Heart Failure Pharmacotherapy

Dusty L. Lisi, MS, PharmD[a,*], Kira Gaddis, PharmD[b], Mahmoud H. Abdou, MD[c]

KEYWORDS

• Heart failure • Ejection fraction • GDMT • Heart failure with reduced ejection fraction • Heart failure with preserved ejection fraction

KEY POINTS

- Professional guidelines direct medication therapy for which includes both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).
- Angiotensin receptor neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonist (MRA), and sodium glucose cotransporter 2 inhibitor (SGLT2i) decrease hospitalizations and mortality for HFrEF patients.
- Medical therapy that provides mortality and morbidity benefits for HFpEF includes SGLT2i, MRA, and ARNI.
- Loop diuretics are the primary therapy used for congestion management in both HFrEF and HFpEF.
- Additional pharmacotherapy that can provide benefit for select patients with HF includes hydralazine/isosorbide dinitrate, digoxin, ivabradine, vericiguat, thiazide diuretics, glucagon-like peptide-1 (GLP-1) agonists, and inotropes.

BACKGROUND

Heart failure (HF) affects more than 6.2 million people in the United States. It is among the leading diagnosis of hospital admissions, accounting for more than 800,000 annual hospitalizations. It carries significant mortality of more than 50% in 5 years.[1] Medical therapy is the backbone of management for patients with HF. Strong evidence has proven benefits on reduction of mortality and in slowing the progression of the disease, reducing the hefty health care cost burden, and improving the quality of life for patients diagnosed with HF by improving symptoms and reducing hospitalizations.[1,2] Furthermore, despite substantial evidence that guideline directed medical therapy (GDMT) provides reduction in the risk of morbidity and mortality, many patients may not be initiated on these appropriate therapies.[3–7]

[a] Department of Pharmacology, Emory St. Joseph's Hospital, Atlanta, GA, USA; [b] Department of Pharmacology, University of Mississippi School of Pharmacy, Jackson, MS, USA; [c] Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA
* Corresponding author.
E-mail address: dusty.lisi@emoryhealthcare.org

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Abbreviations	
ACC	American College of Cardiology
ACEi	angiotensin converting enzyme inhibitor
AHA	American Heart Association
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
Bpm	beats per minute
GDMT	Guideline Directed Medical Therapy
GLP-1 Agonist	glucagon-like peptide-1 gonist
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
I_f	funny channel current
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PDE5 Inhibitor	phosphodiesterase type 5 inhibitor
RAAS	Renin-angiotentin-aldosteron system
SA	sinoatrial
sGC	soluble guanylyl cyclase
SGLT2i	sodium glucose cotransporter 2 inhibitor

INTRODUCTION

Pharmacotherapy for patients who have HF with reduced ejection fraction (HFrEF) is the foundation of management and should be implemented prior to consideration of device therapy. The basis of pharmacotherapy for HFrEF includes 4 pillars: beta-blockers, renin angiotensin aldosterone system modulators (angiotensin converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB], or angiotensin receptor neprilysin inhibitor [ARNI]), mineralocorticoid receptor antagonists (MRA), and sodium glucose cotransporter 2 inhibitors (SGLT2i). These drug classes collectively reduce mortality, reduce or prevent hospitalizations, and facilitate improvement in functional and clinical status. Additional pharmacotherapy has demonstrated a reduction in HF symptoms. These medications/medication classes include diuretics (loop and thiazide), digoxin, ivabradine, and the oral soluble guanylate cyclase stimulator, vericiguat.[1–7]

Contemporary data from recent randomized clinical trials have established a new foundation of successful management of patients with heart failure with preserved ejection fraction (HFpEF). The proven benefits of SGLT2i, MRA, and ARNI have provided evidence to the basis of guideline-directed medication therapy for these patients.[4,5,7]

In this article, we will discuss these different classes of medications and highlight the salient side effects of these agents. **Table 1** provides further information about initial and target dosing, as well as parameters that necessitate dose adjustment or medication discontinuation for heart failure pharmacotherapy.

PHARMACOTHERAPY FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

Renin Angiotensin Aldosterone System Modulators

Angiotensin receptor neprilysin inhibitor

ARNI is a combination of ARB (valsartan) with neprilysin inhibitor (sacubitril).[4-5,7]ARBs are vasodilatory agents that inhibit effects of angiotensin II by directly blocking the angiotensin II receptor.[4–7] Sacubitril is a prodrug that inhibits neprilysin. Neprilysin inhibition increases levels of peptides, including natriuretic peptides, thus enhancing natriuresis and further vasodilation. It also plays a key role in preventing remodeling.[8]

Table 1
Dosing recommendations for heart failure pharmacotherapy

Medication	Initial Dose	Target Dose	Max Dose	Dose Adjust or Discontinue
Angiotensin-Converting Enzyme (ACE) Inhibitors[3–7,12–14]				Hyperkalemia—consider alternative SCr increase by ≥30%: reduce or hold dose New cough—discontinue Angioedema
Captopril	6.25 mg TID	50 mg TID	50 mg TID	CrCl 10 to <50 mL/min, administer BID or daily CrCl <10 mL/min, administer daily. Hemodialysis: give after dialysis on dialysis days.
Enalapril	2.5 mg BID	10–20 mg BID	20 mg BID	CrCl 10–30 mL/min, give 2.5 mg daily in 1 or 2 doses. Max dose 20 mg/day. CrCl <10 mL/min, consider alternate therapy or 1.25 mg daily. Max dose 10 mg once daily. Hemodialysis: Initial dose 2.5 mg three times weekly administered post dialysis on dialysis days. Max dose 10 mg daily.
Lisinopril	2.5–5 mg daily	20–40 mg daily	40 mg daily	CrCl 10–30 mL/min, give 2.5 mg daily as initial dose. CrCl <10 mL/min, consider alternate therapy or 2.5 mg daily. Hemodialysis: 2.5 mg daily. Give after dialysis on dialysis days.
Angiotensin Receptor Blockers (ARBs)[15–17]				Hyperkalemia – consider alternative SCr increase by ≥30%: reduce or hold dose Angioedema
Candesartan	4–8 mg daily	32 mg daily	32 mg daily	CrCl ≤30 mL/min, give 4 mg daily as initial dose. Max dose 16 mg daily. Hemodialysis: give 4 mg daily as initial dose. Max dose of 16 mg daily.
Losartan	25–50 mg daily	150 mg daily	150 mg daily	Hemodialysis: poorly dialyzed. No dose adjustment or supplemental dose needed.

