

# Evidence-Based Heart Failure Management: A Practical Guide for Hospitalists

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## ABSTRACT

Heart failure is a growing global health concern, characterized by high morbidity, frequent hospitalizations, and significant mortality. The classification of heart failure based on left ventricular ejection fraction plays a critical role in diagnosis and management, encompassing heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with improved ejection fraction (HFimpEF). While advancements in therapy have transformed HFrEF management, challenges persist in optimizing treatment for HFmrEF and HFimpEF due to their heterogeneous nature. Emerging strategies emphasize the early and simultaneous initiation of key pharmacologic therapies across these subtypes to maximize clinical benefits. Individual approaches, guided by patient characteristics and evolving evidence, are essential for improving outcomes. This narrative review provides a comprehensive overview of current treatment strategies for the different classifications of HF, highlighting the role of rapid therapy initiation.

## INTRODUCTION

Heart failure represents a significant public health burden. According to the 2019 American Heart Association (AHA) Heart Disease and Stroke Statistics report, an estimated 6.2 million Americans aged 20 and older were living with heart failure in 2016. Furthermore, its prevalence is expected to rise by 46% from 2012 to 2030, affecting more than 8 million adults aged 18 and older. This rising prevalence is attributed to aging populations, improved survival rates following myocardial infarction and other cardiovascular events, and the increasing incidence of risk factors such as hypertension, diabetes, and obesity.<sup>1</sup> These statistics high-

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light the urgent need for effective strategies to manage and prevent heart failure.

Heart failure is commonly classified based on the heart's ejection fraction (EF)—the percentage of blood ejected from the ventricle with each contraction—into heart failure with reduced EF (HFrEF, EF  $\leq$  40%), heart failure with preserved EF (HFpEF, EF  $\geq$  50%), and heart failure with mildly reduced EF (HFmrEF, EF 41%–49%) (Table 1). While HFmrEF lacks randomized controlled trials (RCTs) specific to its treatment, analyses from previous studies suggest these patients may benefit from therapies recommended for HFrEF.<sup>2,3</sup>

Additionally, a recently recognized category—heart failure with improved EF (HFimpEF)—accounts for patients whose EF improves with guideline-directed medical therapy (GDMT) but acknowledges that EF changes are not always unidirectional. EF may decline after initial improvement due to factors such as cardiotoxicity, disease progression, or withdrawal of treatment, and this decline is associated with worse outcomes. The AHA recommends the term HFimpEF for such patients, emphasizing the need for continued GDMT to maintain improved EF and prevent relapse, as EF trajectory is a critical prognostic factor in heart failure management.<sup>2</sup>

## Purpose

Heart failure remains a leading cause of hospitalization and readmissions, placing hospitalists at the forefront of its management. This review provides a concise, evidence-based guide to help hospitalists implement early interventions, including decongestion strategies and disease-modifying therapies—particularly the “four pillars” of HFrEF treatment—to reduce morbidity, mortality, and rehospitalizations. Emphasizing practical strategies for optimizing

care transitions, medication adherence, and cost considerations, this overview supports hospitalists in improving long-term outcomes for patients with heart failure.

## **PATHOPHYSIOLOGY AND CLASSIFICATION OF HEART FAILURE**

HFrEF and HFpEF share many risk factors and comorbidities, yet their underlying pathophysiology reveals significant differences. HFrEF results primarily from impaired systolic function and cardiomyocyte loss, leading to increased left ventricular filling pressures, diastolic dysfunction, and pulmonary venous congestion. These changes often culminate in right heart failure with peripheral congestion, reduced cardiac output, and end-organ hypoperfusion. In HFrEF, systemic and cardiac inflammation is typically secondary to the causes of cardiomyocyte loss, while left ventricular stiffness may vary depending on the extent of fibrosis and titin isoform shifts.

HFpEF, on the other hand, is a multifactorial condition often observed in older females with clusters of noncardiac comorbidities, such as hypertension, type 2 diabetes, and pulmonary disease. The pathophysiology of HFpEF is less understood but is characterized by low-grade systemic and cardiac inflammation, endothelial dysfunction, and capillary dysfunction. These changes precede disease progression, contributing to microvascular inflammation, cardiomyocyte hypertrophy, and fibrosis. Left ventricular stiffness in HFpEF is driven by reduced calcium signaling, titin modifications favoring stiffer isoforms, and increased perivascular and interstitial fibrosis.<sup>4</sup> These mechanisms impair diastolic filling, elevate pulmonary venous pressures, and exacerbate congestion and afterload.

