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Emerging Strategies in the Management of Heart Failure with Preserved Ejection Fraction: Integrating SGLT2 Inhibitors, Lifestyle Interventions, and Multidisciplinary Care

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome characterized by heart failure symptoms despite a left ventricular ejection fraction ≥50%, representing about 50% of all heart failure cases. Its increasing prevalence, driven by an aging population and comorbidities like hypertension, diabetes, and obesity, poses significant challenges due to frequent hospitalizations, impaired quality of life, and high mortality rates. The pathophysiology of HFpEF is multifactorial, involving systemic inflammation, endothelial dysfunction, myocardial fibrosis, and increased ventricular stiffness, indicating a systemic syndrome requiring a multidisciplinary treatment approach. While current guidelines emphasize symptom relief, comorbidity management, and lifestyle changes, the emergence of sodium-glucose cotransporter 2 (SGLT2) inhibitors has revolutionized HFpEF management. Large randomized controlled trials like EMPEROR-Preserved and DELIVER have demonstrated their ability to significantly reduce heart failure hospitalizations and improve quality of life. Additionally, structured exercise training, dietary modifications, and behavioral support have shown benefits in enhancing functional capacity and overall well-being. Multidisciplinary care models involving collaboration among various healthcare professionals have the potential to optimize patient-centered care and improve outcomes. However, challenges persist, including the heterogeneity of HFpEF phenotypes, underrepresentation of high-risk populations in trials, and inconsistent implementation of lifestyle and multidisciplinary interventions. Future directions should focus on personalized treatment strategies guided by deep phenotyping and biomarkers, equitable access to care, and the integration of pharmacological therapies with scalable lifestyle interventions and technology-enabled monitoring systems. Addressing these issues will be crucial in alleviating the global burden of HFpEF and improving patient outcomes.

1. INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a multifaceted and diverse clinical syndrome marked by the presence of heart failure signs and symptoms, even when the left ventricular ejection fraction (LVEF) is ≥50%. This condition also shows evidence of diastolic dysfunction, impaired ventricular relaxation, or elevated filling pressures [1,2]. HFpEF represents about 50% of all heart failure instances and is becoming more prevalent, primarily due to an aging demographic and the increasing incidence of comorbidities such as hypertension, diabetes mellitus, obesity, and chronic kidney disease [3,4]. The condition is linked to considerable morbidity, frequent hospital admissions, and high mortality rates, which are comparable to those observed in heart failure with reduced ejection fraction (HFrEF) [5,6].

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Despite the escalating clinical and public health challenges posed by HFpEF, it continues to be a therapeutic dilemma. In the last twenty years, a multitude of pharmacological trials have not succeeded in showing significant mortality benefits in HFpEF, which has led to its characterization as the "graveyard of clinical trials"[7,8]. In contrast to HFrEF, where various evidence-based drug classes enhance patient outcomes, the management of HFpEF has traditionally concentrated on alleviating symptoms, addressing comorbid conditions, and implementing lifestyle changes rather than pursuing disease-modifying treatments [9,10].

The pathophysiology of HFpEF is complex and multifactorial, encompassing systemic inflammation, microvascular endothelial dysfunction, myocardial fibrosis, and heightened ventricular stiffness [11,12]. These factors are further intensified by comorbidities, indicating that HFpEF transcends a mere cardiac condition and represents a systemic syndrome that necessitates a multidisciplinary and multimodal treatment strategy [13,14]. Recently, sodium–glucose cotransporter 2 (SGLT2) inhibitors have surfaced as a promising therapeutic alternative, with extensive randomized controlled trials demonstrating significant decreases in heart failure hospitalizations and enhancements in health-related quality of life for patients with HFpEF [15,16]. Simultaneously, lifestyle modifications such as exercise training, dietary optimization, and comprehensive cardiac rehabilitation programs have shown positive effects on physical function, symptom burden, and overall quality of life [17,18]. Furthermore, multidisciplinary care models that incorporate cardiologists, primary care providers, nurses, pharmacists, dietitians, and rehabilitation specialists have exhibited potential in optimizing patient-centered care and enhancing outcomes [19, 20].

In light of the swift advancement of evidence, this review seeks to consolidate current insights on emerging strategies for managing HFpEF, emphasizing the integration of SGLT2 inhibitors, lifestyle modifications, and multidisciplinary care for patients with HFpEF. The objective of this review is to underscore how these strategies can be applied in a complementary fashion to enhance patient outcomes in this complex syndrome.

2. METHODS

This review consolidates the existing evidence regarding innovative strategies for managing heart failure with preserved ejection fraction (HFpEF), particularly emphasizing sodium–glucose cotransporter 2 (SGLT2) inhibitors, lifestyle modifications, and multidisciplinary care. We assessed the epidemiology, pathophysiology, and current treatment landscape of HFpEF, followed by a thorough analysis of the mechanisms, clinical trial data, and real-world effectiveness of SGLT2 inhibitors in this demographic. This review further explores the significance of structured lifestyle modifications, which encompass exercise training, dietary changes, and comprehensive cardiac rehabilitation, alongside integrated multidisciplinary strategies to enhance care. For this study, an extensive literature search was performed using PubMed, Scopus, and Google Scholar for peer-reviewed articles published from January 2017 to January 2025. The search terms included "heart failure with preserved ejection fraction," "HFpEF," "SGLT2 inhibitors," "lifestyle intervention," "multidisciplinary care," and associated synonyms. Additional references were identified through backward citation tracking of pivotal articles and clinical guidelines. Studies and expert consensus statements were included if they provided pertinent insights into epidemiology, pathophysiology, treatment effectiveness, or implementation strategies. Preclinical studies, case reports, and articles that were not related to HFpEF were excluded.

