CLINICAL REVIEW

Management of Chronic Heart Failure with Reduced Ejection Fraction

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Heart failure with reduced ejection fraction (HFrEF) is a commonly seen clinical entity in the family physician's practice. This clinical review focuses on the pharmacologic management of chronic HFrEF. Special attention is paid to the classification of heart failure and the newest recommendations from the American Heart Association concerning the use of guideline-directed medical therapy. β blockers, ACE inhibitors, ARBs, mineralocorticoid receptor antagonists are discussed in detail. The new emphasis on sacubitril-valsartan and SGLT2i's as therapies for HFrEF are reviewed, followed by a brief discussion of more advanced therapies and comorbidity management. (J Am Board Fam Med 2024;37:364–371.)

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Heart failure with reduced ejection fraction (HFrEF) is increasing and prevalence and 5-year mortality remains high. Make sure you are including the most recently recommended therapeutics in your treatment plan. This review draws heavily from the American Heart Association (AHA) Guideline for the treatment of heart failure, as well as its evidence with an emphasis on pharmacologic management.[1]

Practice Recommendations

In patients with HFrEF patients should be on the following classes of medications based on their strength of recommendation taxonomy (SORT)

- An angiotensin receptor-neprilysin inhibitor (ARNi) is preferred (SORT B), otherwise an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin (II) receptor blockers (ARB) (SORT A)
- A beta blocker (SORT A)
- A Mineralocorticoid Receptor Antagonist (MRA) (SORT A)
- A Sodium-Glucose Cotransporter 2 Inhibitor (SGLT2i), regardless of the presence of diabetes (SORT A)

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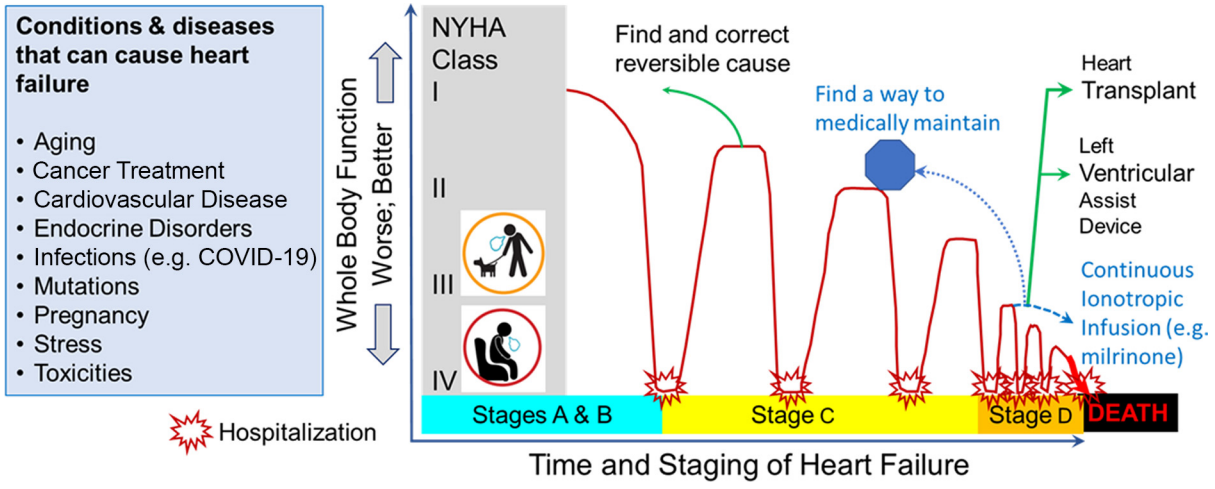
Background

Heart failure (HF) prevalence is increased in the United States. Prevalence has increased from 2007 to 2010 at 5.1 million[2] to 2017 to 2020 approximately 6.7 million.[3] HF prevalence is projected to increase by 46% from 2012 to 2030 to affect more than 8 million American adults.[4] Outside of prevalence, the lifetime risk of HF at 50 years of age has increased between 2 different epochs in the Framingham Heart Study.[3] Incidence seems stable with HFrEF declining and HFpEF increasing.[5] Overall, black individuals have the highest incidence of HF.[6] Risk factors for HF include obesity, hypertension, diabetes, coronary heart disease (CHD), and smoking, among others.[7] Approximately 1 in 3 adults in American have at least 1 risk factor for HF, also known as stage A HF.[8] Worse, COVID-19 adds 11.6 new HF cases per 1000 infections above the expected annual incidence.[9]

