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Pharmacological Therapies in HFrEF: Is Quadruple Therapy a New Standard of Care?

Heart failure is a widely prevalent medical condition with a high burden of morbidity and mortality. It affects more than 6.2 million patients in the United States and approximately 26 million patients globally.[1] (*See Figure 1.*) Approximately 50% of patients with heart failure have heart failure with reduced ejection fraction (HFrEF).[1] HFrEF morbidity and mortality are altered favorably with the use of guideline-directed medical therapy (GDMT). Multiple drug therapies have informed evidence-based therapies for the treatment of HFrEF.

Until recently, triple therapy (beta-blockade, angiotensin-converting enzyme inhibitor [ACEI]/angiotensin receptor-neprilysin inhibition [ARNI], and mineralocorticoid receptor antagonism [MRA]) formed the basis of HFrEF pharmacotherapy.[2] The addition of hydralazine and isosorbide dinitrate combination after optimal doses of triple therapy, particularly in African Americans, also was advocated in the guidelines.[2] The compelling evidence of the mortality and morbidity benefits of the novel sodium-glucose co-transporter-2 (SGLT2) inhibitors beyond benefits derived from triple therapy (with or without diabetes)[3] has led to expert recommendations for the incorporation of these medications in HFrEF treatment algorithms.[4] Even with the optimal use of GDMT, patients with HFrEF have variable periods of clinical stability and persistent residual risk for further deterioration and sudden death.[5] Concomitant use of SGLT2 inhibitors and triple therapy led to significant improvements in HFrEF survival and morbidity.[6] SGLT2 inhibitors, particularly dapagliflozin and empagliflozin, join a class of HFrEF pharmacotherapies with established mortality and morbidity benefits that justify their inclusion in foundational HFrEF therapies. This article discusses the evolution of foundational HFrEF pharmacotherapies, the new role of SGLT2 inhibitors in HFrEF with and without diabetes, and the challenges of navigating these advances in HFrEF pharmacotherapy. This article also will explore other recent novel supplemental therapies with improved morbidity outcomes in HFrEF.

The Basis of Current HFrEF Medical Therapy

Neurohormonal Antagonism as the Basis of HFrEF Therapy

HFrEF progression is explained pathophysiologically by maladaptive responses of the sympathetic system activation and the renin-angiotensin-aldosterone system (RAAS) to an initial cardiac injury. Neurohormonal

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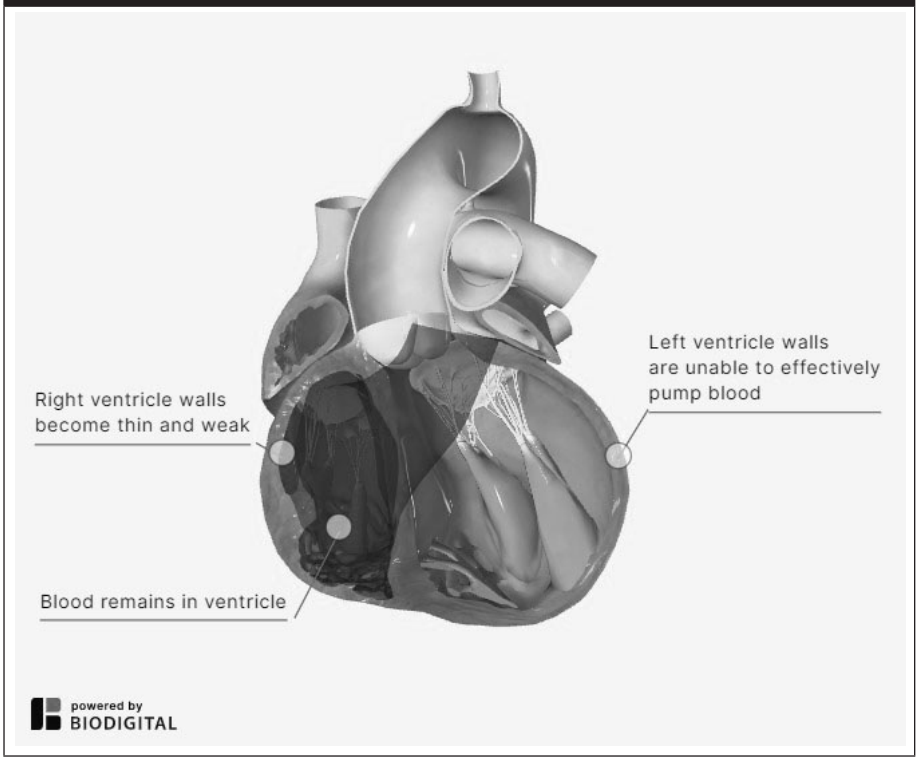
EXECUTIVE SUMMARY

Heart failure affects more than 6.2 million patients in the United States and about 26 million patients globally. Approximately 50% of patients with heart failure have reduced ejection fractions.