3. EPIDEMIOLOGY AND CLINICAL BURDEN

Heart failure with preserved ejection fraction (HFpEF) is increasingly acknowledged as a significant factor in the global heart failure crisis as shown in Figure 1, representing nearly half of all heart failure instances worldwide [2,3]. In the United States and Europe, the prevalence of HFpEF is estimated to be between 3% and 6% in the general population, with rates surpassing 10% among individuals aged over 70 years [5]. The incidence is on the rise, primarily due to an aging population and the increasing prevalence of comorbidities such as hypertension, diabetes mellitus, obesity, atrial fibrillation, and chronic kidney disease.4 HFpEF disproportionately impacts older adults, women, and those with multiple chronic conditions, complicating both diagnosis and management [6].

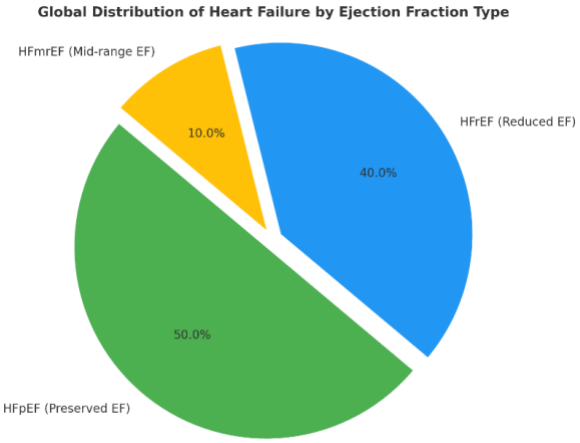

Fig. 1. Global distribution of heart failure by ejection fraction phenotype. HFpEF accounts for ~50% of all cases, followed by HFrEF (40%) and HFmrEF (10%). Adapted from [1].

The clinical trajectory of HFpEF is characterized by frequent hospital admissions, diminished quality of life, and high mortality rates that are comparable to those observed in heart failure with reduced ejection fraction (HFrEF) [7]. The five-year mortality rate in HFpEF can approach 50%, with recurrent hospitalizations contributing significantly to the morbidity burden [8]. Hospitalizations due to HFpEF are linked to longer hospital stays, higher readmission rates, and increased resource utilization compared to many other cardiovascular diseases [9]. Furthermore, the risk of rehospitalization remains elevated, with nearly 30% of patients being readmitted within 90 days of discharge [10]. These occurrences place a considerable economic strain on healthcare systems; in the United States, the annual costs associated with HFpEF are estimated to be in the billions of

dollars, with hospitalizations constituting the majority of these expenses [21].

In addition to its economic effects, HFpEF greatly hinders functional capacity and health-related quality of life. Patients frequently suffer from ongoing symptoms such as exertional dyspnea, fatigue, and diminished exercise tolerance, even with optimal medical treatment, which restricts daily activities and heightens reliance on caregivers [18, 22]. In light of these circumstances, HFpEF poses not only a clinical challenge but also a significant public health issue that requires immediate attention and creative management approaches.

4. PATHOPHYSIOLOGY OF HFPEF

Heart failure with preserved ejection fraction (HFpEF) is increasingly acknowledged as a systemic, multifactorial syndrome rather than merely a condition limited to the myocardium. In contrast to heart failure with reduced ejection fraction (HFrEF), which is primarily characterized by impaired contractility, HFpEF is defined by maintained systolic function coupled with impaired diastolic filling, resulting from increased ventricular stiffness and abnormal myocardial relaxation, frequently influenced by a diverse range of pathophysiological factors [11, 12, 23]. HFpEF does not signify a singular pathological entity but instead represents a complex interaction of abnormalities at the cardiomyocyte level, within the adjacent myocardial tissue, and throughout systemic circulation. The contributions of these processes may differ based on the underlying disease condition; however, a consistent feature noted in nearly all symptomatic HFpEF patients is myocardial fibrosis, which serves as a common pathway leading to diastolic dysfunction and clinical manifestations [13, 24].

A key mechanism in HFpEF is characterized by systemic inflammation and endothelial dysfunction. The healthy vascular endothelium typically manages vascular tone and myocardial function by releasing nitric oxide (NO), an essential homeostatic molecule that influences vascular smooth muscle cells, fibroblasts, and cardiomyocytes. In contrast, in HFpEF, chronic comorbidities such as hypertension, diabetes mellitus, obesity, and chronic kidney disease lead to a sustained low-grade inflammatory state that disrupts NO signaling. This disruption is mainly facilitated by a decrease in cyclic GMP (cGMP) production and the inhibition of protein kinase G activity, resulting in cardiomyocyte hypertrophy, heightened myocardial stiffness, and interstitial fibrosis [24–26]. Moreover, oxidative stress worsens this dysfunction by reducing NO bioavailability and modifying titin phosphorylation, a crucial sarcomeric protein that governs myocardial compliance during diastole. These mechanisms together contribute to the increased passive stiffness of cardiomyocytes and hindered relaxation kinetics, which are essential factors in the pathophysiology of HFpEF [13, 26].

Endothelial dysfunction also initiates the upregulation of vascular adhesion molecules, which aids in the infiltration of inflammatory cells into the myocardium. These cells, particularly macrophages and Th1 T cells, secrete pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, as well as profibrotic mediators including TGF-β, Galectin-3, and connective tissue growth factor. This secretion further activates cardiac fibroblasts and promotes extracellular matrix (ECM) deposition, resulting in myocardial fibrosis [11]. This fibrotic remodeling is not merely structural but also functional, perpetuating the hemodynamic changes characteristic of HFpEF. Notably, inflammatory and metabolic triggers such as diabetes and metabolic syndrome prepare immune cells for heightened fibrotic responses, indicating that HFpEF fundamentally represents a state of immune-metabolic dysregulation [14].

Within the cardiomyocytes, mechanical stretch, neurohormonal activation, and redox imbalance further exacerbate hypertrophy and dysfunction. Chronic oxidative stress, which is heightened in conditions such as obesity and diabetes, disrupts mitochondrial respiration, uncouples the electron transport chain, increases the production of reactive oxygen species (ROS), and diminishes antioxidant systems. This sequence of events interferes with calcium handling, titin phosphorylation, NO signaling, and metabolic efficiency within the cardiomyocyte, creating a profibrotic and proinflammatory microenvironment that hinders diastolic performance and reinforces a cycle of stiffness, inflammation, and dysfunction [11, 12, 26].

Recent findings regarding HFpEF indicate that this syndrome may also be classified as a type of metabolic heart disease. Clinical trials utilizing sodium–glucose cotransporter 2 (SGLT2) inhibitors lend credence to this perspective by revealing not only improvements in hemodynamics but also advantages associated with anti-inflammatory, antifibrotic, and metabolic-modulating properties, highlighting neurohormonal and substrate-level irregularities in patients with HFpEF [14]. These results emphasize the necessity for therapeutic strategies that tackle the wider systemic pathology, rather than concentrating exclusively on cardiac function.

As illustrated in Figure 2, the pathogenesis of HFpEF encompasses a network of interrelated mechanisms, such as cardiomyocyte hypertrophy, fibrosis, endothelial dysfunction, systemic inflammation, and oxidative stress, with myocardial fibrosis serving as the ultimate common pathway across various phenotypes [13]. This intricate convergence of pathways poses considerable challenges for treatment but simultaneously creates new possibilities for phenotype-driven, targeted interventions.

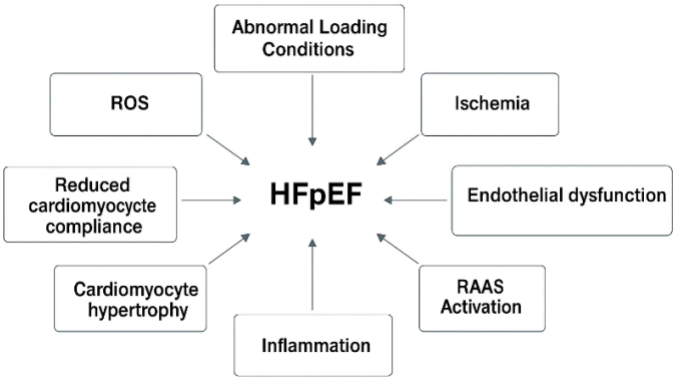

Fig. 2. Depiction of the various interrelated pathophysiological mechanisms that contribute to the onset of HFpEF. Adapted from [11].

5. CURRENT GUIDELINE-BASED MANAGEMENT

The management of heart failure with preserved ejection fraction (HFpEF) has traditionally posed significant challenges within the field of cardiology, primarily due to the lack of therapies that demonstrate a definitive mortality benefit. In contrast to heart failure with reduced ejection fraction (HFrEF), where various pharmacological agents have been proven to enhance survival rates and decrease hospital admissions, the treatment options for HFpEF remain restricted and predominantly focus on symptomatic relief [5, 7, 8]. Most existing therapies are designed to ease symptoms, manage fluid retention, and control associated comorbidities, rather than to reverse or stop the progression of the disease.

Current clinical guidelines, especially those issued by the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA), advocate for a thorough and personalized strategy in the management of HFpEF as shown in Figure 3 [5, 27]. The foundation of treatment begins with addressing volume overload, typically accomplished through the administration of loop diuretics such as furosemide, bumetanide, or torsemide. These drugs are effective in alleviating congestion and enhancing symptoms like dyspnea and edema; however, they do not tackle the fundamental pathophysiological processes nor do they improve long-term outcomes such as mortality or the rate of rehospitalization [7]. It is crucial to carefully adjust dosages to prevent over-diuresis, which may result in hypotension and renal impairment, particularly in older patients with pre-existing comorbidities.

The 2023 ACC Expert Consensus Decision Pathway highlights the necessity of stringent management of comorbid conditions, many of which play a direct role in the pathophysiology and clinical progression of HFpEF. Among the most critical are hypertension, obesity, atrial fibrillation, diabetes mellitus, and chronic kidney disease. The guidelines advocate for proactive management of hypertension, aiming for a target systolic blood pressure generally below 130 mmHg, as elevated blood pressure is a contributing factor to left ventricular hypertrophy and diastolic dysfunction. Depending on individual patient factors, beta-blockers, ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists may be utilized, although their advantages in HFpEF are not as clearly defined as in HFrEF [27].

For patients dealing with obesity, a prevalent and mechanistically significant comorbidity, weight loss through caloric restriction, increased physical activity, and potentially pharmacotherapy (such as GLP-1 receptor agonists) is recommended. Research indicates that weight reduction can enhance exercise capacity, quality of life, and diastolic function in individuals with HFpEF. Structured exercise regimens, encompassing both aerobic and resistance training, are strongly recommended as they improve peak oxygen consumption (VO_2 peak), enhance functional status, and alleviate symptom burden. These non-pharmacologic strategies are deemed vital components of a comprehensive management approach [27].

Atrial fibrillation is another crucial area of concern, being highly prevalent in HFpEF and linked to poorer outcomes. The ACC suggests implementing rate or rhythm control strategies customized to the individual patient, as atrial fibrillation can further hinder diastolic filling and worsen symptoms. Anticoagulation is also essential for patients with thromboembolism risk factors, typically determined by the CHA_2DS_2-VASc score [27].

A significant breakthrough in the management of HFpEF has been achieved with the introduction of sodium–glucose cotransporter 2 (SGLT2) inhibitors. Originally designed for glycemic control in individuals with type 2 diabetes, these medications have proven to be beneficial for heart failure patients, including those with preserved ejection fraction. Supported by strong evidence from extensive randomized controlled trials such as EMPEROR-Preserved and DELIVER, SGLT2 inhibitors like empagliflozin and dapagliflozin have shown considerable reductions in heart failure-related hospitalizations and enhancements in health-related quality of life, irrespective of diabetes status [15, 16, 28]. Consequently, the 2023 ACC guidelines now assign a Class I recommendation to SGLT2 inhibitors for patients experiencing symptomatic HFpEF. This represents the first pharmacological class to receive such a robust endorsement for this patient group and indicates a transition towards disease-modifying therapies in HFpEF.

Nevertheless, significant therapeutic gaps persist. To this point, no pharmacological treatment has reliably shown a substantial decrease in cardiovascular mortality among patients with HFpEF. The diverse nature of HFpEF, which includes various clinical phenotypes such as elderly hypertensives, obese diabetics, or individuals with renal impairment, complicates the implementation of a "one-size-fits-all" strategy. The variety of underlying mechanisms suggests that a medication that is effective for one subgroup may not be effective or could even be detrimental for another [29].

As a result, there is an increasing interest in treatment strategies that are specific to phenotypes, which seek to customize therapy according to the clinical and pathophysiological profile of the patient. For instance, obese individuals with HFpEF may gain more from lifestyle modifications and weight management, whereas those suffering from atrial fibrillation might experience greater advantages from rhythm control and anticoagulation. Additionally, initiatives are in progress to categorize HFpEF subtypes utilizing biomarkers, imaging data, and even machine learning algorithms to direct personalized therapy [29, 30].

Ultimately, the guidelines highlight the importance of multidisciplinary care models to facilitate comprehensive management of HFpEF. These models generally involve cooperation among cardiologists, primary care physicians, heart failure nurses, dietitians, pharmacists, and rehabilitation specialists. Such integrated care can enhance patient outcomes by enabling early detection of deterioration, optimizing medication adherence, managing comorbidities, and promoting lifestyle modifications. Although the implementation of these models varies across healthcare systems, multidisciplinary care is increasingly recognized as vital for providing high-quality, patient-centered care within this complex patient population [30].

In conclusion, while the management of HFpEF has progressed with the introduction of SGLT2 inhibitors and a more organized emphasis on comorbidities and lifestyle changes, there is still a pressing need for therapies that address

the underlying causes of the disease and enhance survival rates. Ongoing research and the refinement of guidelines will be essential to tackle the intricate and diverse nature of HFpEF and to provide more personalized and effective care.

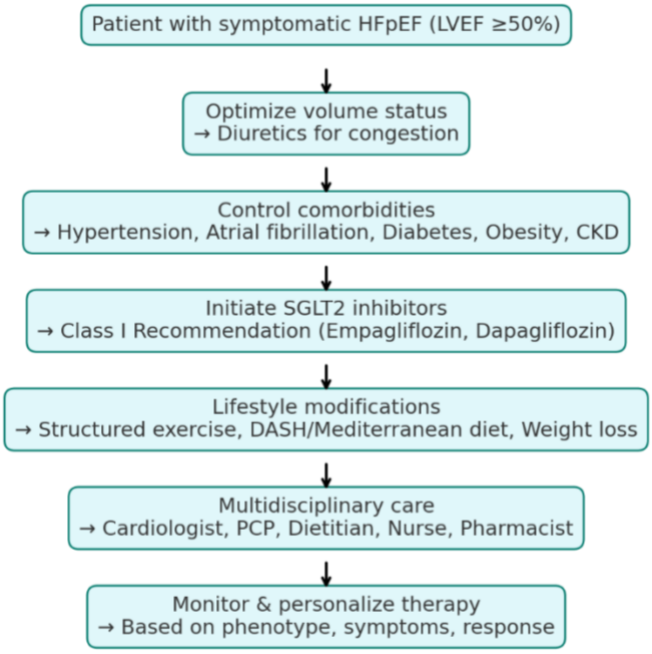

Fig. 3. A systematic approach to the management of HFpEF, highlighting the importance of alleviating symptoms, managing comorbidities, utilizing SGLT2 inhibitors, implementing lifestyle changes, providing multidisciplinary care, and tailoring treatment to individual needs. Adapted from [27].

6. SGLT2 Inhibitors in HFpEF

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have emerged as a revolutionary class of drugs in the treatment of heart failure with preserved ejection fraction (HFpEF). Initially designed for glycemic management in patients suffering from type 2 diabetes mellitus, these agents are the first pharmacological category to exhibit consistent and significant clinical advantages across the entire spectrum of HFpEF, regardless of the presence of diabetes. Their inclusion in clinical guidelines signifies a major shift in the approach to treating this complex condition.

The EMPEROR-Preserved trial and the DELIVER trial are two pivotal randomized controlled trials that confirmed the effectiveness of SGLT2 inhibitors in populations with HFpEF, as illustrated in Table 1. In the EMPEROR-Preserved trial, empagliflozin demonstrated a 21% relative risk reduction in the composite primary outcome of cardiovascular death or hospitalization due to heart failure when compared to placebo (hazard ratio [HR] 0.79; 95% confidence interval [CI], 0.69–0.90; $p < 0.001$) [15, 31]. This advantage was consistently observed across various subgroups, including those with and without diabetes, indicating that the mechanisms of benefit transcend mere glycemic control.

In a similar vein, the DELIVER trial, which assessed the efficacy of dapagliflozin in patients exhibiting mildly reduced or preserved ejection fraction, indicated an 18% decrease in the composite outcome of cardiovascular mortality or exacerbation of heart failure (HR 0.82; 95% CI, 0.73–0.92; $p < 0.001$) [16, 32]. The results were consistent irrespective of left ventricular ejection fraction and across a diverse array of patient characteristics, further reinforcing the position of SGLT2 inhibitors as a cornerstone treatment in HFpEF.

In addition to their hemodynamic and metabolic benefits, SGLT2 inhibitors display a range of pleiotropic effects that render them particularly advantageous for HFpEF, a condition characterized by its multifactorial pathophysiology. These effects encompass osmotic diuresis, which diminishes intravascular volume and alleviates congestion; a reduction in preload and afterload, which decreases cardiac filling pressures and wall stress; and an enhancement in myocardial energetics by facilitating efficient substrate utilization, especially through improved ketone metabolism [33–35]. Furthermore, these agents have shown anti-inflammatory and antifibrotic effects, which may aid in enhancing ventricular compliance and reversing some of the fundamental structural abnormalities associated with HFpEF.

Mechanistically, SGLT2 inhibitors may also affect mitochondrial function, reduce oxidative stress, and enhance endothelial function, all of which are involved in the pathogenesis of HFpEF. These effects go beyond the heart and may impact renal function, vascular tone, and systemic metabolic balance, reinforcing the increasing agreement that HFpEF is a systemic syndrome rather than merely a cardiac condition. By addressing multiple pathways at once, SGLT2 inhibitors provide a more comprehensive approach to alleviating symptoms and modifying the disease in patients with HFpEF [34, 35].

Despite these encouraging results, several significant limitations and gaps in knowledge persist. Although both EMPEROR-Preserved and DELIVER trials indicated reductions in hospitalization rates, neither trial showed a statistically significant decrease in cardiovascular mortality. This raises concerns about whether SGLT2 inhibitors are genuinely disease-modifying agents in HFpEF or if they are primarily effective in managing symptoms and preventing decompensation events [36].

Moreover, the generalizability of these trial outcomes is constrained by the demographic characteristics of the populations studied. The majority of participants were older adults of White ethnicity from high-income countries, which raises issues regarding the relevance of these findings to more diverse groups, including younger individuals, ethnic minorities, and patients from low- and middle-income backgrounds [37]. Furthermore, individuals with advanced chronic kidney disease (CKD), severe frailty, or multiple comorbidities were underrepresented in these studies, despite the fact that these groups make up a substantial portion of the real-world HFpEF population.

There is also a necessity for long-term follow-up data to gain a deeper understanding of the sustainability of benefits, the impact on quality of life over time, safety in polypharmacy contexts, and effects in more advanced disease stages. Although SGLT2 inhibitors are typically well tolerated, potential adverse effects such as volume depletion, hypotension, genitourinary infections, and rare cases of

diabetic ketoacidosis necessitate ongoing monitoring, particularly in frail and elderly patients.

In conclusion, the introduction of SGLT2 inhibitors has revolutionized the therapeutic landscape of HFpEF, providing significant reductions in hospitalization rates and alleviating

Table 1. Summary of Major Randomized Controlled Trials of SGLT2 Inhibitors in HFpEF

Trial	Drug	Population	Primary Outcome	Key Findings	Notable Limitations
EMPEROR-Preserved (2021) [15]	Empagliflozin	LVEF >40%, NYHA II–IV, n=5988	CV death + HF hospitalization	21% RRR in primary outcome; benefit consistent across diabetes status	No mortality benefit; short follow-up
DELIVER (2022) [16]	Dapagliflozin	LVEF >40%, symptomatic HF, n=6263	CV death + HF hospitalization	18% RRR; benefit across LVEF spectrum	Underrepresentation of minorities
PRESERVED-HF (2021) [38]	Dapagliflozin	Symptomatic HFpEF, n=324	KCCQ score change	Improved symptoms & QoL	Small, short-term trial

Note: The EMPEROR-Preserved, DELIVER, and PRESERVED-HF trials demonstrated that SGLT2 inhibitors (empagliflozin and dapagliflozin) improve outcomes in HFpEF, reducing hospitalizations and enhancing symptoms, quality of life, and functional capacity. These findings support their role as potential disease-modifying therapies.

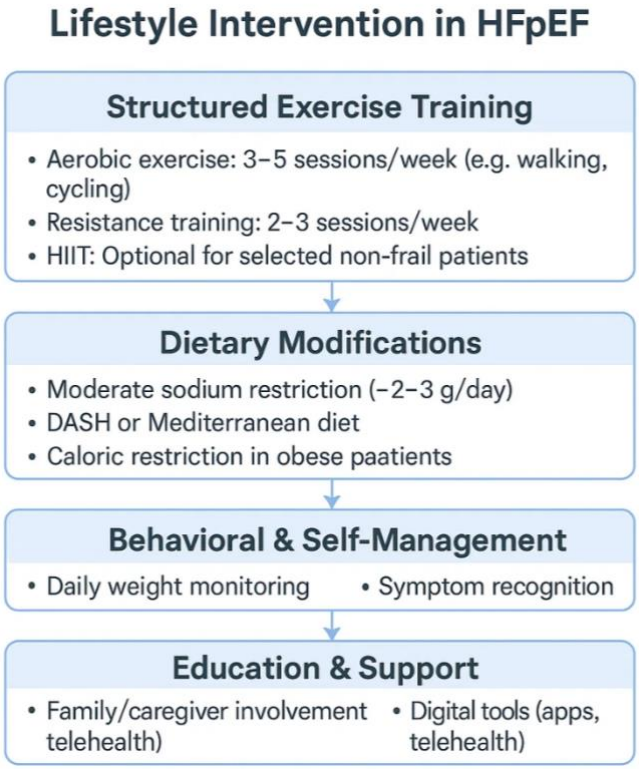

Fig. 4. Summary of essential lifestyle modifications in HFpEF, encompassing exercise, nutrition, behavioral approaches, and support mechanisms aimed at enhancing symptoms and functional ability. Adapted from [18, 22, 27].

Table 2. Lifestyle and Multidisciplinary Strategies in HFpEF Management

Strategy	Evidence Summary	Benefits	Limitations	References
Aerobic Exercise Training	Improves VO_2 peak, 6MWT, and QoL in multiple RCTs	Enhances functional capacity, symptom control	Small sample sizes, adherence issues	[6, 18]
Resistance/HIIT Training	HIIT may yield greater fitness gains vs. moderate exercise	May improve diastolic function and muscle strength	Feasibility in frail elderly uncertain	[4]
Caloric Restriction + Exercise	Synergistic improvement in exercise tolerance, diastolic function	Weight loss, improved metabolic profile	Requires strong adherence	[2]
DASH/Mediterranean Diet	Observational links to improved BP, reduced inflammation	Cardiometabolic benefit, easy integration	Lack of large HFpEF-specific RCTs	[10]
Sodium Restriction	Reduces congestion, improves symptoms	Symptom relief	Excess restriction may activate RAAS	[3]
Specialized HF Clinics	Reduced readmissions by ~30%	Optimized care, early decompensation detection	Limited availability in low-resource settings	[30, 40]
Transitional Care Programs	Lower readmissions, improved survival	Supports medication optimization	HFpEF-specific evidence limited	[41]
Primary Care Integration	Improves access, continuity of care	Facilitates rural outreach	Dependent on strong communication pathways	[35, 42]

symptom burden. Nevertheless, additional studies are necessary to ascertain their effects on long-term mortality and their effectiveness across various patient populations. Nonetheless, their Class I recommendation in the 2023 ACC guidelines highlights their emerging role as a fundamental therapy in the management of symptomatic HFpEF.

7. LIFESTYLE INTERVENTIONS

Lifestyle modification is increasingly acknowledged as a fundamental aspect of managing HFpEF, due to the strong link between this condition and lifestyle-related comorbidities such as hypertension, obesity, type 2 diabetes mellitus, sedentary behavior, and metabolic syndrome [17]. In contrast to pharmacological treatments that typically focus on specific physiological parameters, lifestyle interventions offer a range of benefits by tackling the systemic factors contributing to HFpEF pathophysiology. These interventions not only alleviate symptom burden and enhance functional status but may also affect the long-term progression of the disease as shown in Figure 4.

Among various lifestyle strategies, structured exercise training has shown some of the most compelling evidence for improving clinical outcomes in patients with HFpEF. Results from key trials such as PRESERVE-HF and REHAB-HF indicate that supervised exercise programs significantly enhance peak oxygen uptake (VO_2 peak), six-minute walk distance, and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, which together signify improvements in cardiovascular fitness, daily functioning, and overall quality of life [18, 22]. Furthermore, exercise improves diastolic function, endothelial responsiveness, and skeletal muscle efficiency, which are critical factors that are often impaired in HFpEF.

Aerobic activities, such as brisk walking or cycling, conducted three to five times weekly for 20 to 40 minutes, have been linked to significant improvements in functional capacity. Resistance training, which encompasses light to moderate weightlifting or bodyweight exercises, enhances aerobic training by boosting muscular strength and endurance, thus decreasing physical frailty and the risk of falls among elderly individuals [6]. Recent research indicates that high-intensity interval training (HIIT) may provide greater advantages compared to continuous moderate-intensity exercise in enhancing cardiorespiratory fitness. Nevertheless, the practicality and safety of HIIT for frail, elderly, and multi-morbid patients with HFpEF remain unclear and require further exploration [4]. Current exercise research is frequently constrained by short durations, small sample sizes, and the underrepresentation of high-risk groups such as women, minorities, and individuals with mobility challenges.

Dietary modifications also play a crucial role in managing HFpEF by influencing blood pressure, glycemic control, systemic inflammation, and body weight. It is recommended to limit sodium intake to alleviate volume overload and mitigate symptoms of congestion; however, overly restrictive sodium intake (below 1.5 g/day) may inadvertently stimulate the renin-angiotensin-aldosterone system (RAAS), potentially leading to a worsening of neurohormonal imbalance and increasing fatigue or hypotension in sensitive individuals [3]. Therefore, a moderate sodium restriction tailored to individual tolerance is generally recommended.

The DASH (Dietary Approaches to Stop Hypertension) diet, which is abundant in fruits, vegetables, whole grains, low-fat dairy, and lean protein, has been proven to lower blood pressure, diminish oxidative stress, and enhance endothelial function. Likewise, the Mediterranean diet, noted for its high consumption of monounsaturated fats (such as olive oil), nuts, legumes, fish, and limited red meat, has shown anti-inflammatory properties and a reduction in cardiovascular

risk in observational studies [10]. Although these dietary patterns have not been specifically validated in extensive HFpEF trials, their positive effects on metabolic health render them appropriate for this patient demographic.

In individuals with obesity, a prevalent phenotype in HFpEF, caloric restriction and sustained weight loss have been linked to enhanced VO_2 peak, decreased left ventricular filling pressures, and improved quality of life. The combination of caloric restriction with structured exercise seems to produce synergistic advantages, resulting in more significant enhancements in diastolic function, arterial stiffness, and insulin sensitivity compared to either intervention alone [2]. Additionally, weight loss may lead to a reduction in systemic inflammation and a decrease in pericardial and visceral fat, which are increasingly recognized as factors in the pathogenesis of HFpEF.

In addition to exercise and nutrition, behavioral and self-management support is crucial for the effectiveness of lifestyle interventions. Important self-care practices include daily weight monitoring, adherence to fluid restrictions, early symptom recognition (such as sudden weight gain or breathlessness), medication compliance, and regular follow-up. These practices have been demonstrated to lower the risk of decompensation and hospital readmission [19].

Nonetheless, encouraging long-term commitment to lifestyle modifications continues to pose a significant challenge. Obstacles such as inadequate health literacy, restricted access to nutritious food, insufficient social support, and inconsistent care disproportionately impact socioeconomically disadvantaged populations. Numerous patients also face challenges related to depression or cognitive decline, which hinders their ability to engage in self-care. Consequently, it is essential to implement culturally appropriate and accessible educational initiatives, alongside behavioral counseling and community assistance, to enhance patient involvement and empower them in effectively managing their health conditions.

Digital health solutions, including mobile applications, wearable activity trackers, and telehealth coaching, present promising avenues to facilitate adherence, monitor symptoms, and provide tailored feedback. Nevertheless, research regarding their efficacy specifically within HFpEF populations is still developing and may be constrained by gaps in digital literacy, particularly among older adults.

8. MULTIDISCIPLINARY CARE MODELS

The complexity of HFpEF necessitates a multidisciplinary, patient-focused care approach that addresses both cardiac and extracardiac factors contributing to morbidity and symptom burden [39]. In contrast to HFrEF, which is frequently managed through a pharmacological protocol, patients with HFpEF often exhibit multiple comorbidities, including obesity, diabetes, hypertension, renal dysfunction, and frailty, requiring the involvement of various healthcare professionals. Collaborative care models that include cardiologists, primary care doctors, heart failure nurses, pharmacists, dietitians, physiotherapists, and social workers have been linked to significantly better outcomes, as illustrated in Table 2, which includes reductions in unplanned hospital admissions, enhanced symptom management, and improved health-related quality of life [20].

Specialized Heart Failure Clinics provide organized follow-up care customized to meet the specific needs of individual patients. Research indicates that engagement in these clinics can lead to a decrease in unplanned hospitalizations by as much as 30% [30]. These environments facilitate multidisciplinary evaluations, prompt medication adjustments, and early detection of clinical decline, which together mitigate the risk of decompensation [40]. Nevertheless, access to such specialized services is frequently restricted in low- and middle-income nations, where healthcare infrastructure, financial resources, and trained staff may be insufficient, thereby exacerbating the care disparity for high-risk groups.

Transitional Care Programs serve to connect the period between hospital discharge and outpatient management, which is particularly critical for patients with heart failure (HF). These programs generally encompass home visits conducted by nurses, telemonitoring of vital signs and weight, as well as medication reconciliation and education led by pharmacists. Such approaches have been associated with reduced readmission rates and enhanced survival, although the specific evidence pertaining to heart failure with preserved ejection fraction (HFpEF) populations is still limited and requires additional investigation [41].