Classification

HF occurs when the heart loses its ability to provide sufficient blood to the body. Thus, "HF is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of

Figure 1. Heart Failure Progression. Many underlying disease processes cause the heart to fail. Unless a correctable underlying cause is found and successfully treated, the majority of heart failure (HF) patients will progress in an undulating downward fashion toward death. American Heart Association (AHA) Staging describes the status of HF[1]: A "at risk for HF," has underlying risk but without detectable dysfunction, such as hypertension; B "pre-HF": has underlying cause and detectable cardiac dysfunction but without over heart failure symptoms; C "symptomatic HF": has documented cardiac dysfunction and heart failure symptoms; D "advanced HF": patient has refractory heart failure without chance of meaningful return to an acceptable plateau. The New York Heart Association (NYHA) classification describes a patient's overall function (I: normal; II: moderate exertion causes symptoms; III: mild exertion causes symptoms; IV: symptoms at rest or with minimal exertion). Continuous inotropic infusion can provide a bridge to intervention (heart transplant or left ventricular assist device), bridge to medical treatment to achieve a better plateau, or palliative comfort care.



blood."[1] HF is caused by a number of conditions such as ischemic heart disease, hypertension, valvular heart disease, various causes of nonischemic cardiomyopathy, among numerous others. (Figure 1). HF is defined by 3 major components of stage, left ventricular ejection fraction (LVEF), and patients' ability to function. Stages (A-D) describe the status of the heart in terms of risk, structure, cardiac function, and HF progression (see Figure 1 and Table 1). The failing heart has different underlying pathophysiology and responds differently to treatment based on initial LVEF at diagnosis; therefore, LVEF groupings is used to direct treatment (reduced: LVEF ≤ 40%; improved: previous LVEF ≤ 40% but now better; mildly reduced: LVEF 41 to 49%; and preserved: LVEF ≥ 50%) (Table 2). The New York Heart Association (NYHA) functional classification (I-IV) describes level of exertion that triggers HF symptoms (see Table 3). Of note, a HF stage-C patient can experience NYHA II-IV levels depending on the success of treatment.

Pharmacologic Therapy

Aside from management of comorbidities, the cornerstone of HFrEF treatment is appropriate pharmacologic management, or guideline-directed medical therapy (GDMT) (Table 4). The goals of GDMT are to alleviate symptoms, decrease the structural progression of HF, decrease HF hospitalizations, and decrease cardiovascular (CV) mortality. After treatment with GDMT some patients improve their EF to normal, called HFimpEF, and it is important that medications not be withdrawn because this has been associated with relapse of HF.[10]

Despite evidence that GDMT attains these goals, and that achieving target doses improves on the results, appropriate prescribing remains suboptimal for HF patients.[11–13] The CHAMP-HF study

Table 1. Staging

Stage	Description
A	At-risk for HF but without functional heart disease or evidence of dysfunction
B	Pre-heart failure, or patients with evidence of structural heart disease but not clinical symptoms or signs
C	Symptomatic heart failure
D	Advanced or refractory heart failure

Abbreviation: HF, Heart failure.

Table 2. Classification of Heart Failure

Left Ventricular Ejection Fraction (LVEF)	≤ 40%	41–49%	≥ 50%
Has well developed guideline-directed medical therapy. Medical therapy needs to be continued with improvement in LVEF	Heart Failure with Reduced Ejection Fraction (first presentation)	Heart Failure with Improved Ejection Fraction	
Has not been investigated as separate entity; therefore, there is no data		Heart Failure with Mildly Reduced Ejection Fraction (first presentation)	
Some treatment is possible			Heart Failure with Preserved Ejection Fraction (first presentation)

demonstrated that among patients who were eligible for GDMT, a large number of patients were not prescribed appropriate medications and those that were prescribed were frequently at less than target doses.[14] With this in mind, the core GDMT pharmacologic therapies are described below and in Table 5.

