-up with the clinical pharmacist. She was recently diagnosed with HF (LVEF 35%), initiated on sacubitril/valsartan and metoprolol succinate, and referred to an HF titration clinic to optimize the rest of her GDMT regimen. Her medications include sacubitril/valsartan 49/51 mg twice daily, metoprolol succinate 100 mg daily, and spironolactone 25 mg daily. After 12 months of follow-up, her repeat echocardiogram reveals LVEF 46%. Her vital signs include blood pressure 118/80 mm Hg and heart rate 58 beats/minute. Pertinent laboratory results are K 4.7 mEq/L, SCr 1.0, and eGFR 60 mL/minute/1.73 m^2. Which one of the following is best to recommend to optimize this patient's medical therapy?

   A. Discontinue sacubitril/valsartan because her LVEF has improved.
   B. Continue all of her medications as prescribed.
   C. Change to carvedilol 12.5 mg twice daily.
   D. Decrease the spironolactone dose because her potassium is at the higher end of normal.

5. In which one of the following patients would it be most appropriate to initiate spironolactone?

   A. A 60-year-old woman with NYHA FC III symptoms, K 4.6 mEq/L, eGFR 54 mL/minute/1.73 m^2
   B. A.45-year-old man with NYHA FC II symptoms, K 3.8 mEq/L, eGFR 15 mL/minute/1.73 m^2
   C. An 80-year-old man with NYHA FC III symptoms, K 5.2 mEq/L, eGFR 61 mL/minute/1.73 m^2
   D. A 75-year-old woman with NYHA FC I symptoms, K 3.5 mEq/L, eGFR 40 mL/minute/1.73 m^2

6. A 47-year-old woman presents to your clinic for a follow-up. She has HFpEF (LVEF 50%), T2DM, and chronic stable angina. She is euvolemic on examination. Her

medications include metformin 500 mg twice daily, losartan 12.5 mg daily, metoprolol succinate 50 mg daily, empagliflozin 10 mg daily, and atorvastatin 40 mg daily. Her blood pressure is 144/80 mm Hg, with heart rate 60 beats/minute, A1C 7.1%, K 5.3 mEq/L, and eGFR 30 mL/minute/1.73 m^2. Which one of the following is best to recommend for this patient?

A. Initiate spironolactone 25 mg daily and monitor electrolytes in one week.
B. Change losartan to sacubitril/valsartan 24/26 mg twice daily.
C. Initiate hydralazine/isosorbide dinitrate 37.5/20 mg three times daily.
D. Increase metoprolol succinate to 100 mg daily and monitor blood pressure.

7. A 65-year-old man with HFrEF returns to the HF clinic to assess the next steps in therapy. His echocardiogram reveals an LVEF of 30%–35%, which has slightly improved over his baseline echocardiogram of 25%–30%. He has NYHA FC II symptoms today. His medical history includes type 1 diabetes (A1C 7.8%), MI, and hypothyroidism. His HF medications include valsartan 160 mg twice daily, carvedilol 25 mg twice daily, and spironolactone 25 mg daily. Other medications include levothyroxine 125 mcg daily, insulin glargine 15 units daily, and insulin lispro 5 units with each meal. He is euvolemic on examination. Vital signs include blood pressure 128/78 mm Hg, heart rate 62 beats/minute, and weight 89 kg (dry weight). His laboratory results include K 4 mEq/L and eGFR 55 mL/minute/1.73 m^2. Which one of the following is best to recommend to optimize this patient's GDMT?

A. Change valsartan after a 36-hour washout period before initiating sacubitril/valsartan 49/51 mg twice daily and titrate as tolerated.
B. Add ivabradine 5 mg twice daily and titrate until heart rate is less than 60 beats/minute.
C. Add dapagliflozin 10 mg daily.
D. Change valsartan to sacubitril/valsartan 49/51 mg twice daily and titrate as tolerated.

8. A 70-year-old woman with a medical history significant for CAD (coronary artery bypass graft in 2012), HFrEF (LVEF 40%), dyslipidemia, T2DM, hypertension, chronic kidney disease (CKD), and COPD presents for a routine follow-up. During the visit, it is discovered that she remains dyspneic with walking her dog. Her medications include metoprolol succinate 200 mg daily, sacubitril/valsartan 49/51 mg twice daily, spironolactone 25 mg daily, furosemide 20 mg daily, metformin extended release 1000 mg daily, insulin glargine 30 units daily, and insulin aspart 10 units with breakfast and 20 units with dinner. Vital signs include blood pressure 114/67 mm Hg and heart rate 80 beats/minute. Pertinent laboratory values from today include K 4.8 mEq/L and eGFR 39 mL/minute/1.73 m^2. Which one of the following is best to recommend for this patient?