- Morbidity and mortality are altered favorably with the use of guideline-directed medical therapy, with multiple drug therapies having informed evidence-based therapies for the treatment.
- Drug classes of common disease-modifying agents from inotropic agents to a wide variety of agents including angiotensin II converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, beta-adrenoceptor blockers, mineralocorticoid receptor antagonists, combination vasodilator therapy, sodium/potassium I_f channel blocker, angiotensin II receptor-neprilysin inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, soluble guanylate cyclase stimulators, and cardiac myosin activators.
- Comprehensive quadruple guideline-directed medical therapy should be initiated immediately upon diagnosis and optimized over two weekly intervals, along with a multidisciplinary team approach.

Figure 1. Congestive Heart Failure



antagonism of these biologic pathways has been established to attenuate HFrEF progression.[7-9] In some cases, inhibition of these neurohormonal pathways can reverse cardiovascular remodeling.[10] Neurohormonal blockade of the sympathetic system and RAAS has been the basis of contemporary GDMT.[2]

Left Ventricular Ejection Fraction as a Basis of HFrEF Therapy

Left ventricular ejection fraction (EF) is a measure of cardiac contractility and function. It has been used widely for categorization of heart failure phenotypes into HFrEF (EF < 40%), heart failure with mid-range ejection fraction (HFmrEF; EF 40% to 49%), and heart failure with preserved ejection fraction (HFpEF; EF ≥ 50%). These heart failure categories have been used extensively as key criteria in many clinical trials involving heart failure patients. Accordingly, heart failure management guidelines employ EF thresholds to articulate therapeutic recommendations.[2,11]

Recent proteomic studies demonstrated significant heterogeneity in biologic traits across the spectrum of EF categories.[12,13] Further, patients within a shared etiology of heart failure (e.g., ischemic cardiomyopathy) also show significant overlap in these biologic traits.[12] These findings may explain the observed variability of therapeutic response in heart failure and raise questions about the validity and utility of EF in guiding heart failure therapy.[13] Despite these findings, it is well established that therapeutic response to medical therapy varies with left ventricular EF; patients with HFrEF benefit the most from currently available pharmacotherapy.[14-16] Left ventricular EF offers a pragmatic and reliable tool for risk stratification, prediction, and determination of therapeutic response in heart failure.[17]

Evolution of HFrEF Pharmacotherapy

Historical Perspective on HFrEF Pharmacotherapy

Medical management of HFrEF has evolved significantly over the last three decades. The last 30 years saw a shift from a focus on drug therapies aimed at increasing contractile mechanics (digoxin and inotropes) to disease-modifying therapies. Mortality and morbidity benefits from pharmacotherapy in HFrEF first were demonstrated with vasodilator therapy. A combination of the vasodilators hydralazine and isosorbide dinitrate was associated with increased survival.[18] This was followed by clinical trials demonstrating the mortality and morbidity

benefit with the use of ACEIs and a confirmation of similar benefit with the use of angiotensin receptor blockers (ARBs) in a later trial of HFrEF.[7,19,20]

Subsequent clinical trials, predominantly on background ACEI as standard therapy, showed incremental mortality and morbidity benefit from the addition of a beta-blocker and MRA.[8,21,22] Triple combination therapy with a beta-blocker, ACEI/ARB, and MRA was the standard GDMT for some time. In addition to this triple regimen, combination vasodilator (hydralazine and isosorbide dinitrate) therapy was strongly recommended based on survival and morbidity benefit in a later trial comprising African American patients with advanced heart failure despite optimal GDMT.[23]

Later, ivabradine, an inhibitor of the potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4 receptor, showed lower incidence of hospitalization in HFrEF when added to maximally tolerated beta-blocker therapy in patients with sinus rhythm and resting heart rate greater than 70 beats per minute (bpm).[24] Recently, sacubitril-valsartan, an ARNI, demonstrated superior outcomes of cardiovascular mortality and hospitalization in HFrEF compared to enalapril (an ACEI).[25]

Another recent addition to the therapeutic armamentarium of HFrEF are the SGLT2 inhibitors. In the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial, the addition of dapagliflozin to GDMT resulted in incremental mortality and morbidity benefits independent of diabetes mellitus status.[3] Similar results also were replicated in the Empagliflozin Outcome Trial in Patients with Chronic HFrEF (EMPEROR-Reduced) using another SGLT2 inhibitor, empagliflozin, among HFrEF patients with or without diabetes on GDMT.[26]

Most recently, vericiguat, a novel oral soluble guanylate cyclase stimulator, was shown to decrease the risk of cardiovascular death and hospitalization when added to GDMT in patients with recent hospitalization for heart failure (EF ≤ 45%) and/or recent use of intravenous diuretics.[27]

Class Effects for HFrEF Pharmacotherapies

The rationale for the multidrug therapeutic framework in HFrEF is to target different biologic pathways to modify the trajectory of HFrEF. The following are the classes of important disease-modifying therapies for patients with HFrEF.

