Review Article

Heart Failure with Preserved Ejection Fraction: Challenges and Current Approaches

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Citation: Sikka K. Heart Failure with Preserved Ejection Fraction: Challenges and Current Approaches. Res Heart Yield Transl Med 2026; 21(1):85-97.

https://doi.org/10.18502/jthc.v21i1.21285

Article info:

Received: 21 Oct. 2025
Revised: 14 Nov. 2025
Accepted: 20 Nov. 2025

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ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome associated with substantial morbidity, mortality, and impaired quality of life. Despite its rising prevalence, particularly among older adults and women, HFpEF has historically been characterized as a “therapeutic graveyard” because of decades of inconclusive or neutral clinical trials.

Methods: A secondary qualitative analysis of the literature indexed in PubMed, Scopus, and Embase from January 2018 through June 2025 was conducted. Randomized controlled trials, systematic reviews, meta-analyses, guideline statements, and high-quality observational studies were included. Data were extracted and synthesized thematically across five domains: epidemiology, pathophysiology, diagnostic strategies, therapeutic approaches, and future directions.

Results: Epidemiological data confirm increasing global prevalence, driven by aging demographics and clustering of comorbidities such as obesity, hypertension, diabetes, and atrial fibrillation. Pathophysiological insights highlight a complex, multiorgan syndrome with distinct phenotypes. Diagnostic accuracy remains hampered by overlapping comorbidities, limited biomarker sensitivity in obese or renally impaired patients, and heterogeneity in imaging findings. Artificial intelligence and machine learning approaches are emerging but not yet established in clinical care. Therapeutically, sodium–glucose cotransporter-2 (SGLT2) inhibitors represent the first pharmacologic agents to consistently reduce hospitalization and improve outcomes in HFpEF, while lifestyle modification, rehabilitation, and device-based interventions offer complementary benefits. Emerging strategies emphasize precision medicine, digital health, and biomarker-driven stratification.

Conclusion: HFpEF remains a major unexplained challenge in cardiovascular management. The efficacy of sodium–glucose cotransporter-2 inhibitors can mark a paradigm shift; however, significant weaknesses persist in diagnostic and therapeutic areas. Further progress depends on phenotype-specific, multimodal, and patient-centered strategies that combine clinical care, digital innovation, and molecular research.

Keywords: Heart Failure with Preserved Ejection Fraction; Sodium-Glucose Transporter 2 Inhibitors; Precision Medicine; Artificial Intelligence; Diagnostic Imaging; Cardiovascular Diseases

Introduction

Heart failure with preserved ejection fraction (HFpEF) is another increasingly recognized form of heart failure in which left ventricular ejection fraction is 50% or greater (Hamo et al, 2024).

HFpEF is a heterogeneous and complex medical condition with limited established treatment options compared with heart failure with reduced ejection fraction (HFrEF), which has seen significant therapeutic advances. The HFpEF burden is rising in relation to aging and the increasing prevalence of comorbidities such as obesity, diabetes, hypertension, and chronic kidney disease (Savarese et al, 2022). HFpEF is prevalent among women and older adults and is frequently associated with frailty, pulmonary hypertension, and atrial fibrillation. These factors interact, leading to increased hospitalization, poor quality of life, and mortality, thereby creating a substantial burden on health care systems. The increasing prevalence of HFpEF with age is illustrated in (Figure 1), which shows the percentage of heart failure cases across age groups.

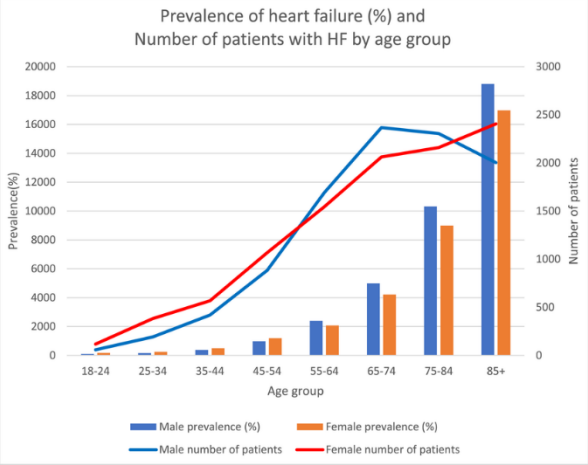

Figure 1. Prevalence of heart failure and number of patients with heart failure by age group in an active population (Liew et al, 2020) (**A**, Prevalence and **B**, patient count).

Despite the increasing impact of HFpEF, treatment advancements have been slow. Clinical trials evaluating medications that were beneficial in HFrEF for many years failed to provide significant improvements in patients (Murphy et al, 2020); hence, it is regarded as one of the most unresolved problems in cardiology. The discipline appears to be entering a new and more optimistic era because of recent discoveries, including evidence supporting sodium–glucose cotransporter-2 (SGLT2) inhibitors, improvements in imaging, and the use of artificial intelligence (AI) in diagnosis (Czupryniak et al, 2024).

The goal of the present study was to present a contemporary analysis of the HFpEF literature. Topics discussed include epidemiology, underlying mechanisms, and diagnostic difficulties; data from recent trials are critically assessed; and new approaches that could improve outcomes for this growing patient population are investigated.

Methods

Study Design

The current review was conducted as a secondary qualitative analysis of published research concerning HFpEF. The rationale for this approach was the complex and heterogeneous nature of HFpEF, which makes quantitative pooling of trial data challenging and, in many instances, methodologically inappropriate. Qualitative synthesis, in contrast, allows for the integration of findings across diverse study designs and populations, enabling a critical appraisal of both consistencies and divergences within the evidence base. The design, therefore, reflects an interpretive framework seeking to contextualize contemporary knowledge, highlight gaps, and identify avenues for future research.

Search Strategy

A comprehensive literature search was undertaken across three major biomedical databases: PubMed, Scopus, and Embase. These platforms were selected given their broad coverage of biomedical sciences, inclusion of both clinical and translational research, and indexing of high-impact journals relevant to cardiovascular medicine. The search was restricted to studies published between January 1, 2018, and June 30, 2025, to capture the most up-to-date insights while allowing sufficient scope to include landmark clinical trials and recent guideline statements that have reshaped clinical practice in HFpEF.

Search strings were developed iteratively and used a combination of Medical Subject Headings (MeSH) and free-text terms. Core concepts

included “heart failure with preserved ejection fraction,” “HFpEF,” “diastolic heart failure,” “epidemiology,” “diagnosis,” “pathophysiology,” “treatment,” “therapy,” “SGLT2 inhibitors,” “precision medicine,” and “artificial intelligence.” Boolean operators were applied to refine retrieval: (“HFpEF” OR “diastolic heart failure”) AND (“diagnosis” OR “treatment” OR “pathophysiology”). Reference lists of recent systematic reviews, meta-analyses, and major guideline documents (eg, from the European Society of Cardiology [ESC] and the American Heart Association [AHA]) were manually searched to ensure comprehensive inclusion of relevant material.

Eligibility Criteria

Eligibility criteria were predefined to ensure the inclusion of high-quality and clinically relevant evidence. Inclusion criteria were as follows: study types including randomized controlled trials (RCTs), systematic reviews, meta-analyses, consensus guidelines, and large-scale observational cohort studies; population of adults (age ≥ 18 years) diagnosed with HFpEF, defined as a left ventricular ejection fraction (LVEF) of 50% or greater or according to guideline-specific diagnostic frameworks; publication in English; and a timeframe of 2018 through 2025, with selected earlier landmark studies (eg, TOPCAT, PARAGON-HF) included if considered essential for context. Exclusion criteria were case reports, conference abstracts, editorials, and expert opinions without systematic methodology; studies published before 2018 unless pivotal to shaping the field; and trials limited exclusively to HFrEF or HFmrEF (heart failure with mildly reduced ejection fraction) populations unless HFpEF subgroup analyses were presented. This structured inclusion framework aimed to balance breadth with rigor, ensuring that the review remained focused on contemporary, evidence-based insights.

Study Selection Process

All retrieved articles were exported to a reference management tool and duplicates were removed. Screening occurred in two stages. First, titles and abstracts were assessed against inclusion criteria, with studies irrelevant to HFpEF or failing to meet methodological standards excluded. Second, a full-text review was undertaken for all potentially eligible articles. Ambiguities regarding eligibility were resolved by consensus following discussion of study design, patient population, and relevance to the thematic scope.

Although this was not a systematic review, elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework were applied to improve transparency. A flow diagram was constructed to outline the number of studies identified, screened, excluded, and included, with reasons for exclusion documented at the full-text stage (Figure 2).

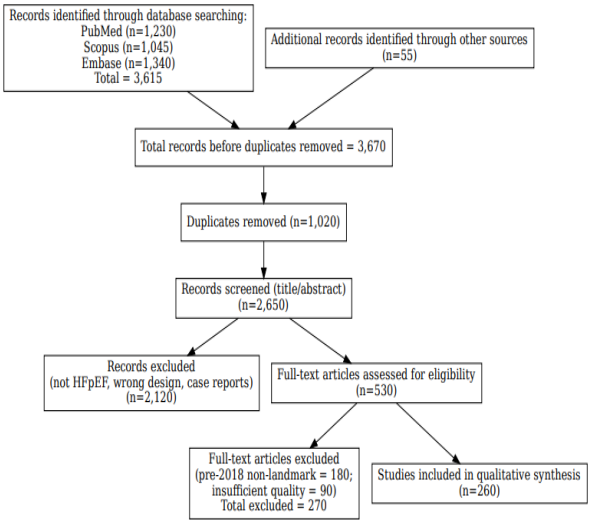

Figure 2. PRISMA 2020 flow diagram summarizing the process of literature identification, screening, eligibility assessment, and final inclusion for qualitative synthesis.

Data Extraction and Thematic Synthesis

A structured data extraction framework was used to capture essential information from each included study. Extracted variables included publication year, study design, sample size, setting, patient demographics, diagnostic criteria for HFpEF, interventions tested (where applicable), and key outcomes.

The extracted evidence was then organized into five thematic domains, reflecting both clinical relevance and the logical progression of HFpEF research:

1.Epidemiology and burden—including prevalence trends, demographic variation, and comorbidity clustering.

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2.Pathophysiology—covering myocardial mechanics, systemic inflammation, vascular dysfunction, and phenotypic heterogeneity.

3.Diagnostic challenges—examining imaging modalities, biomarker performance, and novel diagnostic algorithms, including AI-based approaches.

4.Therapeutic approaches—reviewing pharmacologic interventions, nonpharmacologic strategies, and device-based therapies.

5.Emerging directions—addressing precision medicine, digital health, biomarker-guided therapies, and pipeline pharmacologic agents.

This thematic synthesis reflects qualitative interpretive analysis rather than quantitative aggregation. It allows for meaningful comparison across heterogeneous study designs, highlighting not only areas of consensus but also contradictions and unresolved uncertainties.

Quality Considerations

While a formal bias assessment (eg, Cochrane risk-of-bias tools) was not applied, given the narrative focus, methodological quality was nonetheless considered throughout. RCTs were appraised based on randomization procedures, sample size, statistical power, and outcome definitions. Systematic reviews and meta-analyses were evaluated against reporting standards, with particular attention to heterogeneity and risk of publication bias. Observational studies were interpreted cautiously, with recognition of potential confounding and selection bias. Guideline tatements were assessed in the context of the evidence hierarchy underpinning recommendations. By prioritizing high-quality sources and critically contextualizing lower-quality evidence, the review aimed to ensure robust synthesis while acknowledging limitations inherent in existing literature.

Ethical Considerations

The present article is based solely on previously published studies and does not involve new research with human participants or animals. Therefore, ethical approval and informed consent were not required. The review was conducted in accordance with the principles of the Declaration of Helsinki and the standards of the International Committee of Medical Journal Editors.

Results

Epidemiology

According to the literature, the global prevalence of HFpEF is increasing. This increase can be attributed to improved survival from other cardiovascular diseases, a rising comorbidity burden, and demographic shifts. American and European cohort data suggest that the proportion of heart failure cases classified as HFpEF has steadily increased over the past 2 decades, and it currently accounts for approximately 50% of all heart failure cases (Groenewegen et al, 2020). HFpEF primarily affects older adults, and its incidence rises substantially after age 70 years, with population aging being a primary driver of this trend (Roger, 2021). Despite progress in the treatment of HFrEF, hospitalizations for HFpEF remain common, with associated high morbidity and mortality. This demographic shift poses a substantial burden on health care systems.

A key epidemiological feature of HFpEF is its greater prevalence among women. Large cohort studies have shown that HFpEF is diagnosed more frequently in women than in men (Stolfo et al, 2019). The cause of this sex disparity may involve sex-specific biologic factors, such as the effects of estrogen deficiency, microvascular dysfunction, and distinct cardiac remodeling patterns. Further, women with HFpEF often have a higher burden of comorbidities, such as diabetes, obesity, and hypertension; the interaction of these conditions pathophysiologically contributes to diastolic dysfunction (Coppi et al, 2025).

Substantial racial and ethnic disparities exist. African American individuals in the United States have poorer outcomes and higher prevalence of HFpEF than their White counterparts, which is associated with

disparities in exposure to obesity, hypertension, and socioeconomic determinants of health (Ilonze and Mazimba, 2024). South Asian populations also appear to be at higher risk, although data outside specific study cohorts are limited. These epidemiological patterns underscore the necessity of addressing HFpEF through strategies that target social determinants of health, manage comorbidities, and provide direct cardiac therapy.

Pathophysiology

The pathophysiology of HFpEF is complex, involving systemic, multiorgan, and cardiovascular pathways (Budde et al, 2022). HFpEF is heterogeneous and characterized by diverse underlying mechanisms, whereas HFrEF depends more on systolic dysfunction and is more homogeneous (Simmonds et al, 2020). A primary feature is diastolic dysfunction, which is caused by increased ventricular stiffness, elevated filling pressures, and impaired myocardial relaxation. These alterations lead to pulmonary congestion and exercise intolerance because they impair left ventricular function, particularly during physical activity. The pathophysiology of HFpEF also involves systemic inflammation, endothelial dysfunction, and microvascular impairment. These interrelated mechanisms are conceptually summarized in (Figure 3), which links inflammation and vascular dysfunction to disease progression (D'Amario et al, 2019).

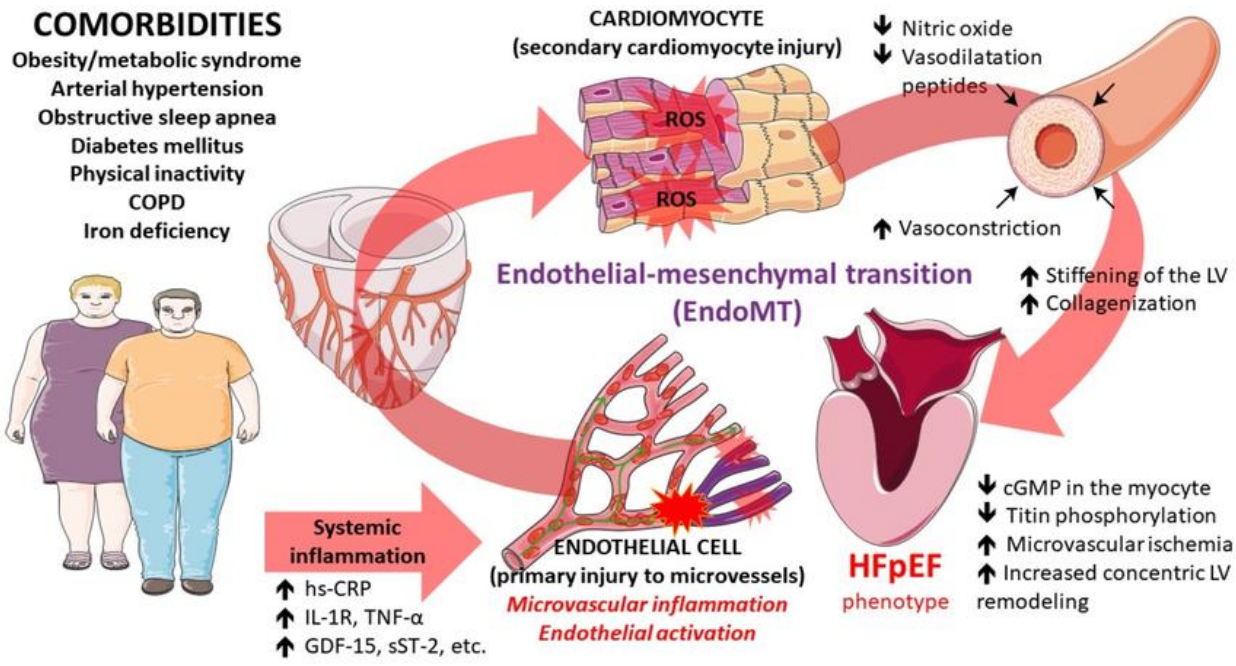

Figure 3. Conceptual pathways linking systemic inflammation, endothelial dysfunction, and microvascular impairment to heart failure with preserved ejection fraction (HFpEF) progression (Domenico D'Amario et al, 2019).

Systemic mechanisms play a vital role beyond diastolic abnormalities. Chronic low-grade inflammation, often driven by comorbidities such as diabetes and obesity, leads to endothelial dysfunction, cardiac fibrosis, and reduced nitric oxide bioavailability (Cifuentes et al, 2025). This cascade reduces oxygen delivery during exercise and impairs vasodilatory capacity, compromising both vascular and myocardial function. In addition, microvascular dysfunction has been linked to myocardial ischemia, which can occur because of impaired coronary microcirculation in the

absence of obstructive epicardial disease (Padro et al, 2020).

The recognition that HFpEF exhibits phenotypic heterogeneity has transformed the understanding of the disease. Phenotype-based analyses reveal subgroups such as frailty-associated HFpEF, atrial fibrillation–associated HFpEF, obesity-associated HFpEF, and hypertensive remodeling (Shah et al, 2020). These phenotypes each have distinct prognoses and clinical features and may have differential responses to treatment. This heterogeneity explains why many previous therapeutic trials failed to show statistical benefit across heterogeneous HFpEF populations. In contrast to a one-size-fits-all approach, contemporary strategies acknowledge this heterogeneity and promote the implementation of precision medicine, which tailors therapy to individual phenotypic profiles.

Diagnostics

Current gaps in the sensitivity and specificity of diagnostic methods continue to make HFpEF difficult to diagnose. Patients often have nonspecific symptoms such as exertional dyspnea, fatigue, and edema. These symptoms overlap with those of other conditions, including anemia, chronic obstructive pulmonary disease, and deconditioning from obesity. This overlap contributes to underdetection, misidentification, and delayed diagnosis. Echocardiography, the cornerstone of diagnosis, assesses diastolic function using parameters such as the E/e' ratio, left atrial volume index, and tricuspid regurgitation velocity. Nonetheless, traditional echocardiographic findings may be inconclusive, particularly in patients with obesity or intermediate ejection fractions. Advanced echocardiographic techniques, such as speckle-tracking strain imaging, can better assess subtle myocardial dysfunction but are not yet widely used in clinical practice. Cardiac magnetic resonance imaging provides superior characterization of myocardial tissue and fibrosis but is used less frequently because of limitations in cost and availability.

N-terminal pro–B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are commonly used biomarkers for risk assessment and diagnosis. Their diagnostic performance in HFpEF is less reliable than in HFrEF. Although specificity is limited, BNP levels can be elevated in chronic kidney disease independent of cardiac function and are often lower in individuals with obesity, limiting sensitivity. Sole reliance on natriuretic peptides therefore risks both overdiagnosis and underdiagnosis. To address these diagnostic limitations, emerging technologies such as machine learning and AI have shown promise. Algorithms trained on multimodal echocardiographic and electrocardiographic data have demonstrated higher accuracy in distinguishing HFpEF from other conditions by detecting subtle patterns not easily recognized by clinicians. These AI-based models have potential for personalized prognostication and risk stratification. Although initial results are promising, these tools are not yet validated for routine clinical application and require further research and regulatory approval before integration into health care systems. To improve diagnostic accuracy, clinicians can apply the 2021 European Society of Cardiology algorithm (Figure 4), which stratifies patients based on clinical suspicion, natriuretic peptide levels, and echocardiographic findings (Formiga et al, 2023).

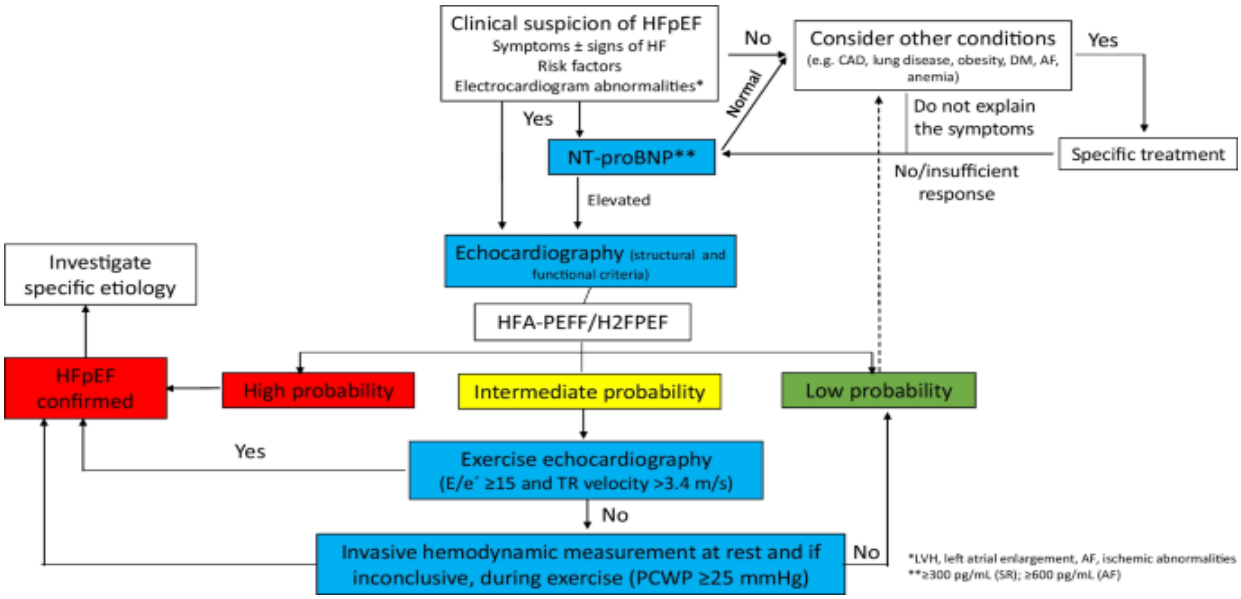

Figure 4. Diagnostic algorithm for hear failure with preserved ejection fraction (HFpEF) as proposed in the 2021 European Society of Cardiology Heart Failure guidelines. Patients are stratified according to clinical suspicion, natriuretic peptide levels, and echocardiographic findings into high, intermediate, or low probability groups. Additional testing, including exercise echocardiography or invasive hemodynamic measurements, may be required for confirmation in cases of intermediate probability. (Francesc Formiga et al, 2023)

Therapeutic Approaches

Historically, treatment of HFpEF has not advanced as much as that of HFrEF, with numerous large pharmacologic therapy trials producing neutral or equivocal results. Mineralocorticoid receptor antagonists, β-blockers, and renin-angiotensin-aldosterone system inhibitors have not consistently reduced morbidity or mortality in broad HFpEF populations. These repeated failures contributed to the characterization of HFpEF as a "therapeutic graveyard." The introduction of SGLT2 inhibitors has altered this landscape. The EMPEROR-Preserved trial demonstrated that empagliflozin significantly reduced the composite end point of hospitalization for heart failure or cardiovascular death in patients with HFpEF, irrespective of diabetes status. This finding was confirmed by the DELIVER trial, which showed comparable benefits for dapagliflozin. These results constitute the first clear pharmacologic advance in HFpEF management and have been incorporated into international guidelines as foundational therapy.

Comprehensive management still relies heavily on nonpharmacologic therapies. Exercise training and structured cardiac rehabilitation programs consistently improve exercise capacity, quality of life, and functional status in HFpEF. For patients with the obesity phenotype, in which metabolic disturbances drive disease severity, weight loss and dietary modification are particularly beneficial. Management of comorbidities, including atrial fibrillation, diabetes, hypertension, and chronic kidney disease, remains crucial because they directly affect prognosis.

Device-based interventions are being investigated but remain largely in the research phase. Interatrial shunt devices, which reduce left atrial pressure, have shown promise in early studies, although longer-term safety and efficacy data are required (Shah et al, 2018). Cardiac resynchronization therapy may benefit a small subset of patients with HFpEF and conduction abnormalities, although data are currently limited. Collectively, these approaches indicate that a multimodal strategy combining lifestyle, pharmacologic, and device-based therapies can be beneficial.

Future Directions

The concepts of precision medicine are being applied more to define the future of HFpEF management. Increased interest in tailoring treatments to patient subgroups on the basis of comorbidities, biomarker and imaging phenotypes have been driven by the understanding of phenotypic heterogeneity. Stratification methods based on proteomic, metabolomic and genomic are under investigation since they would potentially be capable of foreseeing individual treatment responses and discover novel therapeutic targets.

Another crucial element of integrated care is digital health. Wearable technology, telemedicine platforms, and remote monitoring have shown promise in enhancing adherence, identifying early decompensation, and lowering readmissions to hospitals (Po et al, 2024). With their limited mobility and high rates of multimorbidity, elderly people may benefit most from such devices. Clinical studies are promoting a number of new pharmaceutical categories. Although subgroup analyses indicate the possibility of targeted benefit, angiotensin receptor–neprilysin inhibitors (ARNIs) have demonstrated minor advantages in specific HFpEF groups (Yamamoto & Hiromi Rakugi, 2021). The potential of soluble guanylate cyclase stimulators to promote vascular function is being studied. These stimulators increase nitric oxide signaling. Another possible approach is to use anti-fibrotic medications to reverse structural cardiac remodeling (Tran et al, 2025). The therapeutic landscape may change if these innovative therapies are combined with current approaches.

Discussion

HFpEF as a "Therapeutic Graveyard"

HFpEF has been called the graveyard of cardiovascular trials (Borlaug, 2020). This characterization follows decades of neutral or inconclusive results from large RCTs evaluating therapies effective in HFrEF. The increasing prevalence and relatively high morbidity of HFpEF, driven in part by its inherent heterogeneity, have made it resistant to conventional therapeutic approaches. HFpEF encompasses multiple pathophysiologic mechanisms, including diastolic dysfunction, systemic inflammation, vascular dysfunction, and multiorgan involvement, whereas HFrEF is characterized by a more homogeneous systolic dysfunction (Stoicescu et al, 2024). These complexities have consistently prevented the direct translation of pharmacologic strategies from HFrEF to HFpEF populations. Clinical trial results underscore this therapeutic inertia. Quality of life for patients with HFpEF is often poor, and hospitalization and mortality rates remain high. Moreover, HFpEF disproportionately affects older adults and women, groups often underrepresented in therapeutic trials. These findings indicate that HFpEF represents not only a therapeutic challenge but also underlying weaknesses in patient selection, trial design, and disease conceptualization.

Lessons from Historical Failures

The repeated failure of therapeutic trials in HFpEF reflects the complexity of the condition and the challenges of trial design. Despite their established benefit in HFrEF, renin-angiotensin-aldosterone system inhibitors (RAASi), including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, produced largely neutral results in HFpEF cohorts (Rist et al, 2023). Similarly, β-blockers and mineralocorticoid receptor antagonists did not uniformly reduce mortality or hospitalization in HFpEF, with any benefits confined to specific subgroups or secondary outcomes (Serenelli et al, 2020). These neutral findings have been attributed to several factors. First, study populations were

often broad and heterogeneous due to the intrinsic heterogeneity of HFpEF, which may have obscured a treatment signal (Roh et al, 2022). Second, historical variation in diagnostic criteria has compromised internal validity, with some studies including patients with midrange ejection fractions or poorly defined diastolic dysfunction. Third, many tested therapies targeted neurohormonal pathways more central to systolic dysfunction than to HFpEF pathophysiology. These discrepancies underscore the risk of extrapolating therapies across heart failure types. For a complex condition with high comorbidity rates, traditional end points such as all-cause mortality may be insufficient to capture treatment benefit. Although often considered secondary, quality-of-life measures and functional outcomes may be more responsive to intervention in HFpEF. These collective failures highlight the necessity for improved phenotyping, carefully selected end points, and therapies targeting HFpEF-specific pathways.

The Paradigm Shift of SGLT2 Inhibitors

The development of SGLT2 inhibitors represents a paradigm shift in addressing these challenges. The EMPEROR-Preserved trial demonstrated that empagliflozin significantly reduced the composite end point of cardiovascular death or heart failure hospitalization in patients with HFpEF, a finding confirmed by the DELIVER trial using dapagliflozin (Williams and Evans, 2020). Benefits persisted in patients without diabetes, indicating mechanisms beyond glycemic control. SGLT2 inhibitors are innovative because of their pleiotropic effects. Beyond modest diuresis, they improve vascular function, reduce systemic inflammation, enhance myocardial energetics, and modulate renal activity. Unlike previous neurohormonal agents, these multisystem actions align more closely with the multiorgan nature of HFpEF (Talha et al, 2023). SGLT2 inhibitors are the first pharmacologic therapy to show consistent clinical benefit across a broad spectrum of patients with HFpEF. Their rapid incorporation into international guidelines marks a significant advance and ends a long period of therapeutic stagnation in HFpEF. Nonetheless, although SGLT2 inhibitors are a major advance, they are not a cure. The benefit, while substantial, is modest compared with progress in HFrEF, and considerable residual risk remains. The next challenge is to build on this discovery with phenotype-specific approaches and adjunctive therapies.

Toward a Phenotype-Specific and Multimodal Approach

Heterogeneity is among the most consistent findings in HFpEF research. Cluster analyses have identified subgroups, including those linked to obesity, atrial fibrillation, hypertensive remodeling, and frailty (Savji et al, 2018). These phenotypes differ in prognosis, pathophysiology, and potential treatment response. The failure of previous one-size-fits-all approaches underscores the need to shift toward phenotype-specific strategies.
For instance, obesity-related HFpEF may be best managed with weight loss interventions, metabolic optimization, and targeted exercise training (Ramirez et al, 2023). Atrial fibrillation–associated HFpEF may benefit particularly from aggressive rhythm control and anticoagulation (Reddy et al, 2022). Patients with hypertensive remodeling may require more intensive blood pressure control and vascular-targeted therapies. The likelihood of therapeutic success increases when these distinct traits are identified and addressed separately rather than subsumed under a broad HFpEF diagnosis.
A multimodal approach is equally critical. HFpEF typically arises from a combination of systemic and cardiac disturbances rather than

a single mechanism. Therefore, pharmacologic therapy should be combined with comorbidity management, exercise training, lifestyle modification, and, when appropriate, device-based interventions. Given the complexity of the syndrome and its frequent overlap with conditions such as obesity, diabetes, and chronic kidney disease, the focus should be on integrated care.

Integration of Clinical Care, Digital Health, and Molecular Research

Moving forward, the convergence of clinical care, digital health, and molecular research will be critical for HFpEF management. Clinically, patient-centered, multidisciplinary, and proactive care paradigms are required. Specialty heart failure clinics with cardiologists, geriatricians, physiotherapists, and dietitians can provide comprehensive care tailored to individual patient needs.

Digital health technology is likely to be transformative. Remote monitoring via wearable devices, telemedicine platforms, and home-based sensors can support therapy adherence and early identification of decompensation (Jafleh et al, 2024). Preliminary studies suggest digital interventions can improve patient engagement and reduce hospitalization rates, particularly among older adults (Søgaard et al, 2021). In addition to diagnosis, artificial intelligence has potential for predicting decompensation and guiding individualized treatment decisions. Widespread implementation will require validation in large, diverse cohorts and resolution of issues related to data privacy and accessibility.

Future advances are built on molecular and translational research. Proteomic, genomic, and biomarker-based stratification may identify distinct molecular signatures in HFpEF, guiding targeted therapies and enabling precision treatment (Bastos et al, 2025). Current investigations are examining novel pharmacologic classes, such as soluble guanylate cyclase stimulators and antifibrotic agents, that may augment the benefits of SGLT2 inhibitors. Crucially, integrating molecular insights with digital health platforms may enable real-time phenotypic classification and adaptive treatment strategies in clinical practice.

Historically, HFpEF has been a therapeutic graveyard due to decades of neutral trial results and the challenge of managing a complex, heterogeneous condition (Wintrich et al, 2020). Past failures highlight the need for accurate phenotyping, appropriate end points, and therapies targeting HFpEF-specific pathways. The recent efficacy of SGLT2 inhibitors has produced a paradigm shift, demonstrating that meaningful pharmacologic advancement is possible. However, monotherapy is insufficient, as considerable residual risk persists. The future of HFpEF management will require a multimodal strategy integrating pharmacotherapy, lifestyle modification, and, when indicated, device-based interventions. A broader transformation must unite molecular research, digital health innovation, and holistic clinical care. It is through this integration that the field can move beyond incremental progress to deliver effective, personalized treatment for this growing and multifaceted patient population.

Conclusions

HFpEF remains a major unsolved problem in modern cardiovascular medicine. Therapeutic progress has lagged behind that of heart failure with reduced ejection fraction, despite the condition's increasing prevalence and substantial impact on morbidity, mortality, and quality of life. This discrepancy reflects the inherent complexity of HFpEF, which is better characterized as a heterogeneous syndrome with overlapping comorbidities, multiple pathophysiologic pathways, and diverse clinical presentations rather than a

single disease. Consequently, conventional approaches relying on extrapolation from HFrEF treatment have consistently failed in HFpEF cohorts. Recent years, however, have brought significant progress. Sodium–glucose cotransporter-2 (SGLT2) inhibitors have broken a decades-long period of therapeutic stagnation (John et al, 2022). The EMPEROR-Preserved and DELIVER trials demonstrated that empagliflozin and dapagliflozin produce substantial and sustained reductions in heart failure hospitalization and improve patient outcomes (Packer et al, 2021).

These results demonstrate that pharmacologic management of HFpEF is possible and underscore the need to consider mechanisms beyond systolic dysfunction. Unlike conventional neurohormonal agents, the pleiotropic effects of SGLT2 inhibitors—involving renal, vascular, and metabolic mechanisms—align more closely with the multiorgan nature of HFpEF, representing a true paradigm shift. Diagnostic and therapeutic advances are evolving alongside these pharmacologic developments. Artificial intelligence and machine learning methods can enhance diagnostic accuracy by integrating multimodal imaging, biomarker, and clinical data (Xu et al, 2024). Although these tools are not yet ready for routine clinical application, they hold promise for earlier diagnosis, refined phenotyping, and personalized treatment allocation. Similarly, precision medicine is transitioning from theory to practice. By stratifying patients into specific phenotypes (eg, obesity-related, hypertensive, or atrial fibrillation–related HFpEF), therapy can be customized, potentially avoiding the dilution of therapeutic effect seen in large, heterogeneous trial populations.

Notwithstanding these advances, substantial gaps remain. Diagnostic accuracy continues to be hampered by overlap with other chronic conditions, such as obesity and chronic lung disease, while natriuretic peptide biomarkers show reduced reliability in patients with obesity or renal impairment (Licordari et al, 2024). Nonpharmacologic interventions, although promising, remain underutilized and inadequately studied in large trials, with few pharmacologic agents other than SGLT2 inhibitors demonstrating consistent efficacy. Persistent high event rates despite the introduction of SGLT2 inhibitors underscore the imperative to explore novel therapeutic strategies, including soluble guanylate cyclase stimulators, antifibrotic agents, and device-based therapies.

Moving forward, embracing the complexity of HFpEF rather than oversimplifying it will be key to significant progress. The future must focus on phenotype-specific, personalized treatments that target the diverse pathways driving disease progression in different patient subgroups. An integrated strategy combining pharmacologic therapy, comorbidity management, lifestyle modification, and structured rehabilitation will also be essential. Crucially, care models must be interdisciplinary, patient-centered, and adaptable, using digital health tools for monitoring, early intervention, and sustained engagement.

In summary, HFpEF is no longer a completely untreatable condition. The efficacy of SGLT2 inhibitors represents a critical advance and a foundation for further therapy. Still, unmet diagnostic and therapeutic needs remain characteristic of the syndrome. The coming decade presents an opportunity to transform the prognosis for patients with HFpEF by integrating pharmacologic innovation with precision medicine, digital health, and holistic care.

Declarations:

Funding

This study received no specific grant from any

funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The author declares no conflicts of interest.

Acknowledgments

The authors thank the Tehran Heart Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, for providing institutional support. This study was conducted without external funding.

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