Both HFrEF and HFpEF involve fibrosis, although the type and distribution differ. HFrEF often features replacement fibrosis following myocardial infarction, while HFpEF involves perivascular fibrosis linked to metabolic risks and interstitial fibrosis driven by aging and hypertension.<sup>4</sup> Neurohormonal activation—particularly of the renin-angiotensin-aldosterone system (RAAS)—exacerbates fluid retention and vasoconstriction in both conditions, contributing to intravascular congestion.<sup>5</sup> Additionally, endothelin-1, a potent vasoconstrictor, amplifies vascular smooth muscle contraction and afterload.

The natriuretic peptide system, including atrial natriuretic peptide and brain natriuretic peptide, counterbalances neurohormonal activation by promoting vasodilation, natriuresis, and diuresis. However, the clearance of natriuretic peptides by neprilysin and other enzymes can limit their protective effects, further exacerbating heart failure symptoms.<sup>6</sup> This is the basis of sacubitril, a neprilysin inhibitor in the combination drug sacubitril/valsartan, a first-in-class angiotensin receptor/neprilysin inhibitors (ARNI).<sup>6</sup>

Inflammation plays a pivotal role in both HFrEF and HFpEF. Cytokines such as tumor necrosis factor, transforming growth factor beta (TGF-β), interleukin-6, and interleukin-1 contribute to

### **Box. Abbreviations**

- EF:** ejection fraction
- HFrEF:** heart failure with reduced ejection fraction
- HFmrEF:** heart failure with mid-range ejection fraction
- HFimpEF:** heart failure with improved ejection fraction
- HFpEF:** heart failure with preserved ejection fraction
- GDMT:** guideline-directed medical therapy
- MI:** myocardial infarction
- RAAS:** renin-angiotensin-aldosterone system
- VTE:** venous thromboembolism
- ARNI:** angiotensin receptor/neprilysin inhibitors
- ACEI:** angiotensin converting enzyme inhibitor
- ARB:** angiotensin II receptor blocker
- MRA:** mineralocorticoid receptor antagonist
- SGLT2i:** sodium-glucose cotransporter 2 inhibitors
- RALES:** Randomized Aldactone Evaluation Study
- PARADIGM-HF:** Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
- NYHA:** New York Heart Association
- LVEF:** left ventricular ejection fraction
- DAPA-HF:** Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
- EMPEROR-Reduced:** Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction
- EMPEROR-Preserved:** Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction
- TRED-HF:** Withdrawal of Pharmacological Treatment for Heart Failure in Patients With Recovered Dilated Cardiomyopathy
- EPHESUS:** Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
- HF-ACTION:** Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
- CHAMPION:** CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients
- GUIDE-HF:** Hemodynamic-GUIDEd Management of Heart Failure

**Table 1.** Heart Failure Classification

<b>Heart Failure Type</b>	<b>Ejection Fraction</b>	<b>Key Characteristics</b>
HFrEF (Reduced EF)	EF ≤ 40%	Impaired systolic function: Heart cannot pump blood effectively. Commonly caused by ischemic heart disease or MI. <sup>2</sup>
HFmrEF (Mid-Range EF)	EF 41%-49%	Intermediate group with both systolic and diastolic dysfunction. Etiology and treatment often overlap with HFrEF. <sup>2,3</sup>
HFimpEF (Improved EF)	EF > 40% after being ≤ 40%	Indicates improvement in systolic function; typically seen in patients with effective medical or device therapy. <sup>2</sup>
HFpEF (Preserved EF)	EF ≥ 50%	Predominantly diastolic dysfunction; normal pumping but impaired filling. Common in older adults and women. <sup>4,5</sup>

endothelial dysfunction, pulmonary edema, and left ventricular impairment.

Additionally, comorbidities such as diabetes, obesity, and chronic kidney disease contribute to chronic low-grade inflammation, further perpetuating worsening heart failure. The research into anti-cytokine and anti-inflammatory therapies is ongoing.<sup>7</sup>

## MANAGEMENT OVERVIEW

### Inpatient Heart Failure Management

Effective inpatient heart failure management begins with a comprehensive clinical evaluation to assess hemodynamic profiles, evaluate congestion severity, and determine perfusion adequacy. Cardiogenic shock necessitates immediate multidisciplinary intervention and adherence to established guidelines. Timely identification of acute coronary syndrome is critical, as urgent revascularization may be required. In cases without ischemic disease, inflammatory heart conditions should be considered—particularly those presenting with conduction blocks or ventricular arrhythmias. Most heart failure admissions result from gradual worsening of preexisting structural heart disease, often triggered by factors such as arrhythmias, ischemia, or comorbidities. Patients presenting with pulmonary edema and severe hypertension require rapid blood pressure reduction, especially those with HFpEF.<sup>8</sup> Care plans should prioritize addressing precipitating factors, managing comorbidities, and optimizing GDMT to improve outcomes.

Hospitalization is a pivotal opportunity to initiate, maintain, or adjust GDMT—particularly for patients with HFrEF. Continuing GDMT during hospitalization reduces postdischarge mortality and readmission risks, while initiating GDMT during the hospital stay provides significant clinical benefits.<sup>9</sup> Intravenous loop diuretics remain the cornerstone of congestion management, with dose adjustments or the addition of thiazide diuretics or mineralocorticoid receptor antagonists (MRAs) when needed.<sup>8</sup>

Resolving congestion before discharge is crucial, as persistent congestion increases the risks of rehospitalization and mortality. Patients who were started on loop diuretics during hospitalization and were prescribed loop diuretics at discharge had a significantly lower risk of 30-day readmission.<sup>10</sup> Heart failure hospitalization also significantly increases the risk of venous thromboembolism (VTE), particularly within the first 30 days post-discharge but also long term.<sup>11</sup> Prophylactic anticoagulation with agents such as low-molecular-weight heparin, unfractionated heparin, or direct oral anticoagulants is recommended to prevent deep vein thrombosis and pulmonary embolism in high-risk patients.<sup>12</sup>

Monitoring serum electrolytes is a critical component of acute heart failure management, as imbalances are common and closely linked to adverse outcomes. Both hypokalemia ( $K^+ < 4.0$  mmol/L) and hyperkalemia ( $K^+ > 5.5$  mmol/L) are independently associated with increased morbidity and mortality. Hyperkalemia has become more prevalent since the introduction of RAAS inhibitors, particularly following the RALES trial, which highlighted the benefits of

spironolactone in severe heart failure.<sup>13</sup> The availability of newer potassium-lowering agents, such as patiromer and sodium zirconium cyclosilicate, offers promising options to manage hyperkalemia and facilitate the initiation or up-titration of RAAS inhibitors.

Sodium levels also warrant careful attention—hyponatremia ( $Na^+ < 135$  mEq/L) is associated with a higher risk of complications, including cognitive impairment, falls, prolonged hospitalization, readmission, and all-cause mortality. Similarly, hypomagnesemia ( $Mg^{2+} < 1.9$  mg/dL), which affects up to one-third of patients with heart failure, is a significant risk factor for ventricular arrhythmias and sudden cardiac death.<sup>14</sup> Given these risks, routine electrolyte monitoring and timely correction during acute heart failure hospitalization are essential to improve clinical outcomes and ensure the safe implementation of GDMT. Combining comprehensive hemodynamic assessment, optimization of GDMT, effective congestion management, and preventive measures for VTE forms the foundation of effective inpatient heart failure management.

### Pharmacologic Management by Subtype

#### HFrEF

Management of HFrEF has advanced significantly, with contemporary GDMT emphasizing a quadruple therapy approach: ARNI,  $\beta$ -blockers, MRAs, and sodium-glucose cotransporter 2 (SGLT2) inhibitors.<sup>2,15,16</sup> Evidence strongly supports initiating all four drug classes in patients with HFrEF due to their additive life-saving effects. A 2020 analysis showed that 65-year-old patients receiving all four classes gained 4.4 additional life-years compared to those treated with only an angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) and  $\beta$ -blocker.<sup>17</sup> Similarly, a 2022 systematic review and network meta-analysis found that combined treatment with all four drug classes was the most effective in improving outcomes among therapy combinations and extended life expectancy by 7.9 years in 50 years compared to no treatment.<sup>18</sup> For a 70-year-old patient, the use of all four therapies added 5 life-years compared to no treatment. These findings highlight the compounding benefits of comprehensive GDMT and underscore the urgency of initiating and optimizing all four therapies to maximize survival and quality of life for patients with HFrEF.

ARNI—particularly sacubitril/valsartan—has demonstrated superiority over ACEIs in reducing cardiovascular death and hospitalization for heart failure in the PARADIGM-HF trial and is now first-line treatment.<sup>2,19,20</sup> Patients receiving ACEIs or ARBs should transition to ARNI. However, 36 hours should pass before switching from ACEIs due to the risk of angioedema. ACEIs and ARBs are alternatives for patients unable to tolerate ARNI. Caution is required in patients with severe renal impairment or hyperkalemia, and regular monitoring of renal function and electrolytes is necessary.

$\beta$ -blockers—specifically bisoprolol, carvedilol, and sustained

release metoprolol succinate—have proven mortality benefits in HFrEF, which are observed within weeks of initiation and include reduced risk of death and hospitalization.<sup>21</sup> Importantly,  $\beta$ -blockers should be rapidly up-titrated to optimal doses as tolerated.<sup>22</sup> Potential side effects include bradycardia, fatigue, hypotension, and worsening heart failure in the initial stages. They should be avoided in patients with bradycardia and second- or third-degree heart block in the absence of a pacemaker.<sup>23</sup> Monitoring heart rate and blood pressure is essential during initiation and titration.

MRAs such as spironolactone and eplerenone reduce mortality and hospitalization in patients with New York Heart Association (NYHA) class II–IV HFrEF.<sup>24</sup> They are recommended for patients with an estimated glomerular filtration rate  $>30$  mL/min/1.73 m<sup>2</sup> and serum potassium  $<5.0$  mEq/L. Potential side effects include hyperkalemia—particularly in patients with impaired renal function—and gynecomastia with spironolactone. Potassium levels should be monitored, and potassium binding agents can be used to mitigate hyperkalemia when necessary. MRAs should be discontinued if serum potassium exceeds 5.5 mEq/L.<sup>2</sup> In addition to the steroidal MRAs, finerenone—the first US Food and Drug Administration-approved nonsteroidal MRA—has shown efficacy in heart failure and chronic kidney disease, with significant improvements in both kidney and cardiovascular outcomes.<sup>25</sup>

SGLT2 inhibitors, including dapagliflozin and empagliflozin, are a major addition to HFrEF treatment. The DAPA-HF trial and the EMPEROR-Reduced trial demonstrated that these agents reduce the risk of cardiovascular death and hospitalization by approximately 25%.<sup>26</sup> However, potential side effects include urinary tract infections, dizziness, hyperkalemia, edema, and kidney failure.<sup>27</sup> The high cost of these medications also may limit accessibility for some patients.<sup>28</sup> Hospitalists and outpatient clinicians should carefully monitor patients for these adverse effects and educate them about recognizing early signs of complications.

Hydralazine and isosorbide dinitrate H-ISDN remains a class I treatment recommendation for African American patients with NYHA class III–IV HFrEF. However, these therapies should be initiated only after optimizing the quadruple GDMT regimen.<sup>2</sup> The push to initiate all four pillars of GDMT as rapidly as possible is grounded in evidence showing that benefits accrue within days to weeks of initiation. Clinicians should prioritize up-titrating each medication to the target or maximally tolerated doses to achieve optimal outcomes. Coordination across care teams and patient education about adherence and side effects are essential to the therapy's success.

Intravenous (IV) ferric carboxymaltose (FCM) has been shown in some trials to improve NYHA functional class, 6-minute walk distance, and quality of life in patients with iron deficiency anemia and chronic heart failure,<sup>29</sup> whereas other studies have not demonstrated significant improvements in these functional outcomes. However, all trials consistently show that IV FCM significantly reduces the risk of total heart failure hospitalizations.<sup>30</sup>

### **HFmrEF**

There are no prospective RCTs specifically targeting patients with HFmrEF. Current evidence for managing HFmrEF comes primarily from post hoc analyses and subsets of data from heart failure trials, where patients were retrospectively categorized as having HFmrEF. Left ventricular ejection fraction (LVEF) exists on a continuum, and among individuals with LVEF within the range of 41% to 49%, those with lower values appear to respond to GDMT similarly to patients with HFrEF. Therefore, it is reasonable to apply HFrEF treatment protocols to patients in this subgroup, including SGLT2 inhibitors (SGLT2i),  $\beta$ -blockers, ARNI/ACEI/ARB, and MRAs.<sup>2,15</sup> Supporting this approach, the EMPEROR-Preserved trial demonstrated significant clinical benefits of the SGLT2i empagliflozin in patients with symptomatic heart failure and a LVEF greater than 40%.<sup>31</sup> Additionally, post hoc analyses of trials for HFrEF that included patients with LVEF of 41% to 49% suggest that these individuals may derive benefit from GDMT traditionally used in HFrEF management.<sup>32</sup> Repeat assessments of LVEF are recommended for patients with HFmrEF to monitor disease progression and guide therapy adjustments.

### **HFpEF**

HFpEF has historically been challenging to manage pharmacologically due to limited evidence of benefit from many therapies. However, recent clinical trials have provided guidance on effective strategies for treatment of HFpEF, emphasizing GDMT.<sup>33</sup> Primary goals include managing hypertension by titrating blood pressure within an appropriate target range and addressing associated conditions, such as atrial fibrillation, to improve symptoms and outcomes. Managing atrial fibrillation in patients with HFpEF can improve symptoms and overall quality of life. Chronic anticoagulant therapy is recommended for patients with chronic heart failure and permanent, persistent, paroxysmal atrial fibrillation and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or greater for men and 3 or greater for women.<sup>34</sup> Additionally, direct oral anticoagulants are generally preferred over warfarin in eligible patients, based on cost, drug-drug interactions, or other indications.<sup>35</sup> Rhythm control strategies, including catheter ablation or anti-arrhythmic therapy, may be considered based on individual patient characteristics and symptom burden. In the 2 largest RCTs comparing ablation to either amiodarone or standard medical therapy, catheter ablation resulted in absolute risk reductions in death or hospitalization of 10% and 16.5%, respectively.<sup>36,37</sup> Diuretic agents should be used judiciously to alleviate congestion and improve symptoms in patients with HFpEF. The goal is symptom relief while minimizing the risk of volume depletion, electrolyte imbalances, or worsening kidney function.<sup>2</sup>

SGLT2 inhibitors have a Class 2a recommendation and should be initiated in all individuals with HFpEF barring contraindications. These agents have demonstrated significant cardiovascular benefits, including reduced hospitalization for heart failure and

cardiovascular death across all EF subgroups.<sup>31</sup> SGLT2 inhibitors are effective in both ambulatory patients with HFpEF and those with acutely decompensated heart failure. Evidence suggests their benefit is additive to other GDMT, including MRAs and ARNIs.<sup>38</sup> Meta-analyses indicate a consistent reduction in the composite endpoint of heart failure hospitalization and cardiovascular death (hazard ratio [HR], 0.80; 95% CI, 0.73-0.87) in individuals with HFmrEF and HFpEF.<sup>39</sup>

MRAs, ARNIs, and ARBs each have a Class 2b recommendation—particularly for patients with LVEF at the lower end of the HFpEF spectrum.<sup>33</sup> MRAs, such as spironolactone, may reduce hospitalizations in selected subsets of patients with HFpEF. While they have not consistently shown improvements in quality of life or exercise tolerance, MRAs provide balanced diuresis, hypertension control, and reduction in hospitalization rates.<sup>39</sup> ARNIs, such as sacubitril/valsartan, inhibit neprilysin, which augments natriuretic peptides, bradykinin, and substance P to counteract heart failure progression. Although the primary composite endpoint of total heart failure hospitalizations and cardiovascular death was numerically lower with sacubitril/valsartan versus valsartan (HR, 0.87; 95% CI, 0.75-1.01), it did not reach statistical significance, but ARNIs are recommended for their comprehensive cardiovascular effects.<sup>40</sup> ARBs, such as valsartan, serve as a viable alternative when ARNIs are contraindicated or not feasible (eg, due to history of angioedema or financial constraints). Though less effective than ARNIs, ARBs can aid in hypertension control and reducing heart failure-related hospitalizations.<sup>41</sup> For all three classes, careful titration based on patient tolerance, symptoms, blood pressure, potassium levels, and renal function is essential. The management of HFpEF has evolved significantly, with evidence supporting the use of SGLT2 inhibitors, MRAs, ARNIs, and ARBs. These therapies, tailored to individual patient profiles and contraindications, form the cornerstone of modern HFpEF treatment strategies. Achieving optimal blood pressure control and addressing comorbid conditions—such as atrial fibrillation—are critical for improving outcomes. Careful titration and monitoring are essential to maximize therapeutic benefits and minimize adverse effects.

### ***HFimpEF***

In patients with HFimpEF, GDMT should be continued. The TRED-HF trial showed that 44% of patients who recovered, became asymptomatic, and were weaned off therapy experienced a relapse, compared with none of the patients who remained on treatment.<sup>42</sup> Improvement in symptoms, cardiac function, and biomarkers after therapy indicates remission rather than complete and sustained recovery, emphasizing the importance of maintaining treatment to prevent relapse.

### **Diuresis in Heart Failure**

Diuretic therapy is essential in the management of heart failure because of its role in alleviating congestion by reducing fluid retention. Loop diuretics, such as furosemide, bumetanide, and torse-

mide, are the cornerstone of therapy because of their potent natriuretic effects.<sup>8</sup> They act on the thick ascending limb of the loop of Henle, inhibiting the sodium-potassium-chloride cotransporter to enhance sodium and water excretion. In heart failure, neurohormonal activation and hemodynamic changes promote sodium retention, making loop diuretics crucial in overcoming these compensatory mechanisms.<sup>43</sup> Despite their efficacy, prolonged use may lead to diuretic resistance, characterized by increased sodium reabsorption in the distal nephron. The addition of thiazide diuretics, such as hydrochlorothiazide or metolazone, can enhance diuresis in resistant cases.<sup>8</sup> Furthermore, the addition of 50 mg of hydrochlorothiazide per day to usual care in patients with acute decompensated heart failure was associated with improved diuretic efficiency (defined as greater weight loss per dose of intravenous furosemide); however, no statistically significant differences were observed in mortality, symptom burden, or congestion.<sup>44</sup> Loop diuretic dosing should be tailored to clinical status, with hospitalized patients typically requiring higher IV doses. Careful monitoring of urine output and volume status is necessary to prevent excessive depletion while GDMT. By integrating diuretic therapy with GDMT, clinicians can improve symptom control and patient outcomes.

### **Sequencing/Implementation Strategies of GDMT in HFrEF**

The traditional approach to implementing GDMT in heart failure has involved starting each drug class consecutively and gradually up-titrating to the maximally tolerated dose before moving to the next class. Historically, this sequence began with an ACEI, followed by a  $\beta$ -blocker, MRA, and eventually switching ACEI to ARNI and adding SGLT2i. This method, endorsed by earlier guidelines, emphasized stabilization and symptom monitoring at each stage before progressing to additional therapies. For example, the 2008 European Society of Cardiology guidelines recommended up-titrating.<sup>45</sup> However, emerging evidence suggests that a faster approach to initiating and titrating GDMT may provide superior outcomes. Rapid initiation and up-titration have been shown to achieve significant clinical benefits as early as 2 to 4 weeks after therapy initiation. An analysis by Shen et al using data from large RCTs found that faster sequencing strategies reduced cardiovascular death or hospitalizations by as much as 47 events per 1000 patients compared to slower sequencing.<sup>46</sup>

#### ***Starting Two Drugs Simultaneously***

Packer and McMurray advocate for initiating 2 drugs at once, such as a  $\beta$ -blocker and SGLT2i, followed by ARNI and MRA within 2 weeks. This approach seeks to balance rapid optimization with tolerability, leveraging the early benefits of key therapies.<sup>43</sup>

#### ***Starting All Four Drugs Simultaneously at Low Doses***

An alternative proposed by Greene et al involves initiating all four major drug classes— $\beta$ -blocker, ARNI, MRA, and SGLT2i—simultaneously at low doses, followed by gradual up-titration to target doses.<sup>47</sup> This strategy builds on evidence

from the EPHEsus trial, which demonstrated that patients with de novo heart failure could tolerate simultaneous initiation of ACEI,  $\beta$ -blocker, and MRA therapy after acute myocardial infarction.<sup>48</sup> The authors argue that tolerability for other patients with HFrEF should be comparable.

### ***Tailored Sequencing Based on Patient Profiles***

Rosano et al suggest adjusting the sequencing strategy based on patient-specific physiological profiles. For example, patients with low blood pressure and heart rate might benefit from starting with SGLT2i and MRA, whereas those with normal blood pressure and higher heart rates could begin with a  $\beta$ -blocker and ARNI.<sup>49</sup> Traditional sequential GDMT implementation allows for careful monitoring and adjustment but delays the introduction of potentially life-saving therapies. In contrast, faster or simultaneous initiation strategies prioritize early comprehensive treatment, which may reduce mortality and hospitalization. Tailored approaches further enhance therapy sequencing by incorporating patient-specific factors, such as blood pressure, heart rate, and comorbidities. These newer strategies challenge the stepwise approach by emphasizing the urgency of initiating multiple therapies early, with the choice of method guided by patient characteristics, clinical stability, and tolerability to achieve optimal outcomes.

### **Dietary/Lifestyle Recommendations**

Lifestyle and dietary changes are key components in the management of heart failure, helping to alleviate symptoms, improve quality of life, and potentially reduce hospitalizations. While pharmacological treatments remain central to management of heart failure, appropriate modifications to diet and physical activity can enhance patient outcomes.

The AHA recommends a general sodium intake limit of <2300 mg/day for cardiovascular health, though there is insufficient evidence to support this level of restriction specifically for patients with heart failure. While sodium restriction is commonly advised, studies have shown mixed results regarding its impact on clinical outcomes in patients with heart failure.<sup>50</sup> The Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in antioxidants and potassium, can help achieve sodium restriction without compromising nutritional adequacy. The DASH diet also may be associated with reduced hospitalizations for heart failure. A registered dietitian- or nurse-coached intervention that included a sodium restriction of 2-3g/day improved NYHA functional class and reduced leg edema in patients with HFrEF.<sup>51</sup> However, extreme sodium restrictions (eg, <2.5 g/day) have not demonstrated consistent benefits in terms of clinical outcomes, such as mortality or hospital readmissions. Recent pilot studies have explored the effects of different levels of sodium restriction, including providing meals with 1.5 g/day sodium. Some studies suggest that such interventions can reduce urinary sodium excretion and improve quality of life but have not led to improvements in clinical outcomes.<sup>52</sup> Additionally, patients with heart failure often find it challenging

to adhere to dietary sodium restrictions—even with prepared meals or home visits. These findings highlight the complexity of sodium restriction and the need for individualized dietary counseling to optimize management.

Fluid restriction is another important consideration in managing heart failure, particularly for patients experiencing symptoms of volume overload. While there is some evidence suggesting that fluid and sodium restriction interventions can improve symptoms such as leg edema and NYHA functional classification in patients with HFrEF, the overall clinical impact on hospitalization and mortality rates remains uncertain.<sup>2</sup> A meta-analysis of RCTs examining fluid restriction in heart failure found no significant benefit in terms of reduced hospitalizations or mortality. Similarly, fluid restriction did not substantially improve other markers, such as serum sodium levels, serum creatinine, or the duration of IV diuretic use.<sup>2</sup> Despite these mixed results, careful fluid management remains a cornerstone of symptom control in heart failure, particularly in patients with significant volume overload.

Exercise training provides numerous benefits for patients with heart failure and is safe when appropriately implemented. The HF-ACTION trial, which included 2331 patients with a LVEF of 35% or less, demonstrated that exercise training combined with usual care led to modest reductions in cardiovascular mortality and hospitalizations, particularly after prespecified adjustments.<sup>53</sup> Meta-analyses of several smaller trials have shown that exercise training improves functional capacity, exercise duration, and health-related quality of life and reduces the frequency of hospitalizations for heart failure.<sup>54</sup> Cardiac rehabilitation programs, which incorporate medical evaluation, education, psychosocial support, and structured exercise, are recommended for stable patients receiving optimal GDMT and able to participate in physical activity.<sup>55</sup> Dietary and lifestyle modifications, such as sodium restriction, fluid management, and exercise, are important adjuncts to pharmacologic therapy. Although evidence for strict sodium restriction is mixed, adherence to dietary recommendations such as the DASH diet and moderate sodium restriction can help improve symptoms and reduce hospitalizations. A tailored approach that combines dietary guidance from a registered dietitian with participation in cardiac rehabilitation can significantly enhance outcomes and quality of life for patients with heart failure.

### **CardioMEMS**

CardioMEMS has emerged as a transformative tool in heart failure management, advancing beyond traditional noninvasive monitoring methods such as weight, heart rate, blood pressure, and subjective symptoms like dyspnea. Based on microelectromechanical systems (MEMS) technology, CardioMEMS directly targets hemodynamic congestion, which often precedes clinical symptoms by several weeks. The device consists of a small sensor implanted in the pulmonary artery that enables continuous,

real-time measurement of pulmonary artery pressures. Data are wirelessly transmitted to clinicians, allowing proactive therapy adjustments before decompensation occurs. This preemptive strategy has demonstrated substantial clinical impact; studies show CardioMEMS significantly reduces heart failure–related hospitalizations, with real-world data suggesting a 57% reduction—surpassing outcomes observed in controlled settings such as the CHAMPION trial and the GUIDE-HF trial.<sup>56</sup> Reflecting its clinical utility, the AHA and American College of Cardiology have granted a Class IIb recommendation for CardioMEMS use in select adults with heart failure.<sup>2</sup>

Despite these benefits, limitations remain. Safety is a concern; within the first 3 years of approval, more than 5500 devices were implanted in the United States, with at least 155 unique adverse events reported, reflecting a complication rate of approximately 2.8%. Patient selection is critical because certain populations are contraindicated for implantation, including those with active infection, history of pulmonary embolism or deep vein thrombosis, congenital heart disease, indwelling mechanical right heart valves, or coagulation disorders.<sup>56</sup> Furthermore, the procedure requires right heart catheterization, which some patients may not tolerate because of comorbid conditions or procedural risk. Cost also presents a barrier; CardioMEMS is substantially more expensive than standard care, with reported costs ranging from approximately \$25 963 in the United Kingdom to \$201 437 in the United States, limiting accessibility in resource-constrained settings.<sup>56</sup> These factors underscore the need for careful patient selection and cost-benefit evaluation when considering CardioMEMS in routine heart failure management.

## CONCLUSIONS

Heart failure remains a major clinical challenge, requiring patient-centered, evidence-based management. Advances in classification and therapy have led to the “four pillars” approach in HFrEF, improving survival and reducing hospitalizations. Hospitalists play a key role in optimizing inpatient care, ensuring effective decongestion, timely GDMT initiation, and smooth transitions to outpatient management. Although SGLT2 inhibitors show promise across EF ranges, HFpEF and HFmrEF lack well-defined treatments, necessitating further research. Emerging strategies in HFrEF emphasize earlier and more aggressive GDMT implementation to enhance outcomes. Beyond pharmacologic therapy, lifestyle modifications such as sodium restriction and structured exercise improve quality of life. Future heart failure management will incorporate novel pharmacotherapies, regenerative medicine, and artificial intelligence-driven precision care to address treatment gaps, particularly in HFpEF.

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**Table 2.** Heart Failure Management Summary

Type	Management	
HFrEF	Quadruple therapy: ARNI (or ACEI/ARB if intolerant), β-blockers, MRAs, and SGLT2i <sup>2,15,16,27</sup>	Rapid initiation and up-titration are recommended
HFmrEF	Treated similarly to HFrEF with the same quadruple therapy <sup>2,15</sup>	
HFpEF	2A: SGLT2i. <sup>31,57</sup> 2B: MRAs, ARNIs, and ARBs <sup>33</sup>	Key goals: managing hypertension, addressing comorbidities (eg, atrial fibrillation), and relieving congestion
HFimpEF	Continuation of HFrEF therapies is crucial <sup>42</sup>	

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