Renin-Angiotensin-Aldosterone Inhibitors (ACEIs)

This class of drugs antagonizes the deleterious cardiovascular effects of the RAAS in HFrEF. Inhibition of angiotensin-converting enzyme leads to decreased serum angiotensin II and aldosterone, afterload reduction, and reversal of cardiac remodeling, which slow the progression of HFrEF.[19] ACEIs improve mortality, heart failure symptoms, hospitalization, and quality of life in patients with HFrEF.[7] These benefits have been observed even with lower dosages of ACEIs,[28] although efforts should be made to replicate target clinical trial dosages for optimal clinical benefits.

ARBs block angiotensin II at its receptors and have comparable mortality and morbidity benefits to ACEIs in HFrEF.[20] Given a lack of superiority to ACEIs, ARBs should be used only if a patient is intolerant of an ACEI.[2]

The CHAMP-HF (Medical Therapy for Heart Failure with Reduced Ejection Fraction) registry of outpatients in the United States revealed low ACEI/ARB use (27%). Predischarge initiation of an ACEI or ARB for hospitalized patients with HFrEF is associated with improved short-term and long-term mortality and hospitalization.[29] Hitherto, ACEIs generally were considered as first-line therapy in de novo HFrEF, but now have been supplanted by ARNI based on recent expert consensus recommendations.[4] It must be noted that, if there are barriers to access (e.g., cost), then ACEIs still are a viable therapeutic choice.

Beta-Blockers

Beta-adrenoceptor blockade in HFrEF allows for modulation of adrenergic hyperactivity, reversal of cardiac remodeling, and improvement of left ventricular function.[10,30] Beta-adrenoreceptor blockade with carvedilol, metoprolol succinate, and bisoprolol has been demonstrated to improve HFrEF symptoms, hospitalization, and mortality.[8,21,31]

However, there is low uptake of beta-blockers in patients with HFrEF in the United States.[32] Despite the potential to worsen cardiac hemodynamics and heart failure symptoms initially, evidence-based beta-blockers can be initiated safely as soon as a patient with HFrEF is hemodynamically stable.[33,34] Predischarge initiation of beta-blockers in HFrEF is well tolerated, improves short-term and long-term survival, and is associated with greater beta-blocker uptake and retention than post-discharge initiation (91% vs. 73%, $P < 0.0001$).[33,34] Heart failure guidelines suggest the initiation of beta-blockers at lower dosages and gradual escalation to target trial dosages to allow for better tolerability and retention.[2]

Mineralocorticoid Receptor Antagonists

Increased serum aldosterone in HFrEF causes both cardiovascular remodeling through its proinflammatory effects and sodium/water retention. MRAs attenuate these pathophysiological effects, leading to improved outcomes in HFrEF. MRAs improve HFrEF hospitalization and mortality when added to background therapy of ACEI/ARB and beta-blockers in patients with mild to severe HFrEF.[22,35] The CHAMP-HF registry revealed disappointingly low MRA prescription (only 33% of eligible patients with HFrEF received a prescription) in eligible outpatients with HFrEF in the United States.[32]

Concern for potential deterioration in renal function and

hyperkalemia when used alongside ACEI/ARB/ARNI may explain the inertia associated with MRA prescription, although clinical trial evidence has revealed lower HFrEF hospitalization in patients receiving a combination of MRA and ACEI or ARB.[36] Novel therapies for management of acute and chronic hyperkalemia likely will improve uptake and tolerability of GDMT, including MRAs, for patients with HFrEF.[4,15] Patients initiated on MRAs must be monitored closely for electrolytes (especially potassium) and renal function, at least two to three days following initiation, seven days after either initiation or titration, monthly thereafter for three months, and then every three months, depending on the clinical status.[2,4]

Table 1. ACC/AHA Staging and NYHA Classification of HF

ACC/AHA Stages of HF		NYHA Classes of HF	
A	At risk for HF, but without structural heart disease or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
B	Structural heart disease, but without signs or symptoms of HF	II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
D	Refractory HF requiring advanced therapies/interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

ACC: American College of Cardiology; AHA: American Heart Association; HF: heart failure

Combination Vasodilator Therapy

Heart failure is associated with decreased bioavailability of nitric oxide, oxidative stress, cardiovascular remodeling, and endothelial dysfunction.[37] Combination vasodilator therapy with hydralazine (antioxidant) and isosorbide dinitrate (nitric oxide donor) is associated with improved heart failure mortality, hospitalization, and quality of life.[18,23] More robust clinical benefits (all-cause mortality, heart failure hospitalization, and health quality scores) were seen with the addition of fixed-dose hydralazine-isosorbide dinitrate to standard heart failure therapy in African American patients with New York Heart Association (NYHA) class III-IV HFrEF.[23] (*See Table 1.*)

The addition of hydralazine-isosorbide dinitrate, either as fixed individual medications or as a fixed combination, therefore, is recommended for African American patients with NYHA class III-IV HFrEF after achieving target doses or maximally tolerated doses of GDMT (beta-blocker, ARNI/ACEI/ARB, and MRA).[2] Patients should be monitored for hypotension, and consideration should be made for up-titration to optimal doses every two weeks until target doses are achieved.[2]

ARNIs

ARNIs allow for simultaneous angiotensin II receptor blockade and neprilysin inhibition (which prevents degradation of natriuretic peptides and other vasoactive substances). The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study demonstrated the superiority of sacubitril-valsartan in decreasing cardiovascular mortality and heart failure hospitalization in patients with HFrEF on background GDMT including an ACEI or ARB.[25] ARNI therapy causes reversal of cardiac remodeling.[38] More recent studies have demonstrated the safety, tolerability, and efficacy of predischarge (≥ 12 to 24 hours before discharge) initiation of sacubitril-valsartan in hemodynamically stable patients with HFrEF decompensation or acute de novo HFrEF.[39-41] In patients receiving an MRA in the PARADIGM-HF trial, sacubitril-valsartan was associated with lower risks of severe hyperkalemia (K > 6.0; 3.1 per 100 patient-years vs. 2.2 per 100 patient-years; hazard ratio [HR], 1.37; $P = 0.02$).[42]

The recent update to the 2017 heart failure guidelines recommends transitioning patients previously on ACEI/ARB to ARNI in the absence of access barriers.[2,4] When considering transitioning from ACEI, a 36-hour washout period is recommended prior to starting the ARNI to avoid hypotension and angioedema. From a dosing perspective, if a patient is taking an equivalent dose of less than 10 mg daily of enalapril or the equivalent of 160 mg or less of valsartan daily, then the recommended dose of sacubitril-valsartan is 24 mg to 26 mg twice daily. On the other hand, for patients on an equivalent dose of enalapril of greater than 10 mg or an equivalent dose of valsartan more than 160 mg daily, then the initiating dose of 49 mg to 51 mg twice a day would be recommended. Dose titration to a target dose of 97 mg/103 mg is recommended based on tolerability of blood pressure and renal function.[2,4]

SGLT2 Inhibitors

Initially designed for glycemic control in patients with type 2 diabetes mellitus, SGLT2 inhibitors emerged as potential therapeutic agents for HFrEF after demonstrating favorable cardiovascular and renal outcomes in type 2 diabetes patients with heart failure.[43] The mechanisms behind the HFrEF benefits of SGLT2 inhibitors are not fully understood. There is evidence

to suggest that SGLT2 inhibitor benefits in HFrEF probably are mediated through direct preload and afterload reduction, cardiometabolic effects including ketogenesis, and anti-inflammatory effects.[44] SGLT2 inhibitor-induced osmotic diuresis and natriuresis improves both circulatory and interstitial fluid overload, which likely explains their benefit in heart failure hopitalizations.[45] Given the prognostic value of renal function in HFrEF,[46] favorable renal hemodynamics[44] and improved cardiorenal interactions from SGLT2 inhibitors are likely to contribute to beneficial HFrEF outcomes.

The DAPA-HF trial showed that the addition of dapagliflozin to background GDMT in NYHA class II-IV HFrEF patients with and without diabetes was associated with a lower risk for the composite outcome of worsening HFrEF or cardiovascular death (16.3% dapagliflozin group vs. 21.2% placebo group; HR, 0.74; 95% confidence interval [CI], 0.65-0.85; $P < 0.001$).[3] In terms of individual clinical endpoints, dapagliflozin was associated with reductions in the risks of a first episode of worsening heart failure (10% dapagliflozin vs. 13.7% placebo; HR, 0.70; 95% CI, 0.59-0.83), cardiovascular death (9.6% dapagliflozin vs. 11.5% placebo; HR, 0.82; 95% CI, 0.69-0.98), and all-cause death (11.6% dapagliflozin vs. 13.9% placebo; HR, 0.83; 95% CI, 0.71-0.97).[3] The Dapagliflozin Effects on Biomarkers, Symptoms and Functional Capacity in Patients with Heart Failure with Reduced Ejection Fraction (DEFINE-HF) trial extended the potential role of SGLT2 inhibitors in HFrEF by showing improvements in healthcare quality scores in HFrEF patients with or without diabetes.[47] The favorable effects of dapagliflozin on quality of care scores in HFrEF were not accompanied by improvements in N-terminal pro B-type natriuretic peptide measures.[47] Further, the EMPEROR-Reduced trial demonstrated improvement in the composite outcome of cardiovascular death or heart failure hospitalization with the addition of empagliflozin to GDMT in HFrEF patients with and without diabetes (19.4% empagliflozin vs. 24.7% placebo; HR, 0.75; 95% CI, 0.65-0.86; $P < 0.001$).[26] Additionally, heart failure hospitalization and the annual rate of decline in glomerular filtration rate (GFR) were lower in the empagliflozin group compared to placebo (HR, 0.70; 95% CI, 0.58-0.85; $P < 0.001$; and -0.55 mL/1.73m^2 of body surface per year vs. -2.28 mL/1.73m^2 of body surface per year; $P < 0.001$, respectively).[26] The performance of SGLT2 inhibitors in HFrEF patients with glomerular filtration rates less than 20 mL/min/1.73m^2 has not yet been assessed. Meta-analysis of SGLT2 inhibitor clinical trials supports the consistency of these favorable cardiorenal outcomes, including heart failure hospitalization, cardiovascular death, and renoprotection.[48,49] Quadruple therapy (a combination of ARNI, beta-blockers, MRA, and SGLT2 inhibitor) is associated with greater reductions in cardiovascular death and/or heart failure hospitalization in HFrEF when compared to conventional therapy (combination ACEI or ARB and beta-blocker).[6] These favorable HFrEF outcomes call for SGLT2 inhibitor inclusion in foundational disease-modifying agents for HFrEF. Accordingly, the American College of Cardiology Expert Consensus and the Heart Failure Collaboratory panels recommend SGLT2 inhibitors in patients with HFrEF.[4,16]

Other Novel Therapies in HFrEF

Some recent clinical trials have demonstrated benefit in heart failure morbidity (heart failure hospitalization and quality of life, rather than survival benefit).

Sodium/Potassium I_f Channel Blockers

Beta-blocker trials have revealed the prognostic value of resting heart rates in HFrEF. Higher resting heart rates (≥ 60 bpm) are associated with increased mortality in HFrEF.[50,51] Ivabradine slows sinoatrial nodal conduction through specific inhibition of the I_f current.[24] In the Systolic HF Treatment with the I_f Inhibitor Ivabradine (SHIFT) trial, the addition of ivabradine to GDMT in patients with symptomatic stable heart failure and EF ≤ 35% resulted in fewer heart failure hospitalizations or cardiovascular death than placebo (24% vs. 29% placebo; HR, 0.82; 95% CI, 0.75-0.90; $P < 0.0001$).[24] This was driven primarily by decreases in heart failure hospitalizations (21% vs. 16% placebo; HR, 0.74; 95% CI, 0.66-0.83).[24] The use of ivabradine was associated with a higher incidence of symptomatic bradycardia (5% vs. 1% placebo; $P < 0.0001$) and transient visual blurring (3% vs. 1% placebo; $P < 0.0001$).[24] Adjunctive use of ivabradine is recommended for patients with HFrEF (EF ≤ 35%) in sinus rhythm who have resting heart rates greater than 70 bpm while on GDMT, including the maximal tolerated doses of a beta-blocker.[2] Heart rate should be reassessed after two to four weeks of initiation of or titration of therapy. The starting dose in patients younger than age 75 years is 5 mg twice daily with food. If the heart rate still is more than 60 bpm in two to four weeks, then the dose could be increased by 2.5 mg twice daily to a maximum dose of 7.5 mg twice daily. The heart rate should be monitored after each increase in dose. Dose reduction is necessitated if the heart rate goes below 50 bpm. Discontinuation of the medication is recommended if the heart rate is less than 50 bpm at the 2.5 mg twice daily with food dose. For patients older than age 75 years, the starting dose is 2.5 mg twice daily with food.

Soluble Guanylate Cyclase Stimulators

Soluble guanylate cyclase (sGC) stimulators modulate the nitric oxide-soluble guanylate cyclase pathway through production of the second messenger cyclic guanosine monophosphate and were

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Table 2. Common Disease-Modifying Therapeutic Agents in HFrEF

Drug Class	Dosage	Potential Drug Class Adverse Effects
Angiotensin II Converting-Enzyme Inhibitors (ACEIs)		
Captopril	6.25 mg to 50 mg tid	Hypotension, renal dysfunction, hyperkalemia, ACEI-induced dry cough, angioedema
Enalapril	2.5 mg to 20 mg bid	
Fosinopril	5 mg to 40 mg qd	
Lisinopril	2.5 mg to 40 mg qd	
Perindopril	2 mg to 16 mg qd	
Quinapril	5 mg to 20 mg bid	
Ramipril	1.25 mg to 10 mg qd	
Trandolapril	1 mg to 4 mg qd	
Angiotensin II Receptor Blockers		
Candesartan	4 mg to 32 mg qd	Hypotension, renal dysfunction, hyperkalemia, cough
Losartan	25 mg to 150 mg qd	
Valsartan	20 mg to 160 mg bid	
Evidence-Based Beta-Adrenoceptor Blockers		
Bisoprolol	1.25 mg to 10 mg qd	Sinus bradycardia, atrioventricular blockade, hypotension, worsening heart failure
Carvedilol/Carvedilol CR	3.125 mg to 50 mg bid/10 mg to 80 mg qd	
Metoprolol succinate	12.5 mg to 200 mg qd	
Mineralocorticoid Receptor Antagonists[a]		
Spironolactone[22]	12.5 mg to 50 mg qd	Renal dysfunction, hyperkalemia, gynecomastia (spironolactone)
Eplerenone[35]	25 mg to 50 mg qd	
Combination Vasodilator Therapy		
Hydralazine/isosorbide dinitrate[23]	37.7 mg/20 mg to 75 mg/40 mg tid	Hypotension, dizziness, headaches, tachycardia, drug-induced lupus
Sodium/Potassium I_f Channel Blocker		
Ivabradine[24]	5 mg to 7.5 mg bid	Symptomatic bradycardia, QT prolongation, transient visual blurring
Angiotensin II Receptor-Neprilysin Inhibitors[b]		
Sacubitril/valsartan[25]	24 mg/26 mg to 97 mg/103 mg bid	Hypotension, angioedema, hyperkalemia, renal dysfunction
Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors[c]		
Dapagliflozin[3]	10 mg qd*	Volume depletion, euglycemic diabetic ketoacidosis, limb amputations, mycotic urinary tract infections, Fournier's gangrene
Empagliflozin[26]	10 mg qd*	
Soluble Guanylate Cyclase Stimulators[n]		
Vericiguat[27]	2.5 mg starting dose; 2.5 mg to 10 mg qd*	Symptomatic hypotension, syncope, anemia, renal dysfunction
Cardiac Myosin Activators[n]		
Omecamtiv mecarbil[57**]	25 mg to 50 mg bid	Elevated troponin, potential for myocardial ischemia at higher doses

HFrEF: heart failure with reduced ejection fraction; qd: once daily; bid: twice daily; tid: three times daily
[a] contraindicated in patients with creatinine > 2.5 mg/dL and/or eGFR < 30 mL/min/1.73m^2; [b] high risk of angioedema with concomitant ACEI use — a washout period of 36 hours must be observed, and smaller starting doses of ARNI used when initiating therapy in patients on low-dose ACEI therapy; [c] caution must be exercised with initiation of dapagliflozin and empagliflozin in HFrEF and eGFR ≤ 30mL/min/1.73m^2 and ≤ 20 mL/min/1.73m^2, respectively; [n] novel therapy; * target doses in drug trial; ** product does not have an expected release to market date

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first approved for use in pulmonary arterial hypertension.[52] Activation of sGC by its endogenous ligand nitric oxide results in the generation of cyclic guanosine monophosphate (cGMP), which modulates cardiovascular function through the downstream effects of vasodilation, inhibition of smooth muscle proliferation, platelet aggregation, leukocyte recruitment, and reversal of vascular remodeling.[53] In HFrEF, endothelial dysfunction and oxidative stress cause decreased bioavailability of nitric oxide and relative deficiency of sGC, leading to decreased cGMP production.[54] Vericiguat stimulates sGC through a nitric oxide independent binding site and sensitizes it to endogenous nitric oxide, leading to increased cGMP production.[55] The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) assessed the effects of adding vericiguat, a novel sGC stimulator, to GDMT in patients with NYHA class II-IV heart failure and EF < 45% after recent hospitalization or use of intravenous diuretics.[27] The incidence of the composite outcome of cardiovascular death or first hospitalization for heart failure was lower in the vericiguat group compared to placebo (35.5% vs. 38.5% placebo; HR, 0.90; 95% CI, 0.82-0.98; $P = 0.02$).[27] Adverse events, including symptomatic hypotension (9.1% vs. 7.9%, $P = 0.12$) and syncope (4.0% vs. 3.5%, $P = 0.13$), were more common than placebo in the vericiguat group. Vericiguat was approved recently by the Food and Drug Administration (FDA) for the treatment of patients with heart failure and EF < 45% to reduce the risk of cardiovascular death and heart failure hospitalization after recent hospitalization or the need for outpatient intravenous diuretics.

Cardiac Myosin Activators

Selective cardiac myosin activators improve myocardial contractility and function by enhancing myosin-actin cross-bridges within cardiomyocytes.[56] Unlike previously studied inotropes, this class of pharmaceutical products was demonstrated to increase the duration of cardiac systole and ejection fraction.[56] The addition of omecamtiv mecarbil, a selective cardiac myosin activator, to GDMT in patients with symptomatic heart failure and EF < 35% was associated with a lower incidence of a composite outcome of a heart failure event (hospitalization or urgent visit for heart failure) or death from cardiovascular causes compared to placebo (37.0% vs. 39.1% placebo; HR, 0.92; 95% CI, 0.86-0.99; $P = 0.03$). There was no difference in heart failure symptoms, and there was a nonsignificant trend toward increased mortality in the omecamtiv mecarbil group compared to placebo (19.6 vs. 19.4 placebo; HR, 1.01; 95% CI, 0.92-1.11).[57] Omecamtiv mecarbil has not yet been approved for use in HFrEF.

Drug Selection in HFrEF

New advances in HFrEF pharmacotherapy inspire hope, but also make management of HFrEF more complex. A lack of both direct incremental and head-to-head clinical trials to compare the performance of currently available HFrEF disease-modifying agents against each other complicates the medical management of HFrEF. Increasingly, clinicians must contend with the question of what therapeutic agent to prioritize and what sequence to follow to achieve optimal GDMT. Expert consensus pathways suggest a multipronged approach. Individual patient factors, including clinical context, comorbidities, race, sex, age, frailty, and socioeconomic factors, including insurance and access, can help inform drug selection. Consideration also must be given to the unique adverse effects profile of each therapeutic agent to allow for tailored therapy where GDMT-limiting adverse effects may arise. (*See Table 2.*) Although it is challenging, and not pragmatic enough to apply universally, therapeutic agents must be used in tandem with the clinical trial inclusion and exclusion criteria.

Comprehensive (quadruple) GDMT must be initiated immediately when a patient is diagnosed with HFrEF and optimized over two weekly intervals to clinical trial dosages or maximal tolerated dosages.[4] Predischarge initiation of GDMT promotes the uptake and retention of GDMT, although one must consider the clinical context, including the existence of congestive symptoms, hypotension, and renal dysfunction. Small drug dosages at initiation of therapy and gradual up-titration to target clinical trial or maximally tolerated dosages may be more practical and tolerable in patients, such as the elderly, in whom hypotension, renal dysfunction, and frailty commonly accompany HFrEF. A multidisciplinary team approach to the management of HFrEF and a timely referral of HFrEF patients to advanced heart failure cardiologists can help mitigate the challenge of managing a rapidly changing landscape of HFrEF pharmacotherapy and potentially help clinical outcomes.[4]

Summary

There is a rapid evolution in the landscape of disease-modifying pharmacotherapies in HFrEF. However, adoption and uptake of these evidence-based therapies has been and remains low.

There is a need for clinicians to evolve with these rapidly changing times and champion the implementation of new scientific evidence to improve clinical outcomes in patients with HFrEF.

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CME Questions

1. A 56-year-old African American male presents to your office two weeks after he is discharged from the hospital for newly diagnosed heart failure with reduced ejection fraction. Transthoracic echocardiogram showed findings consistent with dilated cardiomyopathy with left ventricular ejection fraction of 37% and mild mitral regurgitation. Currently, he is taking aspirin 81 mg daily, metoprolol succinate 25 mg daily, sacubitril/valsartan 24 mg/26 mg twice daily, and furosemide 20 mg daily. He has mild dyspnea with exertion, but has no cough, orthopnea, lower extremity swelling, or paroxysmal nocturnal dyspnea. He has a blood pressure of 120/78 mmHg, a heart rate of 92 bpm, and a respiratory rate of 14 breaths/min. The rest of the patient's physical examination is unremarkable. What is your next best step in managing the patient's heart failure?
   a. Increase metoprolol succinate to 50 mg daily.
   b. Add ivabradine 2.5 mg twice daily and reassess the patient in two weeks.
   c. Add spironolactone 25 mg daily.
   d. Add hydralazine-isosorbide dinitrate 37.5 mg/20 mg three times daily.
2. A 55-year-old African American male with a past medical history of atrial fibrillation, chronic kidney disease (stage 3b), and hypertension comes to your office following hospitalization for decompensated heart failure. He reports dyspnea with walking, but has no orthopnea or paroxysmal nocturnal dyspnea. He is frustrated by the recurrent hospitalizations for heart failure despite adherence to medical therapy. He was diagnosed with nonischemic cardiomyopathy three years ago; his most recent echocardiogram showed mild to moderate left ventricular hypertrophy and dilation (ejection fraction 20% to 25%). His current medications include metoprolol succinate 100 mg daily, enalapril 20 mg daily, spironolactone 25 mg daily, and furosemide 40 mg twice daily. His renal function has been stable with a blood urea nitrogen of 30 mg/dL and creatinine of 2.3 mg/dL. His physical examination is unremarkable, and his blood pressure and heart rate are 110/84 mmHg and 70 bpm, respectively. What is the best next step in the management of this patient's heart failure?
   a. Refer the patient to an advanced heart failure specialist to optimize his current heart failure management.
   b. Add ivabradine 2.5 mg twice daily and reassess the patient in two weeks.
   c. Increase metoprolol succinate to 200 mg daily for tighter heart rate control.
   d. Adjust enalapril to 20 mg twice daily.
3. A 55-year-old Caucasian female with a past medical history of heart failure as a result of ischemic cardiomyopathy status post biventricular pacemaker placement six months ago, type 2 diabetes mellitus, and chronic kidney disease (stage 2) presents to your office for review after a recent hospitalization for worsening heart failure. Her recent echocardiogram showed a left ventricular ejection fraction of 38%. Her current medications include aspirin 81 mg daily, metformin 1,000 mg twice daily, carvedilol 25 mg twice daily, sacubitril/valsartan 97 mg/103 mg twice daily, spironolactone 25 mg daily, and furosemide 40 mg twice daily. Her renal function is stable with blood urea nitrogen of 26 mg/dL and creatinine of 1.4 mg/dL; her electrolytes are normal. She feels better and reports no complaints other than dyspnea with moderate physical activity. Her blood pressure and heart rate are 120/70 mmHg and 55 bpm, respectively. Further physical examination is unremarkable except for bibasilar crackles and moderate lower extremity edema. What is the best next step in managing this patient's heart failure?
   a. Adjust the patient's carvedilol dosage.
   b. Increase the patient's spironolactone to 50 mg daily.
   c. Consider the addition of a sodium-glucose co-transporter-2 inhibitor.
   d. Consider vasodilator therapy with hydralazine and isosorbide dinitrate.
4. A 49-year-old African American male presents to establish care after relocation from the Midwest. He has an established diagnosis of nonischemic cardiomyopathy and heart failure, and an echocardiogram done within the last three months showed left ventricular dilation and an ejection fraction of 35%. He has had three admissions for heart failure exacerbation in the past one