In general, the most recent guideline recommends individualized titration of GDMT to target doses while maximizing the number of classes of medications utilized with careful monitoring of patient vital signs, symptoms, and serial laboratory evaluation.[1] Typically, most trials of newer medications study it as an additional medication to preexisting GDMT, which means that patients frequently are started on a ARNi/RAAS inhibitor or β blocker first, followed by an MRA, and subsequently by an SGLT2i (see below). In the HF guidelines the method of initiation, both sequencing and titration, of GDMT is specifically listed as an evidence gap and opportunity for further research. One author (CT) prefers maximizing categories of medications over maximizing individual dosages. It must be noted that no medication is benign, and all medications have a risk for adverse effects.[15]

In the pivotal trials, the number-needed-to-treat (NNT) for a decrease in all-cause mortality for each of the core HFrEF medications was less than 100 when standardized over 12 months, from a high of 80 for sacubitril-valsartan, to a low of 18 for mineralocorticoid receptor antagonists (Table 6).[1] These numbers decrease further when standardized to 36 months. A limitation of many studies, however, is that they are often industry funded and the most recent guidelines have many authors who disclosed relationships with pharmaceutical companies.

In a patient with chronic HFrEF, who is not hospitalized, there are 4 classes of essential medications that must be considered. Diuretics should be utilized for decongestion in patients with volume overload to relieve symptoms but are not included in the discussion below.

Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

The medications that act on the RAAS include the ARNi, ACEi, and ARBs. All 3 categories of medications require monitoring of blood pressure, creatinine clearance, and serum potassium.

Sacubitril-valsartan, the only ARNi currently available, is recommended in patients with NYHA class II or III heart failure who do not have hypotension, a history of angioedema, and do not have barriers to taking the medication due to cost.[16] Current guidelines prefer an ARNi instead of an ACEi or ARB because ARNI provided better survival than ACEi.[1] If an ARNi is not possible, then prescribing an ACEi is reasonable, provided that there is no history of angioedema.[17] If the patient is intolerant of an ACEi due to angioedema or chronic cough, an ARB is acceptable as the risk of recurrent angioedema is similar to placebo.[18–20]

Table 3. New York Heart Association Classification

Class	Description
I	Patients with heart disease with no limitation of physical activity.
II	Patients with heart disease with slight limitation of physical activity. Ordinary activity produces symptoms, but no symptoms are produced at rest.
III	Patients with marked limitation of physical activity. Less than ordinary activity creates symptoms, but no symptoms are produced at rest.
IV	Patients cannot perform physical activity without symptoms. Symptoms may be produced at rest.

Table 4. Comorbid Conditions in Heart Failure with Reduced Ejection Fraction

Comorbid Condition	Recommendation	Evidence Rating
Hypertension	Uptitration of medications according to GDMT to maximum tolerated dosages	SORT A[1]
Diabetes	SGLT2i as initial therapy for hyperglycemia	SORT A[10]
Iron deficiency	Intravenous iron repletion	SORT B[9]
Central Sleep Apnea	Adaptive servo-ventilation should not be used as it increases mortality	SORT A[1]
Atrial fibrillation	Guideline directed management should be pursued, including consideration of rhythm control and left atrial appendage closure in select patients	SORT A vs B depending on component of therapy[1]
Valvular heart disease	Manage according to current guidelines	See relevant guideline[11]
Ischemic heart disease	Should be considered in cases of HF to facilitate diagnosis and management	SORT B[1]

Abbreviations: HF, Heart failure; GDMT, guideline-directed medical therapy.

When switching between an ARNi either to or from an ACEi the minimum duration between the 2 types of medication is 36 hours.

It is important to note that none of the above medications should be combined due to risk of life-threatening hyperkalemia and, in the setting of an ACEi + ARNi, risk of angioedema.

β Blockers

β blockers remain one of the mainstays of treatment of chronic HFrEF. To date, there are only 3 that are shown to reduce mortality: sustained-release metoprolol succinate, carvedilol, and bisoprolol.[21–23] β blockers typically should be initiated at low doses and carefully advanced to target doses, as listed in Table 5. Contraindications include bradycardia and second- or third-degree heart block in the absence of a pacemaker. Careful consideration is suggested in patients with NYHA class IV HF, asthma, recent hospitalization, and signs of hypervolemia.