A. Initiate empagliflozin with communication with primary care provider because of diabetes.
B. Make no change because she is receiving maximum tolerated GDMT.
C. Titrate spironolactone to 50 mg daily.
D. Change from metoprolol succinate to carvedilol 12.5 mg twice daily.

9. A 68-year-old man with a medical history significant for HFpEF, hypertension, obstructive sleep apnea (using continuous positive airway pressure), COPD, and persistent atrial fibrillation presents for a routine follow-up. He reports nocturnal dyspnea and daytime fatigue with NYHA FC III symptoms. His medications include metoprolol succinate 100 mg daily, warfarin titrated to goal INR 2–3, rosuvastatin 20 mg daily, bumetanide 3 mg twice daily, and K 10 mEq twice daily. A recent transthoracic echocardiogram reveals an LVEF of 60%. Pertinent laboratory values from today include SCr 0.9 mg/dL, eGFR 75 mL/minute/1.73 m^2, and K 4.6 mEq/L. Other pertinent assessments include blood pressure 110/68 mm Hg, heart rate 73 beats/minute, jugular venous pressure 8 cm H_2O, and weight 145 kg (stable). Which one of the following is best to recommend for this patient?

A. Initiate dapagliflozin 10 mg daily with reduction in bumetanide to 1 mg twice daily.
B. Initiate dapagliflozin 10 mg daily and monitor daily weight and blood pressure.
C. Initiate sacubitril/valsartan 24/26 mg twice daily with reduction in bumetanide to 1 mg twice daily
D. Initiate spironolactone 25 mg daily with reduction in bumetanide to 1 mg twice daily

10. A 55-year-old man who presents to the HF clinic with a new diagnosis of HFrEF (LVEF 30%, ischemic etiology) and NYHA FC II symptoms is returning for a 2-week follow-up. His medical history includes T2DM, osteoporosis, CAD, and dyslipidemia. His cardiac medications are enalapril 5 mg twice daily (initiated 2 weeks ago), carvedilol 12.5 mg twice daily, furosemide 60 mg daily, and rosuvastatin 5 mg daily. His vital signs in the clinic are blood pressure 138/77 mm Hg, heart rate 80 beats/minute, and stable weight (81 kg). Pertinent laboratory values include SCr 2.2 mg/dL (increased from 1.9 mg/dL since his last visit), BUN 25 mg/dL, and K 5.2 mEq/L. Which one of the following is best to recommend for this patient?

A. Add spironolactone 12.5 mg daily.
B. Decrease enalapril to 2.5 mg twice daily.
C. Increase carvedilol to 25 mg twice daily.
D. Discontinue enalapril and add hydralazine/isosorbide dinitrate 37.5/20 mg three times daily.

11. A 65-year-old woman presents to the HF clinic with newly diagnosed HFrEF (LVEF 30%, NYHA FC II symptoms). She is euvolemic on examination, has occasional shortness of breath, and has trace lower extremity edema. Her medical history includes nonischemic cardiomyopathy, obstructive sleep apnea, and iron deficiency anemia. Her weight has been stable since diagnosis. Her medications include lisinopril 5 mg daily, amlodipine 10 mg daily, and furosemide 20 mg daily. Her vital signs today include blood pressure 110/77 mm Hg and heart rate 70 beats/minute. Pertinent laboratory values include SCr 1.0 mg/dL, K 4.3 mEq/L, and eGFR 65 mL/minute/1.73 m^2. Which one of the following is best to recommend for this patient?

    A. Discontinue amlodipine; initiate metoprolol succinate 12.5 mg daily and spironolactone 12.5 mg daily.
    B. Discontinue amlodipine; switch lisinopril to sacubitril/valsartan 49/51 mg twice daily.
    C. Discontinue furosemide and amlodipine; initiate spironolactone 12.5 mg daily.
    D. Discontinue amlodipine; initiate spironolactone 25 mg daily. initiate

12. A 74-year-old African American man (weight 82 kg) with a medical history significant for HFrEF, dyslipidemia, CAD (after a 2-vessel coronary artery bypass graft and non–ST-segment elevation MI), CKD, T2D, and microalbuminuria is followed by a renal and cardiology clinic. He reports a 4.5-kg weight loss over the past month. Recent echocardiography reveals LVEF of 37%. His medications include carvedilol 25 mg twice daily, sacubitril/valsartan 24/26 mg twice daily, torsemide 60 mg twice daily, potassium chloride 20 mEq twice daily, spironolactone 12.5 mg daily, and simvastatin 40 mg daily. His vital signs today include blood pressure 110/80 mm Hg and heart rate 74 beats/minute. His laboratory values include eGFR 35 mL/minute/1.73 m^2, K 4.7 mEq/L, BUN 47 mg/dL, SCr 2.2 mg/dL, and A1C 6.7%. Which one of the following medication changes is best to recommend for this patient?