The integration of Primary Care is essential for providing continuous and accessible care to patients with HFpEF. A successful collaboration between hospital-based specialists and primary care teams enables the prompt identification of symptom worsening and swift intervention. The “spoke-hub-and-node” model exemplifies this system, where tertiary care centers function as the central “hub,” regional hospitals operate as “nodes,” and primary care clinics act as the “spokes,” ensuring that specialized input is readily available while keeping care within reach of patients' homes [35, 42]. This model is particularly beneficial in rural and underserved areas, where geographic and socioeconomic challenges may impede access to specialists.

9. FUTURE DIRECTIONS

Despite recent progress, including the incorporation of SGLT2 inhibitors, structured lifestyle modifications, and multidisciplinary care frameworks, significant challenges and unmet needs persist in the management of HFpEF. This condition continues to impose a disproportionate burden regarding morbidity, functional decline, and hospitalizations, while mortality rates have remained largely static, highlighting the necessity for innovative and more personalized strategies [1].

A primary obstacle to therapeutic advancement is the clinical and pathophysiological diversity of HFpEF. This syndrome includes a broad spectrum of phenotypes influenced by various combinations of cardiovascular and extracardiac comorbidities such as obesity, diabetes, chronic kidney disease, atrial fibrillation, hypertension, and frailty [23]. The limited effectiveness of single-target pharmacological treatments in HFpEF compared to HFrEF indicates that a one-size-fits-all treatment approach is insufficient. Consequently, precision medicine strategies are becoming increasingly relevant. These strategies encompass machine learning-based clustering, deep phenotyping, and biomarker-guided

algorithms that can assist in identifying treatable subgroups and customizing therapeutic regimens accordingly [43].

Equity in clinical research and healthcare delivery represents another urgent issue. Populations most impacted by HFpEF, particularly elderly and frail individuals, women, and those residing in low- and middle-income countries, are significantly under-represented in randomized controlled trials [21]. Furthermore, existing clinical guidelines frequently neglect sex-specific differences in HFpEF pathophysiology, such as increased concentric remodeling, heightened ventricular stiffness, and a greater prevalence among women, which may influence treatment responsiveness [12]. Addressing these disparities will necessitate deliberate trial designs that are inclusive and stratified by age, sex, socioeconomic status, and geographic location.

While lifestyle interventions such as structured exercise, dietary optimization, and behavioral support have shown significant advantages in enhancing exercise tolerance and health-related quality of life, their practical application in real-world settings is still limited. The challenges faced include brief intervention durations in studies, low adherence rates, insufficient follow-up, and the difficulty of scaling these programs across various health systems [22]. Additionally, adherence to lifestyle recommendations tends to be lower in socioeconomically disadvantaged communities, where obstacles like poor access to nutritious food, limited mobility, and inadequate health literacy are prevalent.

Similarly, the effectiveness of multidisciplinary care models has been well-documented in decreasing hospital readmissions and enhancing symptom management. Nevertheless, widespread implementation remains inconsistent due to issues such as inadequate reimbursement models, limited availability of specialists, fragmented care coordination, and a lack of infrastructure to support ongoing multidisciplinary engagement [39].

To bridge these gaps, future research should concentrate on integrated care models that synchronize personalized pharmacologic therapies with scalable, culturally tailored lifestyle interventions and technology-enabled monitoring systems. For example, the use of wearable devices for continuous monitoring of fluid status, heart rate, and activity levels could facilitate real-time identification of clinical deterioration, enabling timely therapeutic modifications. Furthermore, AI-driven clinical decision support tools may assist physicians in phenotype-specific treatment planning, thereby enhancing precision and consistency in care delivery [19]. However, it is essential that these digital solutions are validated within HFpEF-specific populations and incorporated into clinical workflows in a cost-effective and user-friendly manner.

Equity within the health system must continue to be a primary consideration in future planning. Access to specialized HFpEF clinics, cardiac rehabilitation, innovative therapies, and patient education resources is frequently unevenly allocated, with rural areas, ethnic minorities, and low-income groups encountering significant obstacles. Addressing these inequalities will necessitate coordinated policy changes, investment in rural and primary care infrastructure, and collaborative partnerships across healthcare, community, and technology sectors [40].

In conclusion, the future of HFpEF management hinges on personalization, integration, and equity. A model that merges advanced diagnostics, tailored therapy selection, and scalable delivery systems based on evidence yet flexible enough to accommodate diverse populations offers the most potential for alleviating the global burden of HFpEF and improving patient outcomes.

10. Conclusion

Heart failure with preserved ejection fraction (HFpEF) poses an increasing clinical and public health challenge, influenced by an aging demographic and a complex interaction of cardiovascular and systemic comorbidities. Despite recent progress, including the advent of SGLT2 inhibitors, structured lifestyle modifications, and multidisciplinary care frameworks, HFpEF continues to be characterized by significant morbidity, frequent hospital admissions, and stagnant mortality rates. The multifaceted nature of its pathophysiology demands a shift from generalized treatment approaches to precision medicine strategies that consider individual phenotypes, comorbidity profiles, and social determinants of health. Furthermore, it is vital to address disparities in access to care, the underrepresentation of certain groups in research, and the limitations of care delivery systems to ensure equitable advancements. The integration of personalized pharmacotherapy with scalable, culturally sensitive lifestyle interventions and technology-enabled monitoring offers potential for revolutionizing HFpEF management. Ultimately, a holistic, patient-centered strategy informed by phenotypic profiling, multidisciplinary collaboration, and health system equity will be essential for enhancing quality of life and long-term outcomes for this diverse and vulnerable patient population.

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