Mineralocorticoid Receptor Antagonists (MRAs)

In patients with HFrEF and NYHA Class II to IV an MRA should be utilized to reduce both morbidity and mortality.[24–26] Both spironolactone and eplerenone can cause life-threatening hyperkalemia. Patients are eligible if their eGFR is > 30 mL/min/1.73 m^2 and their serum potassium is <5 mEq/L. Regardless of initiation, careful monitoring of renal function and potassium is required, especially with any other medication that place the patient at risk for hyperkalemia and acute renal failure, such as diuretics and RAAS inhibitors. Spironolactone is associated with an incidence of gynecomastia of approximately 10%,[22] whereas eplerenone is noted have an incidence of gynecomastia similar to placebo.[23]

Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)

In patients with chronic symptomatic heart failure a newer recommendation is to add an SGLT2i to the pharmacologic regimen to reduce HF hospitalizations and CV mortality regardless of the presence of diabetes.[27,28] Patients should be monitored for euglycemic ketoacidosis, genital and soft tissue infections. Care should be taken to avoid hypovolemia when combining an SGLT2i with a diuretic.

Additional Medications and Therapies

After considering the above medications there remain several additional pharmacologic options. For patients who have refractory symptoms digoxin may be considered but does not offer mortality benefit.[29,30] For patients who identify as African American isosorbide mononitrate in combination with hydralazine can be considered to improve symptoms and mortality.[31,32] In patients on maximal GDMT and with a HR ≥ 70 and in sinus rhythm ivabradine may be beneficial.[33]

For patients fitting specific criteria, as detailed in Table 5, automated implanted cardioverter defibrillator (AICD) and cardiac resynchronization therapy (CRT) are options.[1]

Eventually, many HF patients will progress to the point of needing advanced care. Advanced care is best coordinated with an advanced heart failure and transplant cardiologist (AHFTC). Some thresholds for AHFTC referral include cardiogenic shock (SBP < 90 mmHg with signs of end organ dysfunction), needing inotropic support, needing to decrease GMDT, worsening

Table 5. Therapies for Heart Failure with Reduced Ejection Fraction[1]

Drug Class		Initial Dose	Target or Maximum Dose	Comments
ARNi				1. Avoid if hemodynamically unstable, history of angioedema, or potassium level ≥ 5 mmol/L 2. Preferred over ACE-I and ARB due to superior efficacy
	Sacubutril-valsartan	24/26 mg twice daily if ACE inhibitor or ARB naïve or 49/51 mg twice daily with adequate blood pressure (SBP ≥ 120 mmHg)	97/103 mg twice daily	Original study excluded patients with SBP < 100 mmHg
ACE Inhibitor				1. Similar restrictions to ARNi 2. Use if ARNi is not feasible
	Captopril	6.25 mg 3 times daily	50 mg 3 times daily	
	Enalaprol	2.5 mg twice daily	10–20 mg twice daily	
	Lisinopril	5 mg daily	20–40 mg daily	
	Ramipril	1.25–2.5 mg daily	10 mg daily	
ARB				1. Class preferred with history of angioedema or intolerance to ARNi and ACEi 2. Use if ARNi is not feasible
	Candesartan	4–8 mg daily	32 mg daily	
	Losartan	25–50 mg daily	50–150 mg daily	
	Valsartan	20–40 mg twice daily	160 mg twice daily	
Beta Blocker				1. Class-wide risk of hypotension, worsening asthma, and contraindicated in untreated high-degree heart block 2. Limit to carvedilol, metoprolol succinate, and bisprolol; It is not class-wide benefit.
	Carvedilol	3.125 mg twice daily	25–50 mg twice daily	6.25 mg is the minimal effective dose. Benefits increases with increasing dose to 25 mg.
	Metoprolol succinate extended release	12.5–25 mg daily	200 mg daily	
	Bisoprolol	1.25 mg daily	10 mg daily	
SGLT2i				Risk of euglycemic ketoacidosis and urinary tract infections
	Dapagliflozin	10 mg daily		
	Empagliflozin	10 mg or 25 mg daily		25 mg if patient also has type-2 diabetes.
MRA				Dose-adjustment or contraindicated depending on renal and potassium status; do not use if potassium level ≥ 5 mmol/L or Cr ≥ 2.5 mg/dL. Avoid if eGFR < 30 mL/min.
	Spironolactone	12.5–25 mg daily	25–50 mg daily	Risk of gynecomastia, breast pain, menstrual irregularities, decreased libido
	Eplerenone	25 mg daily	50 mg daily	Lower risk of gynecomastia