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Table 1
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Medication	Initial Dose	Target Dose	Max Dose	Dose Adjust or Discontinue
Valsartan	20–40 mg BID	160 mg BID	320 mg daily	Use with caution CrCl <30 mL/min. Hemodialysis: poorly dialyzed. No dose adjustment or supplemental dose needed.
Angiotensin receptor neprilysin inhibitor (ARNI)[8–11]				History of angioedema Hyperkalemia—consider alternative
Sacubitril/Valsartan	24/26 mg BID 49/51 mg BID	97/103 mg BID	97/103 mg BID	eGFR <30: start at initial dose and titrate upward cautiously. Safety and efficacy data are limited, especially for eGFR <20. Severe liver impairment (Child-Pugh class C), use not recommended
Beta-blockers[3–7]				Do not abruptly stop due to risk of causing or worsening coronary insufficiency. Use caution when starting in NYHA class IV symptoms or recent exacerbation. Bradycardia Hypotension
Metoprolol succinate[18,22]	12.5–25 mg daily	200 mg daily	200 mg daily	When converting from metoprolol tartrate to succinate, use the same total daily dose. Note patients may have different clinical response, so they should be closely monitored.
Carvedilol[20,23]	3.125 mg BID	25 mg BID	≤85 kg: 25 mg BID >85 kg: 50 mg BID	
Bisoprolol[19,21]	1.25 mg daily	10 mg daily	10 mg daily	Renal replacement therapy: start with low initial dose and reduced maximum dose. Hemodialysis: give dose after hemodialysis on dialysis days
Mineralocorticoid receptor antagonists (MRAs)[3–7]				Hyperkalemia or worsening renal function: change to every other day dosing or discontinue. Potassium 5.5 or greater: discontinue

Spironolactone[24,26]	eGFR ≥50 12.5–25 mg daily eGFR 30–49 12.5 mg daily or every other day	50 mg daily 25 mg daily	HF: 50 mg daily Other: up to 400 mg daily 25 mg daily	Gynecomastia—discontinue and change to eplerenone. Hemodialysis: not routinely recommended. Limited trial data with initial dosing of 12.5 mg daily up to maximum of 25 mg daily.
Eplerenone[25,27,28]	eGFR ≥50 25 mg daily eGFR 30–49 25 mg every other day	50 mg daily 25 mg daily	HF: 50 mg daily Other: up to 300 mg daily	eGFR ≤ 30: use is contraindicated. Hemodialysis: poorly dialyzable. Use is not routinely recommended. Intial dose: 25 mg every other day to a max of 25 mg daily.
Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors				Do not use in patients with hyperglycemia or type 1 diabetes. Acute decrease in eGFR >10% associated with slower long-term eGFR decline. Thus, it is not associated with CKD progression. Hold if patient develops urinary tract infection, yeast infection, or skin infection. Once infection resolves, may try to reinitiate. If there are recurrent infections or if patient develops Fournier's gangrene, SGLT2i should be discontinued. Increase blood glucose monitoring and consider insulin dose reduction when initiating in patient who also has diabetes requiring insulin.
Dapagliflozin[31,33]	10 mg daily	10 mg daily	10 mg daily	eGFR <25: do not initiate, but may continue in patients already receiving. Hemodialysis: avoid use
Empagliflozin[30,32,34]	10 mg daily	10 mg daily	HF: 10 mg daily Diabetes: 25 mg daily	eGFR <30: not recommended for diabetes HF benefits shown if eGFR ≥20. Hemodialysis: avoid use
Vasodilators[40,41]				
Hydralazine/isosorbide dinitrate	37.5/20 mg TID	75/40 mg TID	225/120 mg daily	
Hydralazine	25 mg TID	75 or 100 mg TID	300 mg daily	eGFR <10: may reduce to every 12 h
Isosorbide dinitrate	20 mg TID	40 mg TID	120 mg daily	

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Table 1
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Medication	Initial Dose	Target Dose	Max Dose	Dose Adjust or Discontinue
Cardiac Glycoside				
Digoxin[42–44]	0.125–0.25 mg daily	Individualized dosing	0.25 mg daily	Target serum concentration: 0.5 to <0.9 ng/mL Renal dysfunction, low lean body mass, age >70 y: lower initial dose, for example, 0.125 mg daily or every other day. Dosing nomogram available for various CrCl and body weights. Renal replacement therapy: avoid use if possible or initial dose of 0.0625 mg every other day or three times per week.
I(f) Channel Inhibitor				
Ivabradine[45,46]	2.5 mg BID	7.5 mg BID	7.5 mg BID	HR <50 bpm or bradycardia symptoms, reduce dose by 2.5 mg BID or discontinue if at lowest dose
Soluble Guanylate Cyclase (sGC) Stimulator				
Vericiguat[47,48]	2.5 mg daily	10 mg daily	10 mg daily	SBP <90 mm Hg: reduce dose or discontinue if current dose is 2.5 mg
Diuretics[2–7]				
Loop				Oral dose equivalence: Furosemide 40 mg = torsemide 10–20 mg = bumetanide 1 mg. eGFR $\leq$30: higher doses may be needed. Anuric: not recommended
Furosemide[35,36]	20–40 mg daily or BID		600 mg daily Single dose: 80–200 mg	Continuous IV infusion: initial rate 5 mg/hr up to max of 40 mg/hr. Subcutaneous: preprogrammed on-body infusor delivers 80 mg over 5 hours

Torsemide[36]	10–20 mg daily		200 mg daily given as 100 mg BID Single dose: 50–100 mg	Higher than usual doses may be required with nephrotic syndrome.
Bumetanide[36]	0.5–1 mg daily	10 mg daily	10 mg daily	Continuous IV infusion: initial rate 0.5 mg/hr up to max of 2 mg/hr.
Thiazide				Optimize loop diuretic therapy before adding. Continue until euvolemia restored. Some patients may need to continue intermittently. Assess volume status daily or at least every 2–3 days.
Hydrochlorothiazide[36]	25 mg daily or BID		200 mg daily	Dose may be increased based upon response and tolerability. CrCl <10 mL/min: not recommended due to lack of efficacy. Renal replacement therapy: avoid use
Chlorothiazide[36]	250–500 mg daily or BID		2000 mg daily	May administer every other day or on specified days of the w. CrCl <30 mL/min: ineffective unless combined with loop. CrCl <10 mL/min: avoid use Renal replacement therapy: avoid use
Metolazone[36]	2.5–5 mg daily		20 mg daily or 10 mg BID	Hemodialysis: 3 times per week Peritoneal dialysis: not recommended due to lack of efficacy. Other renal replacement therapy: not recommended

Abbreviations: BID, twice daily; bpm, beats per minute; CrCl, creatinine clearance rate (mL/min); eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); HR, heart rate; I(f), Channel Inhibitor: funny channel inhibitor; SBP, systolic blood pressure; TID, three times daily.

Results of the PARADIGM HF (Prospective Comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial provided initial validation of superiority of ARNI in reducing cardiovascular and all-cause mortality or worsening HF in comparison to ACEi.[9] In the PIONEER HF (Comparison of sacubitril/valsartan versus enalapril on Effect on nt-pro-BNP in Patients Stabilized from an Acute Heart Failure Episode) study, use of sacubitril-valsartan when initiated for acute decompensated HF demonstrated a significant reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and reduced rates of rehospitalization.[10] Moreover, results of the TRANSITION (A Multicenter, Randomized, Open Label, Parallel Group Study Comparing Pre-discharge and post-dischange treatment initiation with LCZ696 in Heart Failure Patients with Reduced Ejection Fraction Hospitalized for an Acute Decompensation Event) study helped to prove that initiation of sacubitril-valsartan during hospitalization or following hospital discharge in patients with worsening HF and a history of HFrEF is safe and does not significantly increase the occurrence of side effects.[11]

Sacubitril-valsartan should be initiated in patients with NYHA class II-III to reduce HF symptoms and death both in ambulatory HFrEF patients, as well as prior to discharge in patients hospitalized with acute HF. Further, patients with HFrEF who are tolerant of ACEi or ARB should be considered for transition to ARNI, due to the enhanced benefits in significant reduction in mortality compared to ACEi or ARB.[2–7] Based upon the degree of benefit associated with ARNI in HF patients, it is no longer required to first initiate ACEi or ARB prior to ARNI initiation.[4,5] Although ARNI is a first-line recommendation, it may not be financially feasible for all patients. Therefore, ACEi or ARB can be considered as alternate therapies.[3–7]

ARNI is contraindicated when patients have a history of angioedema, regardless of etiology, during pregnancy or lactation, severe hepatic impairment (Child-Pugh C), with aliskiren in patients who also have diabetes, or history of hypersensitivity with ACEi or ARB. Adverse effects in patients receiving sacubitril/valsartan include symptomatic hypotension, acute kidney injury, and angioedema. ACEi should not be co-administered with ARNI due to the increased risk for angioedema, as observed in previous studies.[8] It is proposed that this increased risk for angioedema is secondary to ACEi and neprilysin inhibitors both increasing circulating levels of bradykinin. To reduce this potential risk, ACEi should be stopped for 36 hours or longer before starting ARNI. In addition, sacubitril/valsartan should not be considered in patients who have previous history of angioedema with ACEi due to the potential increased risk for recurrence. Monitoring in patients taking ARNI should include blood pressure, renal function, and potassium levels.[4–8]

Angiotensin converting enzyme inhibitors

ACEi are vasodilators that decrease preload and afterload, vasopressin and aldosterone production, and block sympathetic stimulation by blocking conversion of angiotensin I to angiotensin II. They also increase bradykinins resulting in slowing or prevention of cardiac remodeling and enhanced vasodilation. The effects of ACEi on bradykinins also increase the side effect of dry cough, as well as the risk for angioedema.[4–7]

The benefits of ACEi were established in multiple randomized clinical controlled trials. A reduction in all-cause mortality was seen in patients receiving ACEi compared to placebo.[12–14] These conclusions from these studies indicate that the benefits provided by ACEi appear to be a class effect; therefore, any ACEi can be selected for initiation based upon what is most cost-effective for the patient. Initial doses should be low and up titrated after 1 to 2 weeks if patients are tolerating therapy.[2–7]

ACEi are contraindicated in women who are pregnant or planning pregnancy due to the risk for teratogenicity and death of the exposed fetus. ACEi are also contraindicated in patients with hypersensitivity to any ACEi, angioedema (history with previous ACEi, idiopathic, or hereditary), combined use with aliskiren, or administration within 36 hours of receiving ARNI. Significant adverse effects include hyperkalemia, acute kidney injury, cough (10%), and angioedema (<1%; may change to ARB, cross-reactivity 10%). Monitoring for patients taking ACEi should include renal function, blood pressure, potassium, liver enzymes and any signs/symptoms of liver failure, neutropenia in patients with history of collagen disease or renal impairment, and symptoms of angioedema.[3–7]

Angiotensin receptor blockers

ARBs can be used in patients who cannot tolerate ACEi due to cough or angioedema. ARBs inhibit effects of angiotensin II by directly blocking the angiotensin II receptor. They do not affect angiotensin converting enzyme or affect the breakdown or elimination of kinin and, as a result, have a reduced risk of cough and angioedema.[3–7]

There are 3 ARBs that have demonstrated reduction in mortality and HF symptoms and hospitalizations. These include losartan, candesartan, and valsartan. In patients with HFrEF who cannot tolerate or afford ACEi or ARNI, ARBs can be used to reduce mortality due to cardiovascular causes and HF-related hospitalization.[15–17] Similarly to ACEi and ARNI, ARBs should be started at the lowest dose and titrated upward every 1 to 2 weeks if patients are tolerating therapy. Significant adverse effects include hyperkalemia, acute kidney injury, and rare occurrence of angioedema.[3–7]

Beta-Blockers

Beta-blockers that have been evaluated in patients with HFrEF and demonstrated benefit include metoprolol succinate, bisoprolol, and carvedilol.[3–7] Metoprolol succinate and bisoprolol selectively block beta-1 cardiac receptors and the subsequent effects of sympathetic neurotransmitters, including norepinephrine.[18,19] Effects include reduction of heart rate, life-threatening ventricular arrhythmias, death of cardiac cells, hypertrophy of the cardiac muscle, and vasoconstriction. Carvedilol non-selectively blocks both beta-1 cardiac receptors and alpha-1 peripheral receptors, which provide additional reduction in blood pressure and systemic vascular resistance.[20] Bisoprolol is the most cardio-selective beta-blocker.

Beta-blockers are recommended to be initiated in patients who are euvolemic and asymptomatic for HF. When beta-blockers are initiated, they should be started at the lowest dose and titrated upward every 2 weeks if the patient is asymptomatic and tolerating therapy (eg, no hypotension or bradycardia) until reaching the target dose or medication intolerance. Beta-blockers should not be abruptly stopped due to increased risk for sympathetic overload and clinical deterioration, even in cases of decompensated HF, unless there is a concern for low cardiac output and impaired perfusion or in patients who progress to cardiogenic shock.[18–20]

Greater reduction in mortality has been observed in patients who are able to receive higher beta-blocker doses that are more consistent with the target doses achieved in clinical trials.[21] Therefore, doses for other GDMT, such as ACE/ARB/ARNI may need to be reduced to allow further up-titration of beta-blocker doses. In patients with HFrEF, beta-blockers reduce mortality and hospitalization, improve left ventricular ejection fraction, and improve HF symptoms. To reduce the risk of HF-related hospitalization and mortality, beta-blockers should be initiated in patients with clinically stable HFrEF.[22–24]

Beta-blockers are contraindicated in patients with second- or third-degree heart block or sick sinus syndrome unless patient has functioning pacemaker, cardiogenic

shock, or decompensated HF. The most common side effects include bradycardia and hypotension. Fatigue or weakness can occur during dose titration upward but usually resolves or lessens within 1 to 2 weeks.[18–20]

Mineralocorticoid Receptor Antagonists

MRAs, which are also referred to as aldosterone antagonists, are a class of medications used in HF that includes spironolactone and eplerenone. These agents competitively bind to the mineralocorticoid receptors in the distal convoluted renal tubule, preventing aldosterone from binding, which results in potassium retention and sodium and water excretion.[25,26] Studies have concluded that the use of spironolactone and eplerenone were shown to significantly reduce morbidity and mortality in patients with HFrEF.[27–29]

Initial dosing for the spironolactone and eplerenone in heart failure is 25 mg orally daily with a target dose of 50 mg orally daily. A common side effect of both eplerenone and spironolactone is hyperkalemia, while spironolactone also has an adverse effect of gynecomastia.[25,26] Monitoring parameters for mineralocorticoid receptor antagonists include renal function and serum potassium levels. Routine monitoring of renal function and serum potassium should be performed based on each individual patient's clinical status. Checking at 1 week, 4 weeks, followed by every 3 months, respectively, may be appropriate. With initiation of treatment or up titration, more frequent monitoring may be warranted for changes in the clinical status of the patient. MRAs are not recommended for patients with an estimated glomerular filtration rate of $\leq$30 mL/min/1.73 m^2 or serum potassium $\geq$5.0 mEq/L.[3–7]

Additionally, finerenone is a nonsteroidal MRA because it is devoid of a steroidal ring and not associated with an adverse effect of gynecomastia. Finerenone is not currently approved for use in HF but was shown to reduce the risk of kidney failure, cardiovascular events, and hospitalization for HF in patients with chronic kidney disease and type 2 diabetes mellitus. Some data have also shown the benefit of finerenone in HFpEF.[5]

Sodium-Glucose Co-transporter 2 Inhibitors

SGLT2i are recommended in HFrEF because this medication class has been shown to reduce hospitalizations due to HF and cardiovascular mortality in patients with or without type 2 diabetes. SGLT-2 receptors are located on the proximal convoluted tubules of the kidney and reabsorb glucose, as well as sodium that is filtered through the glomerulus. When this receptor is inhibited, it results in the excretion of sodium and glucose, producing mild diuresis. The mechanism for this class benefit in HF is not fully understood. However, there are proposed theories, including reductions in cardiac preload and afterload, plasma volume, arterial stiffness, and changes in cardiac metabolism.[4,5]

Although empagliflozin was initially used for its antihyperglycemic properties in type 2 diabetes mellitus, the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose) trial is what first suggested a benefit in HF. There was a significant reduction of the endpoint hospitalizations due to HF in those treated with empagliflozin in comparison to placebo.[30,31]

Results from the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) studies both concluded that patients experienced a reduction in cardiovascular mortality or hospitalizations due to HF in comparison to placebo, despite whether patients had a diabetes mellitus diagnosis.[32,33]

Dapagliflozin and empagliflozin are both dosed at 10 mg orally daily for HF. Adverse effects associated with this medication class include volume depletion (1% – 3%), genital mycotic infections (2% – 7%), urinary tract infections (6% – 9%), and ketoacidosis (<1%). Patients at higher risk include females and previous history of genital mycotic infections. Ketoacidosis is a rare adverse effect, although patients may be at an increased risk with prolonged periods of fasting, especially in illness or perioperatively. Thus, SGLT2i are recommended to be held for at least 3 days prior to scheduled surgery. SGLT2i are also not recommended to be started in the setting of uncontrolled hyperglycemia.[34,35]

Medications that Should Be Considered in Select Patients with Heart Failure with Reduced Ejection Fraction

Isosorbide dinitrate and hydralazine

Isosorbide dinitrate produces relaxation of arterial and venous vascular smooth muscle, which results in reduction in end-diastolic pressure of the left ventricle (preload). Hydralazine is a direct peripheral vasodilator that reduces systemic vascular resistance (afterload).[3–7]

In the A-HeFT (African-American Heart Failure) trial, isosorbide dinitrate and hydralazine were given to patients with HFrEF who self-identified as Black to determine if there is reduced mortality. The trial was terminated early due to significantly higher mortality observed in the placebo group compared to patients receiving isosorbide dinitrate and hydralazine. Therefore, isosorbide dinitrate and hydralazine should be added to reduce hospitalization due to HF and mortality in self-identified black patients with left ventricular ejection fraction (LVEF) of 45% or less with severe HF symptoms despite already receiving GDMT (ACEi/ARB, beta-blocker, and MRA).[36,37] Isosorbide dinitrate with hydralazine can also be considered as alternative therapy for ARNI/ACEi/ARB in patients with stage C HFrEF who have a history of intolerance, allergy, or worsening renal function.[3,7]

Isosorbide dinitrate and hydralazine are available as separate tablets, as well as combination product. When the individual medications are used, they should be administered at the same time to mimic how the medications were administered in clinical trials. The lowest dose should be initiated and titrated upward every 2 to 4 weeks as tolerated. The combination product can be initiated and titrated quickly to target dose, as tolerated, over 3 to 5 days. Hydralazine is contraindicated in patients with coronary artery disease and rheumatic mitral valve disease. Isosorbide dinitrate should not be used in combination with phosphodiesterase type 5 (PDE-5) inhibitors due to the risk for severe hypotension. Adverse effects associated with isosorbide dinitrate and hydralazine include hypotension, headache, and drug-induced lupus. Drug-induced lupus most commonly presents with weight loss, fever, and pain in the muscles and joints.[3–7]

Digoxin

Digoxin is a cardiac glycoside. It inhibits an enzyme (sodium-potassium ATPase) that regulates the level of sodium and potassium in cardiac cells. By the enzyme inhibition, the sodium level is increased and results in increased calcium levels, which is thought to increase the strength of contraction of cardiac muscle cells. Digoxin also slows the heart rate and the degree of stimulation caused by the sympathetic nervous system.[38] The digoxin investigation group (DIG) trial demonstrated that use of digoxin in addition ACEi and diuretics in patients' HF those have LVEF of 45% or less does not reduce the risk of mortality. In the secondary endpoints, there was a significant reduction in hospitalizations for worsening HF observed in patients receiving digoxin compared to the placebo group (26.8% vs 34.7%).[39,40]

Digoxin should be started at 0.125 mg daily in most patients. Every other day dosing should be considered in patients with reduced lean body mass, renal dysfunction (creatinine clearance < 30 mL/min), or age greater than 70 years. No loading dose is required or recommended for use of digoxin in HF patients. Serum digoxin levels can be monitored once steady-state is achieved, approximately 5 to 7 days after initiation of a daily regimen. The goal serum level is 0.5 to 0.9 ng/mL.[3–7,38] Patients with digoxin levels of 1.2 ng/mL or greater in the post-hoc analysis of the DIG trial were observed to have an increased risk of mortality compared with placebo.[40] Monitoring for digoxin includes electrolytes, as well as serum creatinine. Symptoms of digoxin toxicity can include visual (blurry vision, light sensitivity, and blue-green halos around light), gastrointestinal (anorexia, nausea, and vomiting), central nervous system (confusion), hyperkalemia, and cardiac (heart block, bradycardia).[37] Patients who are elderly, have renal dysfunction, and/or electrolyte abnormalities, specifically hypokalemia, have greater risk for digoxin toxicity at serum levels within the therapeutic range. Therefore, some patients may have increased risk for mortality in the setting of subclinical digoxin toxicity. Subclinical toxicity is defined as the occurrence of a negative patient outcome or adverse effect in the setting of an otherwise normal medical dose and serum level.[41]

Initiation of digoxin can be considered to reduce all-cause and HF hospitalizations in patients with symptomatic HFrEF who are already receiving guideline-directed therapy with ACEi or ARNI, beta-blocker, and MRA.[3–7]

Ivabradine

Ivabradine blocks a channel in the cardiac cells that is responsible for the funny channel current (I_f), which is the cardiac pacemaker and controls heart rate. The primary effect of heart rate reduction is within the sinoatrial (SA) node, and there does not appear to be an effect on the repolarization of the ventricles or contractility of the heart.[42] Therefore, ivabradine is only effective in patients with sinus rhythm. The SHIFT (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine) trial demonstrated that patients with moderate to severe HF or history of worsening HF (LVEF of 35% or less) who received ivabradine in addition to guideline-directed therapy had reduced HF hospitalizations and death from cardiovascular causes compared to placebo. The benefit appeared to be heavily driven by HF hospitalizations.[43]

For further reduction in HF hospitalizations and death from cardiovascular causes in patients with symptomatic HF and ejection fraction of 35% or less, ivabradine initiation should be considered. It is recommended that patients are first titrated to maximally tolerated beta-blocker dose or are unable to tolerate beta-blocker therapy and have a heart rate greater than 70 bpm, in addition to ACEi or ARB and MRA.[4,5,7] Ivabradine should be started at 5 mg twice daily. In patients who have bradycardia or a history of defects in conduction, initial dosing should be 2.5 mg twice daily. Dose can be increased after 2 or more weeks if the heart rate is greater than 60 bpm to the maximum dose of 7.5 mg twice daily. Dose should not be increased in patients with a heart rate of 50 to 60 bpm, and patients with symptomatic bradycardia (heart rate <50 bpm) should have the dose decreased (if applicable) or discontinued. Patients who have creatinine clearance of 15 ml/min or less should be initiated on the lowest dose and only titrated if the patient is tolerating therapy. Ivabradine use is contraindicated in patients who have severe liver impairment defined as Child-Pugh class C, atrial fibrillation or flutter, HFpEF, acute decompensated HF, sick sinus syndrome, clinically significant bradycardia or hypotension, heart block (SA node or third-degree), administration with strong CYP3A4 (cytochrome P450 3A4 enzyme) inhibitors, and atrial pacemaker dependence. Side effects include bradycardia,

hypertension, atrial fibrillation, arrhythmias, vertigo, and visual disturbances (diplopia and visual impairment).[42]

Vericiguat

Vericiguat is a soluble guanylyl cyclase (sGC) stimulator that directly binds and stimulates sGC, the primary receptor of nitric oxide in smooth muscle, and increases cGMP production. The benefits of cyclic guanosine monophosphate (cGMP) in HF include vasodilation, improvement in endothelial function, and decrease in fibrosis and remodeling of the heart.[44]

The VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) evaluated patients with symptomatic HF (NYHA II-IV) with ejection fraction less than 45%, elevated natriuretic peptides, and recent worsening of HF (hospitalized $\leq$6 months or recently received intravenous diuretic therapy without hospitalization) receiving standard therapy. Patients receiving vericiguat had reduced cardiovascular death or hospitalization due to HF compared to placebo.[45] Therefore, to further reduce cardiovascular mortality and HF hospitalizations, vericiguat could be used in HFrEF patients with severe and worsening symptoms who are already receiving standard therapy.[3,4,7] Vericiguat should be initiated at 2.5 mg once daily and administered with food. The dose can be increased every 2 weeks if the patient is tolerating the medication to the target dose of 10 mg daily. Vericiguat should not be administered during pregnancy, lactation, or in patients who are taking other sGC stimulators. It is not recommended to be co-administered in patients receiving nitrates or PDE-5 inhibitors as they were excluded from clinical trials and have an increased risk for hypotension. The most common adverse effects are anemia, hypotension, dyspepsia, and nausea.[44]

Pharmacotherapy for Heart Failure with Preserved Ejection Fraction

Pharmacotherapy for patients who have HFpEF is less well-established until recently. The SGLT2 inhibitors, MRAs, and ARBs/ARNI have proven to provide benefit for patients with HFpEF.[3–7]

The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) and DELIVER (Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction) trials investigated the benefits of empagliflozin and dapagliflozin in patients with HFpEF. The results showed that patients receiving empagliflozin or dapagliflozin were significantly less likely to experience the composite outcome of hospitalization/worsening HF or cardiovascular mortality.[46,47]

TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) evaluated the use of spironolactone in symptomatic HF patients with an LVEF $\geq$45%. Although spironolactone did not result in less incidence of the composite primary outcome of HF hospitalizations, aborted cardiac arrest, and cardiovascular mortality, it did result in fewer occurrences of HF hospitalizations in comparison to placebo.[48] More recently, data regarding the safety and efficacy of finerenone in HFpEF have emerged. The FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure) trial sought to investigate whether finerenone would improve cardiovascular mortality and worsening HF events in patients with HFpEF. Results demonstrated a reduction in cardiovascular deaths and worsening HF events in patients who have LVEF of 40% and received finerenone.[49]

Although the use of ARNI in patients with HFpEF did not demonstrate significant reduction in all-cause or cardiac mortality in PARAGLIDE-HF and PARAGON-HF, there

is a strong evidence that the use of sacubitril-valsartan was associated with significant reduction in NT-proBNP levels.[50,51] Post-hoc analysis from large clinical trials demonstrated that certain subgroups of patients with HFpEF including female patients, patients with recent hospitalizations related to HF, and patients with mildly reduced ejection fraction (<50%) do derive the benefit of reduced HF hospitalizations or urgent HF visits (worsening HF) and death associated with cardiovascular causes Therefore, it is concluded that in select patients the use of ARNI is highly recommended.[50–53]

Diuretics

Diuretics are routinely recommended in patients with HFrEF and HFpEF to relieve symptoms of fluid overload, hepatic congestion, HF hospitalization, and shortness of breath. Diuretics reduce pulmonary congestion, peripheral edema, and symptoms of HF; however, they do not demonstrate a reduction in mortality in HF patients. Diuretics inhibit sodium reabsorption. Loop diuretics work more proximally in the ascending loop of Henle and inhibit 20% to 25% of sodium reabsorption, whereas thiazide diuretics work in the distal tubule and inhibit 10% to 15% of sodium reabsorption. Diuretics should be used in combination with guideline-directed therapy.[3–7,54,55]

Loop diuretics are recommended to be utilized first-line in patients with significant congestion and volume overload. Furosemide has limited oral bioavailability, and some patients may respond better to torsemide or bumetanide.[3–7] It has been suggested by some small studies that torsemide may better decrease HF symptoms in comparison to furosemide; however, the studies were not large enough to substantiate this claim. The effect of torsemide in comparison to furosemide on all-cause mortality was evaluated in hospitalized patients with new onset or worsening HF in the TRANSFORM-HF (Torsemide Comparison with Furosemide for Management of Heart Failure) trial. Results demonstrated that there was no significant difference in mortality or all-cause hospitalizations.[56]

For patients on chronic use of loop diuretics who demonstrate decreased urine output and fluid accumulation despite increasing doses of loop diuretic, diuretic resistance should be considered. Thiazide or thiazide-like diuretics can be added to provide dual nephron blockade, increase the net natriuretic effect, and improve decongestion.[3,4,55]

Common thiazide diuretics that are utilized for nephron blockage include hydrochlorothiazide, chlorothiazide (both oral and intravenous), and metolazone. Chlorothiazide has 30% to 50% oral bioavailability compared to 65% to 75% for hydrochlorothiazide. Both have short elimination half-lives of less than 3 hours, whereas metolazone has 65% oral bioavailability and a significantly prolonged elimination half-life as long as 2 days. Furthermore, the potential for side effects can be more significant and prolonged with metolazone compared to hydrochlorothiazide and chlorothiazide. Therefore, based upon oral absorption, elimination half-life, and similar efficacy, hydrochlorothiazide is considered the safer option for nephron blockade.[55]

There is a novel formulation for furosemide administration that allows patients to self-administer the medication subcutaneously at home to treat fluid overload associated with HF (NYHA II-III). It can be used in addition to oral diuretic therapy, especially in patients who experience recurrent episodes of fluid overload with or without hospital admission. This formulation of furosemide can increase weight loss, reduce congestion, and improve functional ability.[57,58]

Adverse effects of diuretics include electrolyte abnormalities (hyponatremia, hypokalemia, and hypomagnesemia), increased uric acid and gout flare, and ototoxicity presenting initially as tinnitus.[3–7,55] Supplementation with oral potassium and/or magnesium may be needed in some patients to maintain electrolyte levels within the

normal range. MRAs can also be used in conjunction with diuretics for the management of HFrEF or HFpEF and to lessen the risk for hypokalemia associated with loop and/or thiazide diuretics.

ADJUNCT PHARMACOTHERAPY IN HEART FAILURE

Inotropes

Patients with advanced-stages HFrEF, ACC/AHA stage D, who have received GDMT with continued worsening of cardiac output and HF symptoms or who are unable to tolerate addition or titration of GDMT may be evaluated for initiation of inotropic therapy with dobutamine or milrinone. In the setting of worsening HF and hospitalization for cardiogenic shock, inotropes may temporarily be utilized to improve perfusion, fluid removal, and hemodynamic stabilization during hospitalization. In patients who are determined to have reduced cardiac output, inotrope therapy can be considered as a bridge to continue in the outpatient setting until patients can be evaluated for advanced HF therapies including placement of left ventricular assist device or heart transplant. For patients who are deemed not to be candidates for advanced HF therapies, inotropes may be continued as a palliative measure to lessen HF symptoms, including fatigue and shortness of breath, and improve the patient's quality of life. Inotropes do not improve mortality during hospitalization or as chronic therapy; furthermore, using inotropes outside of bridge therapy or palliation can be harmful to patients due to the potential for side effects including arrhythmias and catheter-related infections.[4,5]

Dobutamine stimulates beta-1 adrenergic receptors of the heart, resulting in increased heart rate and contractility. Initial dosing is 2.5 mcg/kg/min and is usually titrated upward by increasing dose by 2.5 mcg based upon further decrease of the patient's cardiac output. It has a short half-life elimination of 2 minutes and is eliminated through metabolism in the tissue and hepatically. Dobutamine should not be used in combination with beta-blockers due to the drug-drug interaction that may lessen the effects of the inotrope.[59] Milrinone is a phosphodiesterase inhibitor that works selectively in both vascular and cardiac tissue that causes inotropic effects, as well as vasodilation. Initial dosing is 0.25 mcg/kg/min and is usually titrated upward by increasing dose by 0.125 mcg, if needed, to increase the cardiac output. Milrinone has a longer elimination half-life of 2 to 3 hours and is eliminated by the kidneys. Therefore, in patients with worsening renal function and lower blood pressure, dobutamine may be used over milrinone.[60] The most common side effects for both inotropes are hypotension and cardiovascular arrhythmias, more commonly ventricular (>10%).[59,60]

Iron

Anemia and iron deficiency are two important comorbidities in patients with HF. It affects both HFrEF and HFpEF. It is associated with increased symptom burden, increased mortality, and hospitalizations, reduced exercise capacity and physical well-being, and reduced quality of life.[61,62] There are various suspected causes of iron deficiency in HF, which include impaired intestinal absorption due to edema in the gastrointestinal walls, malnutrition, inflammation, and increased release of hepcidin, and decreased iron absorbed in the gastrointestinal tract.[63] It is recommended that intravenous iron is administered to patients who have ferritin less than 100 ng/mL or ferritin between 100 and 300 ng/mL with transferrin saturation <20%.[3–6,61,62] Common adverse effects include hypertension/hypotension, injection site reaction, and dizziness.

Principles for initiation of pharmacotherapy for heart failure

In patients who have HFrEF, based upon the strength of evidence and consensus among HF providers, if blood pressure and renal function allow, initial therapy should include renin angiotensin aldosterone system modulators in combination with evidence-based beta-blocker. The RAAS modulator should be ARNI. When patients are unable to receive ARNI, then therapy with ACE or ARB can be used alternatively. The next agents to consider for initiation include either or both MRA and SGLT2 inhibitors. MRA and SGLT2 inhibitors are also pharmacotherapy classes that can be considered initially when patients have a blood pressure or heart rate that prohibits initiation of RAAS modulator or beta-blocker therapy. Hydralazine in combination with isosorbide dinitrate can be considered for addition in Black patients who continue to experience HF symptoms after initiation of RAAS modulator, beta-blocker, MRA, and SGLT2 inhibitor or as an alternative to RAAS modulator in patients who have renal dysfunction or history of intolerance. Most patients require loop diuretic with or without thiazide diuretic to control their fluid level and symptoms of HF. Further pharmacotherapy that can be considered for additive benefits in reduction in HF symptoms include ivabradine, digoxin, and vericiguat. Ivabradine can be initiated in patients with heart rate (HR) $\geq$70 bpm with normal sinus rhythm. Digoxin could also be considered for patients who continue to experience HF symptoms. Digoxin can safely be used in patients who have atrial fibrillation in addition to their HF.[3–7] For each of the therapies, they should be started at the lowest dose and titrated upward, as tolerated, to the target dose. The all-cause mortality reduction observed in HFrEF patients receiving the 4 pillars of GDMT for heart failure (RAAS modulator, beta-blocker, MRA, and SGLT2 inhibitor) compared to no treatment is 75%.[4] Refer to **Fig. 1**. Initiation of medications for patients with stage C HFrEF for the process of adding GDMT and other therapies for HF for further explanation of medication initiation for HFrEF.

Based upon available data and experience for management of patient with HFpEF, diuretics (scheduled or as needed) are recommended first-line for fluid management, followed by SGLT2i to reduce hospitalizations due to HF and death due to

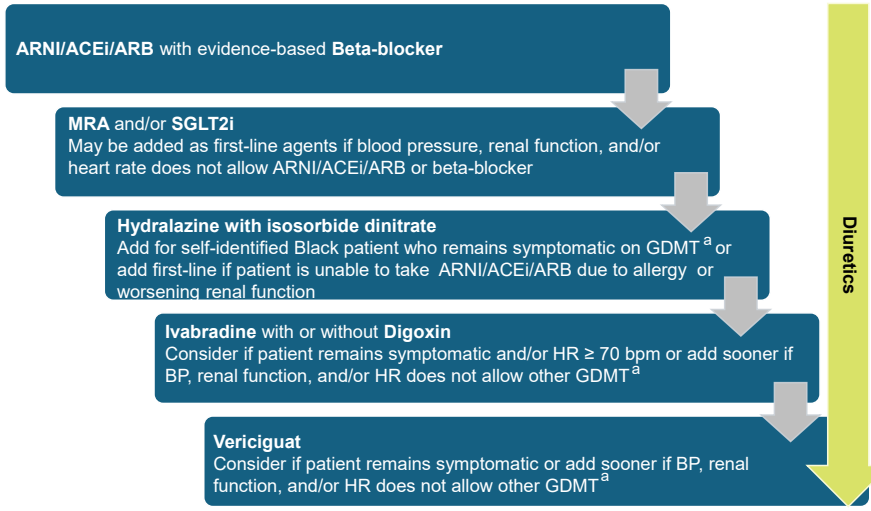

Fig. 1. Sequence of heart failure medication initiation. Heart failure with reduced ejection fraction. [a]GDMT: ARNI/ACEi/ARB+beta-blocker+MRA+SGLT2i±Hydralazine/isosorbide dinitrate.

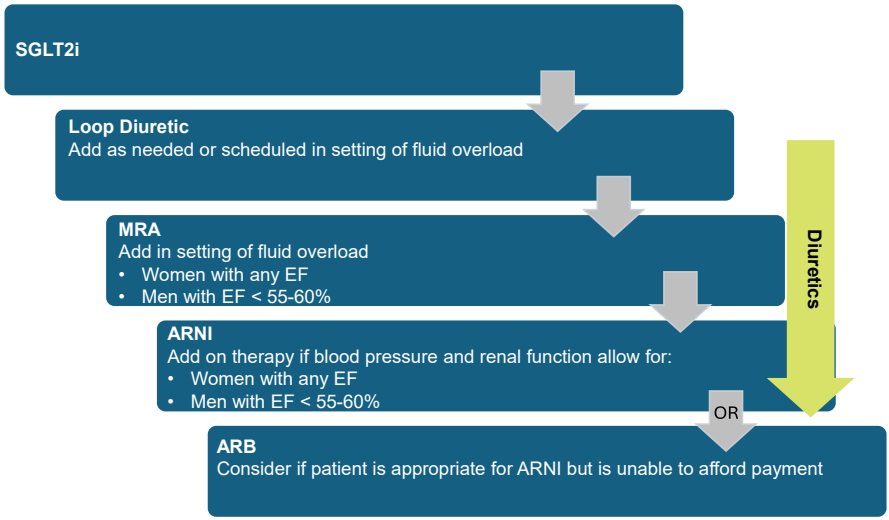

Fig. 2. Sequence of heart failure medication initiation. Heart failure with preserved ejection fraction.

cardiovascular causes, MRAs and/or ARBs can be considered to reduce hospitalizations, and ARNI can be considered for HFpEF patients with lower range ejection fraction to reduce hospitalizations when financially feasible for the patient.[3–7,53] Refer to Fig. 2. Initiation of medications for patients with HFpEF for the process of adding GDMT for HFpEF.

Notably, beta-blockers, ACEi, and nitrates have failed to demonstrate any significant benefits in patients with HFpEF; therefore, the use of these agents is not emphasized by the HF guidelines, but patients may be taking for other underlying comorbidities.

SUMMARY

Clinical trials in patients with HF have established the framework of pharmacotherapy for HFrEF patients, which include renin angiotensin aldosterone system modulators, beta-blockers, MRAs, and SGLT2i. Benefits observed have not been interdependent on background therapies. Target doses achieved in clinical trials are ideal goals. However, initiation of comprehensive medication therapy at doses tolerated by the patient provides superior HF benefits with improved survival, reduced HF-related symptoms, and reduced HF hospitalizations. Financial limitations may still prevent or delay initiation of ARNI and/or SGLT2i at the present time, but these barriers will begin to resolve with more time and evidence. Additional pharmacotherapy to reduce HF symptoms can be tailored to provide precise benefits. These agents include digoxin, vasodilators, vericiguat, and/or ivabradine.[64] Diuretics have an integral role in maintaining fluid balance and controlling symptoms for patients who have either HFrEF or HFpEF.

Pharmacotherapy for patients with HFpEF has expanded to include SGLT2i, MRA, and ARNI. As further studies and experiences are available, there will be a clearer understanding of the potential comprehensive benefits of these therapies in HFpEF patients. Further clinical studies will help delineate when to add each pharmacotherapy class and to individualize therapeutic options based on demographic, hemodynamic, and biochemical profiles.[3–7]

CLINICS CARE POINTS

- Renin angiotensin aldosterone system blockers (ARNI, ACEi, or ARB), beta-blockers, mineralocorticoid receptor antagonist (MRA), and sodium glucose cotransporter 2 inhibitor (SGLT2i decrease HF hospitalizations and mortality in patients with HFrEF.
- Medical therapy including, SGLT2i, MRA, and/or ARNI, provide mortality and morbidity benefits for HFpEF.
- Primary therapy for congestion management in patients with both HFrEF and HFpEF involves loop diuretics.
- Select patient with HF have additional benefits with the addition of other pharmacotherapy, including hydralazine/isosorbie dinitrate, digoxin, ivabradine, vericiguat, thiazide diuretics, GLP-1 agonists, and inotropes.

DISCLOSURES

The authors have nothing to disclose.

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