Vascular Health and Risk Management

Dovepress
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REVIEW

Clinical Advances in Heart Failure with Preserved Ejection Fraction: A Systematic Review of Therapeutic and Mechanistic Evidence

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Video abstract

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Background: Heart failure with preserved ejection fraction (HFpEF) has emerged as the predominant of heart failure (HF), particularly among aging populations and individuals with a high burden of comorbidities. Its underlying pathophysiological mechanisms are complex, multifactorial and, heterogeneous.

Objective: This systematic review aims to synthesize contemporary evidence on the epidemiology, pathophysiology, diagnostic challenges, and therapeutic strategies for HFpEF, with especially emphasis on emerging clinical approaches and future research directions.

Methods: A comprehensive systematic literature search was conducted using PubMed, Scopus, Web of Science, and the Cochrane Library, covering publications from January 2015 through June 2025. Eligible studies included randomized controlled trials (RCTs), observational cohort studies, systematic reviews, meta-analyses, and current clinical guidelines talking key aspects of HFpEF.

Results: HFpEF now accounts for more than 50% of all HF diagnoses worldwide. Although it shares overlapping clinical features with other cardiovascular (CV) and systemic disorders, recent advances in echocardiographic techniques and the use of circulating biomarkers have substantially improved diagnostic accuracy. Current management strategies primarily focus on comorbidity control, optimization of volume status, structured exercise and rehabilitation programs, and the adoption of novel pharmacological therapies, most notably sodium glucose cotransporter 2 (SGLT2) inhibitors. Notable recent advances include the nonsteroidal mineralocorticoid receptor antagonist finerenone, which demonstrated reductions in worsening HF events and CV mortality in patients with heart failure with mildly reduced ejection fraction (HFmrEF) and HFpEF in the FINEARTS-HF trial. In addition, incretin-based therapies such as semaglutide (STEP-HFpEF program) and tirzepatide (SUMMIT trial) have shown clinically meaningful improvements in symptoms, exercise capacity, weight reduction, and composite CV or HF outcomes, notably in obesity-associated HFpEF phenotypes.

Conclusion: HFpEF continues to pose substantial diagnostic and therapeutic challenges owing to its marked heterogeneity and historically limited treatment options. Advances in phenotypic classification, personalized therapeutic strategies, and integrated multidisciplinary care models are critical for improving long-term outcomes in this expanding patient population. The emergence of finerenone and glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (GLP-1/GIP) receptor agonists, including semaglutide and tirzepatide, represents a promising extension beyond SGLT2 inhibitors, particularly in cardiometabolic and obesity-driven HFpEF. However, further incorporation into clinical guidelines and validation through real-world evidence remain necessary.

Plain Language Summary: Heart failure with preserved ejection fraction (HFpEF) is currently the most common form of heart failure (HF), especially among older adults and individuals with multiple chronic conditions such as diabetes mellitus (DM), hypertension (HTN), and obesity. Unlike traditional heart failure with reduced ejection fraction (HFrEF), in which the heart's pumping ability is impaired, HFpEF occurs when the heart muscle becomes stiff and does not relax properly. This leads to symptoms such as shortness of breath, fatigue, and fluid retention.

https://doi.org/10.2147/VHRM.S578698
Received: 3 November 2025
Accepted: 10 February 2026
Published: 10 March 2026

This systematic review examined global research between 2015and 2025 to better understand how HFpEF develops, how it is diagnosed, and which treatments are most effective. The findings indicate that HFpEF accounts for more than half of all HF cases worldwide. Although diagnosis remains challenging, recent improvements in cardiac imaging and blood-based biomarkers have enhanced diagnostic accuracy. Current treatment approaches focus on managing related conditions, maintaining appropriate fluid balance, and encouraging exercise-based rehabilitation. Promisingly, newer medications, particularly sodium-glucose cotransporter 2 (SGLT2) inhibitors, have demonstrated meaningful benefits in this patient population.