year but, unfortunately, he failed to tolerate lisinopril because of life-threatening angioedema. His current medications include carvedilol 25 mg twice daily, spironolactone 25 mg daily, and furosemide 40 mg daily. He has longstanding stable dyspnea on exertion but has no cough, orthopnea, and paroxysmal nocturnal dyspnea. On physical examination, the patient has a blood pressure of 107/90 mmHg, a heart rate of 58 bpm, and mild basilar crackles. What is the next best step in managing this patient's heart failure?

a. Check his renal function and electrolytes for possible initiation of sacubitril/valsartan.
b. Consult cardiology.
c. Check his renal function and electrolytes for initiation of a sodium-glucose co-transporter-2 inhibitor.
d. Increase his furosemide dosage for optimal blood pressure and volume control.

5. A 62-year-old Caucasian female with a past medical history of coronary artery disease and chronic heart failure with reduced ejection fraction presents for a follow-up review after a recent hospitalization for decompensated heart failure. She has had multiple hospitalizations for heart failure despite adherence to carvedilol 12.5 mg twice daily, losartan 100 mg daily, spironolactone 25 mg daily, and furosemide 40 mg daily. Currently, she feels better despite persistent dyspnea with walking. Her last echocardiogram showed an ejection fraction of 35%. She has no renal dysfunction. She has mild jugular venous distension and bibasilar crackles. Her blood pressure and heart rate are 128/78 mmHg and 60 bpm, respectively. What is the next best step in managing the patient's heart failure?
   a. Offer the patient vericiguat.
   b. Increase furosemide dosage for better volume control.
   c. Offer the patient vasodilator therapy with hydralazine and isosorbide dinitrate.
   d. Consider a switch in therapy from losartan to sacubitril/valsartan.
6. Which of the following provides a list of heart failure medications with a proven mortality benefit in heart failure with reduced ejection fraction?
   a. Bisoprolol, vericiguat, omecamtiv mecarbil, and furosemide
   b. Bisoprolol, sacubitril/valsartan, hydralazine/isosorbide dinitrate, and dapagliflozin
   c. Carvedilol, losartan, ivabradine, and spironolactone
   d. Metoprolol succinate, lisinopril, vericiguat, and digoxin
7. A 72-year-old male has just been discharged after a recent hospitalization for heart failure exacerbation. He feels much better and has no symptoms other than mild shortness of breath on exertion. He failed to tolerate sacubitril/valsartan 24 mg/26 mg twice daily because of worsening renal function and hypotension. He has no orthostasis, and his blood pressure and heart rate are 96/64 mmHg and 60 bpm, respectively. The patient currently is taking metoprolol succinate 25 mg daily and furosemide 20 mg daily. His renal function is stable with a normal blood urea nitrogen and creatinine. What is the next best step?
   a. Attempt sacubitril/valsartan again and reassess in two weeks.
   b. Attempt low-dose lisinopril and up-titrate in two weeks, if tolerated.
   c. Attempt vericiguat and assess for tolerance in two weeks.
   d. Attempt a sodium-glucose co-transporter-2 and assess for tolerance in two weeks.

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