Continued

Table 5. Continued

Drug Class		Initial Dose	Target or Maximum Dose	Comments
Additional Therapies				Comments
Hydralazine plus nitrate				Comments
	Fixed-dose combination	20 mg isosorbide dinitrate/37.5 mg hydralazine three times a day	40 mg/75 mg 3 times a day	1. If patient is intolerant of RAAS inhibition 2. African American patients on maximum GDMT needing additional benefit
	Separate isosorbide dinitrate and hydralazine	20 mg isosorbide dinitrate and 25 mg hydralazine both three times a day	40/75 three times a day	
Cardiac glycoside				Comments
	Digoxin	0.125–0.25 mg daily	No target dose	Care with decreased creatinine clearance
Selective sinus node inhibitor				
	Ivabradine	2.5–5 mg twice daily	7.5 mg twice daily	Used if HR ≥ 70 in setting of maximal GDMT
Soluble guanylate cyclase inhibitor				
	Vericiguat	2.5 mg daily	10 mg daily	1. Use for patients who cannot tolerate or is already on all 4 major categories of beta-blocker, ARNi, Anti-aldosterone, and SGLT2i. 2. Can cause hypotension, this is a major limitation
Implanted Devices	**Device**	**Class-1 Indication per AHA/ACC/HFSA**	**Benefit**	**Comments**
	Automated implanted defibrillator (AICD)	LVEF≤ 30%, NYHA class-1, > 40 days post MI, expected to live > 1 year	Only prevents sudden cardiac death (SCD) thereby reducing mortality	Does not improve cardiac function
	Automated implanted defibrillator (AICD)	LVEF≤ 35%, NYHA class 2–3, expected to live > 1 year	Only prevents SCD thereby reducing mortality	Does not improve cardiac function
	Cardiac resynchronization therapy (CRT) with defibrillator	LVEF≤ 35%, NYHA class 2–3, or on chronic IV infusion, expected to live > 1 year, left bundle branch block on ECG with QRS duration ≥ 150 ms	Improves quality of life, reduce hospital re-admission, prevents SCD, reduce mortality	1. Can improve cardiac function in ~ 2/3 of cases 2. Can provide benefit with CRT-P (i.e., without defibrillation option)

[1]2. 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* May 3 2022;79(17):e263-e421. doi:10.1016/j.jacc.2021.12.012.

renal function, LVEF ≤ 25%, persistent NYHA class 3 to 4 symptoms, and ≥ 2 unplanned hospital visits within 12 months (admission or ER visit) (see Table 7).[34] Advanced heart failure therapy includes chronic inotropic infusions, mechanical circulatory support (MCS), and heart transplantation. Chronic inotropic infusions can bridge patients to a more permanent solution.[1] Early referral is recommended before significant end organ dysfunction, such as end stage renal disease and pulmonary hypertension, which precludes advanced therapies.

Management of Associated Conditions

Comorbidities in patients with HFrEF should be appropriately managed to prevent worsening of heart failure (Table 3). Hypertension, diabetes, atrial fibrillation, and valvular disease can all contribute to heart failure and therapy should follow published guidelines. Avoidance of excessive salt intake is reasonable to reduce congestive symptoms based on limited data.[1] IV iron in the setting of iron deficiency and heart failure is associated with decreased cardiovascular death and hospitalizations according to 2 meta-analyses.[35] The distinction between obstructive or central sleep apnea is difficult to make clinically, and treatment is dependent on the type.[1] Statins are recommended for patients with HF secondary to ischemic heart disease and can reduce HF hospitalizations.[36] Ischemia and atherosclerosis should be considered in all cases of heart failure and appropriate workup performed, which is beyond the scope of this review.

Conclusion

The most recent evidence makes several changes to the management of chronic HF. An emphasis on ARNi's and the addition of SGLT2i's lie at the heart of the changes, with the continuing strong recommendation for β blockers and MRA's. Ensure that eligible patients are on an appropriate regiment to reduce HF hospitalizations and cardiovascular mortality, and do not withdraw therapy in the setting of HFimpEF.

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