    A. Increase sacubitril/valsartan to 49/51 mg twice daily.
    B. Initiate dapagliflozin 10 mg daily.
    C. Increase spironolactone to 25 mg daily and discontinue potassium.
    D. Add hydralazine 25 mg three times daily/isosorbide dinitrate 20 mg three times daily.

13. A 50-year-old man with newly diagnosed HFrEF (LVEF 31%) presents for a follow-up with a clinical pharmacist for the management of HF. During his last visit, he was initiated on metoprolol succinate 50 mg daily and dapagliflozin 10 mg daily. Today, his vital signs include blood pressure 142/86 mm Hg and heart rate 70 beats/minute. His weight is stable, and he is euvolemic on physical examination. A laboratory assessment shows eGFR 61 mL/minute/1.73 m^2 and K 4.3 mEq/L. Which one of the following is the best next step to optimize the patient's GDMT?

    A. Initiate spironolactone 25 mg daily.
    B. Initiate sacubitril/valsartan 24/26 mg twice daily.
    C. Increase the metoprolol dose to 100 mg daily.
    D. Initiate lisinopril 10 mg daily.

14. A 73-year-old woman (weight 95 kg) with a medical history significant for COPD, HFrEF, hypertension, T2DM (A1C 8.2%), atrial fibrillation, history of chronic UTIs, nonobstructive CAD, morbid obesity, and stage 3 CKD presents for a follow-up after 1 year. The most recent confirmed EF was 40% by multigated acquisition scan. In the past, titration of GDMT has been limited because of elevated K concentrations (5.4 mEq/L), declining renal function (eGFR 25 mL/minute/1.73 m^2), and low blood pressure (105/68 mm Hg). Her vital signs today are blood pressure 110/65 mm Hg, heart rate 76 beats/minute, respiratory rate 24 breaths/minute, and Sao_2 97% on room air. Her medications include metoprolol succinate 50 mg daily, lisinopril 10 mg daily, torsemide 60 mg daily, ibuprofen 200 mg as needed for pain, and warfarin 5 mg daily. Which one of the following is best to recommend to manage this patient's HF?

    A. Repeat basic metabolic panel to consider optimization of GDMT and discontinue ibuprofen.
    B. Repeat basic metabolic panel, consider ivabradine 5 mg twice daily, and discontinue ibuprofen.
    C. Initiate empagliflozin 10 mg daily because she has both T2DM and HF and discontinue ibuprofen.
    D. Change lisinopril to sacubitril/valsartan 49/51 mg twice daily after a 36-hour washout period and discontinue ibuprofen.

15. A 76-year-old woman presents with mild exertional dyspnea and dizziness, which she noticed recently while walking. She becomes short of breath when walking up hills but still walks about ¼ mile per day. She believes her symptoms of dizziness began with initiation of sacubitril/valsartan 24/26 mg twice daily. She enjoys her morning walking routine and wants to know if she can discontinue sacubitril/valsartan. She has had mild pedal edema in the evenings for many years. She has a history of HFrEF (LVEF 30%), hypertension, MI 2 years ago, depression, gastroesophageal reflex disease, and dyslipidemia. Her medications consist of carvedilol 12.5 mg twice daily, sacubitril/valsartan 24/26 mg twice daily, furosemide 20 mg daily, aspirin 81 mg daily, sertraline 50 mg daily, omeprazole 20 mg daily, and simvastatin 20 mg at bedtime. Her vital signs today include blood pressure 110/78 mm

Hg and heart rate 80 beats/minute. Her physical examination reveals trace edema in both extremities; lungs are clear, and weight is stable (73 kg). Laboratory findings show SCr 1.2 mg/dL and K 4.5 mEq/L. Which one of the following is best to recommend for this patient?

A. Change from carvedilol to metoprolol succinate 100 mg daily and monitor blood pressure and symptoms.
B. Discontinue sacubitril/valsartan 24/26 mg twice daily and monitor blood pressure and symptoms.
C. Discontinue furosemide, which will help with her symptoms of dizziness.
D. Make no changes to her medications and monitor blood pressure and symptoms.

Learner Chapter Evaluation: Updates in the Management of Heart Failure

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.
12. The activity met the stated learning objectives.
13. If any objectives were not met, please list them here.

OTHER COMMENTS

14. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
15. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter: