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The Role of the Four Pillars in Heart Failure with Reduced Ejection Fraction (HFrEF) and Heart Failure with Preserved Ejection Fraction (HFpEF): How Different?

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KEYWORDS

HFrEF, HFpEF, four pillars of therapy, SGLT2 inhibitors, heart failure

ABSTRACT

Heart failure (HF) remains a major clinical challenge, with two main phenotypes: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). These conditions exhibit distinct pathophysiology, clinical manifestations, and therapeutic responses, requiring distinct management approaches. The four pillars of HFrEF therapy—renin-angiotensin system (RAS) inhibitors, β-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors—have been shown to reduce mortality and morbidity. In contrast, HFpEF management focuses more on risk factor control and symptom-based therapy, with SGLT2 inhibitors being the only treatment that has shown significant clinical benefit. This literature review aims to evaluate the different roles of the four pillars of therapy in both phenotypes of heart failure and their implications for clinical practice. Although HFrEF treatment has made significant progress with strong clinical trial evidence, HFpEF management still requires further exploration to identify more effective strategies. Therefore, a deeper understanding of each phenotype's pathophysiology and therapeutic response is essential to improve patient outcomes and optimize heart failure management.

INTRODCUTION

Heart failure (HF) is a condition caused by structural or functional abnormalities of the heart with elevated natriuretic peptide levels and objective evidence of pulmonary or systemic congestion (Bozkurt et al., 2021). HF is a global health problem worldwide (Feng et al., 2024). It affects millions of people worldwide, resulting in high morbidity and mortality (Rahamim et al., 2021). Economically, HF imposes an economic burden on health care systems, especially in low and middle income countries where access to health care is a challenge (Mahmood et al., 2024).

According to 2019 global data, 56.19 million cases of HF have been reported worldwide, with a marked increasing between 1990 and 2019, especially in developing countries increasing (Yan et al., 2023). In the United States, more than 6 million people are living with HF (Virani et al., 2020). According to the 2019 Global Burden of Disease (GBD) data, the age-adjusted prevalence of HF in Asia ranges from 211.86 to 1,032.84 cases per 100,000 population, with China (1,032.84 cases), Indonesia (900.90 cases), and Malaysia (809.47 cases) had the highest rates. In contrast, Nepal (211.86 cases), Bhutan (255.54 cases), and Bangladesh (275.00 cases) had lowest HF prevalence (Feng et al., 2024).

Based on left ventricular ejection fraction (LVEF), HF is classified into three main

categories: according to the 2021 European Society of Cardiology (ESC) guidelines, HFrEF is defined as HF with EF ≤ 40%, while HFpEF is characterized by an EF ≥ 50%. In addition, HFmrEF (heart failure with slightly reduced ejection fraction) with EF ranging from 41% and 49% was previously classified as mid-range heart failure (Bozkurt et al., 2021; Rahamim et al., 2021). HFmrEF accounts for approximately 10–25% of all heart failure cases and shares more with HFrEF than HFpEF in share characteristics (Laksono, 2023).

The pathophysiological differences between HFrEF and HFpEF involve multiple mechanisms, including systemic inflammation, endothelial dysfunction, cardiomyocyte hypertrophy, titin protein alterations, and myocardial fibrosis (Simmonds et al., 2020). HFrEF is typically characterized by impaired myocardial contractility due to ventricular remodeling, leading to decreased cardiac output. In contrast, HFpEF is primarily associated with impaired ventricular relaxation, resulting in increased filling pressures without significant reduction in EF.

HF management involves four main therapeutic pillars: pharmacotherapy, device therapy, non-pharmacological management, and management of comorbidities. Pharmacotherapy includes angiotensin-neprilysin receptor blockers (ARNIs), β-blockers, MRAs, and SGLT2 inhibitors, which are effective in improving the prognosis in HFrEF patients. However, the effectiveness of pharmacological therapy in HFpEF is still an evolving area of research. Device therapies such as implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) are more commonly used in HFrEF patients with specific indications, while HFpEF management focuses on controlling comorbidities, including hypertension, obesity, and metabolic disorders (Bozkurt et al., 2021).

Several previous studies have comprehensively discussed the pathophysiology and clinical characteristics of HFrEF and HFpEF. For instance, Simmonds et al. (2020) and Schwinger (2020) have explored the cellular and molecular differences between both phenotypes, while Haydock and Flett (2022) and Murphy et al. (2020) emphasized the clinical diagnosis and prognostic implications of HFrEF. In terms of therapy, Docherty et al. (2022), Straw et al. (2021), and Tromp et al. (2022) presented strong evidence regarding the effectiveness of the four foundational drugs—ARNIs, beta-blockers, MRAs, and SGLT2 inhibitors—in improving outcomes for HFrEF. However, evidence for HFpEF remains inconsistent and limited. Studies such as CHARM-Preserved (Docherty et al., 2022) and EMPEROR-Preserved (Mahmood et al., 2024) provide partial insights, but no consensus has been reached regarding optimal pharmacological strategies for HFpEF patients. This gap in therapeutic clarity, especially for HFpEF, highlights the need for a comparative analysis that not only outlines current evidence but also evaluates the distinct effectiveness of these four pillars in both HF phenotypes.

Despite significant advances in HFrEF therapy, the optimal treatment option for HFpEF remains a challenge. Investigating the effectiveness of the four pillars of therapy in each HF subtype is essential to develop a more targeted treatment approach. Therefore, this study aims to analyze the differences in the roles of the four pillars of therapy in HFrEF and HFpEF to provide deeper insight into the appropriate treatment strategy for both conditions.

METHOD RESERACH

This study employed a narrative literature review approach to explore and compare the effectiveness of the four main pillars of heart failure therapy in patients with Heart Failure with Reduced Ejection Fraction (HFrEF) and Heart Failure with Preserved Ejection Fraction (HFpEF). The review focused on identifying clinical trials, systematic reviews, and meta-analyses published between 2018 and 2024 that discussed therapeutic outcomes of angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists

(MRAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors in HFrEF and HFpEF populations.

The literature search was conducted using electronic databases including PubMed, Scopus, and ScienceDirect. The following keywords were used in various combinations: "heart failure," "HFrEF," "HFpEF," "four pillars," "ARNI," "beta-blockers," "mineralocorticoid receptor antagonists," "SGLT2 inhibitors," "clinical outcomes," and "therapy response." Articles were included if they met the following criteria: (1) published in English, (2) involved adult human subjects, (3) provided comparative or outcome-based data related to at least one of the four treatment pillars in either HFrEF or HFpEF patients, and (4) were peer-reviewed.

Data were synthesized descriptively to highlight the differences in pharmacologic effectiveness, mortality and morbidity outcomes, and clinical recommendations for each type of heart failure. No statistical meta-analysis was performed, as the goal of this review was to provide a narrative comparison supported by existing evidence.

RESULT AND DISCUSSION

A. Definition of *Heart Failure with Reduced Ejection Fraction* (HFrEF)

Heart failure with reduced ejection fraction (HFrEF) is a subtype of heart failure characterized by the presence of clinical signs of heart failure, physical signs of congestion and hypoperfusion, and objective evidence of left ventricular dysfunction with left ventricular ejection fraction (LVEF) of <40% (Haydock & Flett, 2022; Murphy et al., 2020). The condition results from excessive activation of the sympathetic nervous system and neurohormonal axis, including the renin-angiotensin-aldosterone system, which initially serves as a compensatory mechanism but becomes maladaptive over time. The resulting fluid retention, hemodynamic changes, and increased myocardial fibrosis contribute to progressive left ventricular dysfunction (Haydock & Flett, 2022).

B. Definition of *Heart Failure with Preserved Ejection Fraction* (HFpEF)

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome of heart failure characterized by the presence of heart failure symptoms and signs but normal or near normal (≥50%) LVEF (Naing et al., 2019). Unlike HFrEF, which has a mechanism, HFpEF is not a single disease entity, but rather the result of a variety of conditions affecting left ventricular diastolic function. This complexity makes the diagnosis and management of HFpEF more challenging; the prevalence of HFpEF is increasing with an aging population and increasing risk factors such as hypertension, diabetes, and obesity. In addition, the diagnosis of HFpEF requires a comprehensive echocardiography evaluation, including assessment of left ventricular volume, left atrial volume, and diastolic function. These complexities pose significant challenges in managing patients with HFpEF, especially in an already overburdened global healthcare system (Naing et al., 2019).

C. Prevalence and Incidence of Heart Failure

Globally, it is estimated that approximately 60 million people are living with heart failure (Vos et al., 2020). The prevalence of heart failure varies between 0.37% and 6% across countries (Figure 1), according to the Global Burden of Disease (GBD) study, the prevalence of heart failure increased by 29.4% from 2010 to 2019, with approximately 69.2% of heart failure patients reside in low- and middle-income countries (Shahim et al., 2023; Wei et al., 2023).

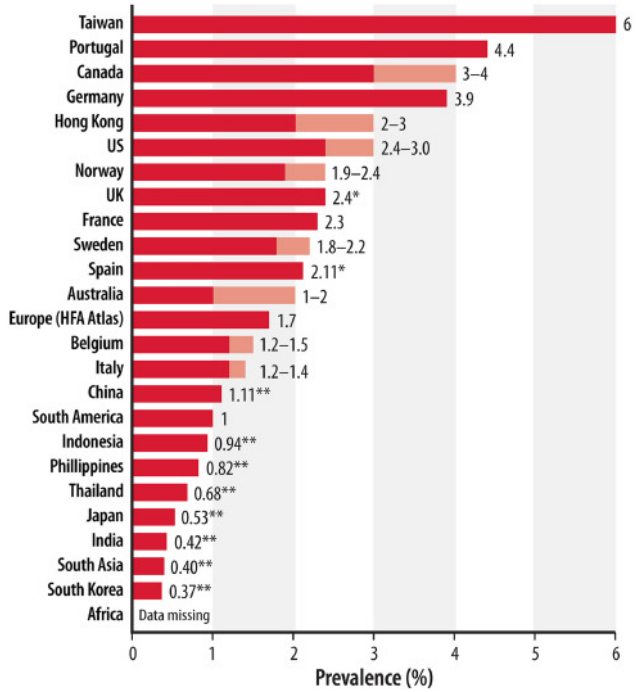

Figure. 1 Global prevalence of heart failure (Bozkurt et al., 2021)

In addition, the demographic distribution of heart failure patients varies widely worldwide. In Asia-Pacific, the Middle East, and America in particular, younger people are at higher risk of developing hearth failure, with the average age of HFrEF patients about 10 years younger than those in Europe and North America (Elasfar et al., 2020; Groenewegen et al., 2020). In sub-Saharan Africa, more than half of heart failure patients are younger than 55 years (Agbor et al., 2018). Denmark data indicate a trend toward a lower average age of heart failure onset. Specifically, the proportion of patients under 50 years of age diagnosed with heart failure doubled from 3% in 1995 to 6% in 2012 (Christiansen et al., 2017). Whether this earlier onset is due to increased awareness of heart failure, or whether biological and epidemiological factors are also contributing, its unclear. Nevertheless, these findings emphasize that heart failure is not limited to the elderly; data on the various hearth failure phenotypes classified by EF are limited; prevalence data from various global databases from the three heart failure phenotypes by LVEF classification are shown in Figure 2 (Bozkurt et al., 2021).

	HFrEF EF <40%	HFmEF EF = 40-49%	HFpEF EF ≥50%
European Society of Cardiology (ESC) long-term registry (n=9138)[a]	60%	24%	16%
Global Congestive Heart Failure Registry (G-CHF) (n=23,047)[b]	54%	21%	24%
Asian Sudden Cardiac Death in Heart Failure Registry (ASIAN-HF) (n=6480)[c]	81%	NR	~16%
Japan (n=1245)[d]	36%	21%	43%
HF in Five African Countries: INTERnational Congestive Heart Failure Study (INTER-CHF) Study (n=1294)[e]	53.7%	30.1%	16.2%
China Cardiovascular Association Database–Heart Failure Registry (n=230,637)[f]	35.6%	20.6%	43.8%
Management of Cardiac Failure program in Northern Sydney Australia (n=5236)[g]	47.8%	14.9%	37.4%
Haiti Cardiovascular Cohort (n=93 among 2981 in CVD Cohort)[h]	71%	6.5%	22.6%

Figure. 2 Prevalence of heart failure (Bozkurt et al., 2021)

D. Pathophysiological Differences Between HFpEF and HfrEF

The primary patogenesis of HFrEF is acute or chronic loss of cardiomyocytes, such as following myocardial infarction, genetic mutations, myocarditis, or valvular disease, leading to cell death. This condition results in contracctile dysfunction, eccentric remodeling, and excessive fibrous tissue formation; cardiomyocytes in HFrEF become elongated, and myofibril density is reduced (Schwinger, 2020; Simmonds et al., 2020).

Conversely, HFpEF is characterized by structural and cellular changes that impair left ventricular relaxation, including cardiomyocyte hypertrophy, interstitial fibrosis, impaired myocyte relaxation function, and inflammation. HFpEF is often associated with chronic comorbidities such as hypertension, type 2 diabetes, obesity, renal failure, and sleep apnea, and exacerbates inflammatory processes HFpEF endothelial dysfuction, often observed in HFpEE endothelial dysfunction, often observed in HFpEF, contributes to disease progression through neurohormonal activation, vasoconstriction, and oxidative stress (Simmonds et al., 2020).

HFpEF patients are generally older and women are nearly twice as common as men. HFrEF, on the other hand, is more common in men, possibly due to a higher incidence of myocardial infarction; HFmrEF (heart failure with moderate ejection fraction) can progress to either HFpEF or HFrEF, but is more commonly associated with coronary artery disease as is HFrEF. Furthermore, differences in myocardial titin protein levels and calcium handling between HFpEF and HFrEF reflect fundamental differences in their pathophysiological mechanisms (Schwinger, 2020).

E. Four pillars of heart failure treatment

The Four pillars of heart failure treatment refer refer to the four main drug combinations recommended for the management of heart failure: ARNIs (angiotensin receptor-neprilysin inhibitors), beta-blockers, MRAs (mineralocorticoid receptor antagonists), and SGLT-2 inhibitors (sodium-glucose cotransporter-2 inhibitors). ARNIs help with vasodilation and reduce the workload of the heart; beta-blockers decrease heart rate, lower blood pressure, and help prevent further cardiac damage. MRA facilitates the elimination of excess sodium and water, reducing fluid accumulation and improving cardiac function. Initially developed for diabetes, SGLT-2 inhibitors have also been found to benefit heart failure by decreasing fluid overload and enhancing cardiac function. These four medications are recommended for early implementation in heart failure management to reduce mortality, prevent hospitalizations, and potentially support cardiac structural recovery. Drug selection may be influenced by patient comorbidities and financial constraints, but their use should be encouraged whenever possible to achieve better heart failure management outcomesg (Docherty et al., 2022; Straw et al., 2021; Tromp et al., 2022).

Differences in the four pillars of heart failure therapy between HFrEF and HFpEF are crucial in determining appropriate treatment approaches (Docherty et al., 2022).

1. **Inhibitor Renin-Angiotensin:**

   In HFrEF, inhibition of the renin-angiotensin system (RAS) is highly effective in reducing cardiovascular mortality and hospitalizations. Trials such as CONSENSUS, SOLVD-Treatment, and PARADIGM-HF have demonstrated significant benefits of ACE inhibitors and ARNI in reducing mortality and hospitalizations in patients with low LVEF (≤35%). RAS inhibition improves the clinical condition of HFrEF patients by reducing left ventricular dilation and enhancing cardiac function (Docherty et al., 2022).

In HFpEF, the benefits of RAS inhibition are more limited. Trials such as CHARM-Preserved showed that angiotensin receptor blockers (ARBs), such as candesartan, did not lead to significant reductions in mortality or hospitalizations. However, some data suggest a reduction in hospitalizations in patients with slightly lower LVEF (around 50%) (Docherty et al., 2022).

2. **Beta-Blocker:**
   Beta-blockers have been shown to reduce mortality and hospitalizations in patients with HFrEF. Large trials such as COPERNICUS and CIBIS-II have demonstrated that beta-blockers, including carvedilol, bisoprolol, and metoprolol, significantly reduce mortality and improve quality of life in patients with LVEF ≤35% (Docherty et al., 2022).
   Data on beta-blockers in HFpEF are more limited. No major trials have shown significant benefits in patients with LVEF >40%. A meta-analysis reported that while some benefit was observed in patients with HFmrEF (LVEF 40–49%), there was no effect in patients with LVEF ≥50% (HFpEF). This suggests that beta-blockers are more effective in patients with HFrEF than in those with HFpEF (Docherty et al., 2022).
3. **Antagonis Reseptor Mineralokortikoid (MRA):**
   In HFrEF, MRAs such as spironolactone have been shown to reduce mortality and hospitalizations. Studies such as RALES demonstrated a 30% reduction in mortality risk in patients with LVEF ≤35% receiving spironolactone, making it a Class I treatment recommendation for HFrEF (Docherty et al., 2022).
   In HFpEF, evidence of MRA benefits is more limited. Trials in HFpEF patients have not shown significant reductions in mortality or hospitalizations. Although some studies suggest potential benefits for selected patients, MRAs do not exhibit the same effectiveness as in HFrEF (Docherty et al., 2022).
4. **Inhibitor SGLT2:**
   SGLT-2 inhibitors, such as empagliflozin and dapagliflozin, have demonstrated significant benefits in reducing cardiovascular mortality and hospitalizations in patients with HFrEF. They serve as an essential adjunct therapy in HFrEF management, even in patients already receiving ACE inhibitors, beta-blockers, and MRAs (Docherty et al., 2022).

The benefits of SGLT-2 inhibitors in HFpEF are emerging, with trials such as EMPEROR-Preserved showing a reduction in HF hospitalizations and some additional benefits in HFpEF patients. However, their impact on mortality remains limited (Docherty et al., 2022).

Overall, treatment for HFrEF is more focused on RAS inhibition, beta-blockers, and MRAs, with strong evidence supporting long-term outcomes improvement. In contrast, HFpEF treatment faces challenges in achieving consistent results, with therapy primarily limited to RAS inhibitors and potential benefits from SGLT-2 inhibitors, although the outcomes remain less robust compared to HFrEF.

CONCLUSION

HFrEF and HFpEF exhibit fundamental differences in pathophysiology, risk factors, and therapeutic responses. HFrEF is primarily driven by impaired myocardial contractility, whereas HFpEF is associated with ventricular relaxation dysfunction and increased filling pressures. Although the four pillars of heart failure management—pharmacotherapy, device therapy, non-pharmacological management, and comorbidity management—are crucial for both conditions, their efficacy is more well-established in HFrEF than in HFpEF. The treatment of HFpEF remains a significant challenge due to its heterogeneous etiology and

pathophysiology, necessitating a more personalized approach. Further research is needed to optimize treatment strategies that can improve the quality of life in patients with both types of heart failure.

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