Overall, HFpEF is not a single disease but a complex clinical syndrome that requires individualized and multidisciplinary care. Continued research into its biological mechanisms and targeted therapies is essential to improving quality of life (QoL) and long-term outcomes for this rapidly growing group of patients.

Keywords: heart failure with preserved ejection fraction, epidemiology, pathophysiology, sodium glucose co-transport inhibitors, therapeutic challenge

Introduction

Heart failure with preserved ejection fraction (HFpEF) has become a predominant and increasingly prevalent subtype of heart failure (HF), currently accounting for more than half of all HF diagnoses worldwide. This trend is particularly evident among older adults and individuals with cardiometabolic comorbidities, including hypertension (HTN), diabetes mellitus (DM), and obesity.[1,2] In contrast to HF with reduced ejection fraction (HFrEF), for which robust evidence-based therapeutic strategies are well established, and heart failure with mildly reduced ejection fraction (HFmrEF), which is frequently grouped with HFpEF in clinical trials and practice guidelines because of overlapping management approaches despite distinct pathophysiological mechanisms, HFpEF remains diagnostically challenging and therapeutically constrained.[3,4] Over the past decade, increasing scientific attention has been directed toward the complex interplay of structural, functional, and systemic abnormalities underlying HFpEF. Central contributors include left ventricular diastolic (LVD) dysfunction, coronary microvascular inflammation, and progressive myocardial fibrosis, all of which collectively impair ventricular compliance and elevate intracardiac filling pressures.[5–7]

This maladaptive remodeling most commonly manifests as concentric left ventricular hypertrophy (LVH) and diffuse interstitial myocardial fibrosis, features observed in the majority of patients with HFpEF and strongly associated with increased myocardial stiffness and adverse hemodynamic consequences.[8] At the molecular level, these changes are driven by activation of transforming growth factor beta (TGF-β) signaling pathways, dysregulation of matrix metalloproteinases (MMPs), and inflammatory cytokine mediated fibroblast proliferation, culminating in excessive extracellular matrix deposition and fibrotic remodeling.[9,10] The epidemiological landscape of HFpEF has evolved substantially, with rising incidence reported across both high-income and low- to middle-income countries (LMICs). Data from the Global Burden of Disease (GBD) study and large-population based cohort analyses demonstrate a disproportionate burden among older women and individuals with coexisting conditions such as HTN, DM, obesity, and atrial fibrillation (AF).[11,12] Valvular heart disease (VHD) is also frequently observed in this population, with moderate or greater aortic stenosis (AS) or aortic regurgitation (AR) identified in approximately 6–8% of HFpEF cases, further accelerating disease progression and worsening clinical outcomes.[13] Despite its growing prevalence, HFpEF is remains underdiagnosed, largely because hallmark symptoms including exertional dyspnea, fatigue, and reduced exercise tolerance overlap extensively with those of other cardiac and noncardiac disorders, complicating timely recognition and appropriate management.[14] Current international guidelines define HFpEF by the presence of a left ventricular ejection fraction (LVEF) ≥50%, accompanied by objective evidence of structural cardiac abnormalities and elevated left ventricular (LV) filling pressures.[15] Circulating natriuretic peptides, notably N terminal pro B type natriuretic peptide (NT proBNP), play a central role in diagnostic evaluation. However, NT proBNP levels do not reliably reflect the presence or severity of myocardial fibrosis or LVH and are influenced by sex, race, renal function, and adiposity, which may reduce diagnostic sensitivity in selected patient subgroups.[16,17] Emerging biomarkers, including soluble suppression of tumorigenicity 2 (sST2), galectin 3, and growth differentiation factor 15 (GDF 15), have demonstrated potential for improving diagnostic accuracy and risk stratification in HFpEF, although their routine clinical application remains under investigation.[18,19]

Importantly, conventional diagnostic frameworks do not fully capture the marked heterogeneity of HFpEF. Contemporary clinical and translational studies have identified multiple phenotypic subsets, including inflammatory, metabolic, and fibrotic variants, each characterized by distinct pathobiological pathways, clinical trajectories, and therapeutic responses.[20,21] Clinically, HFpEF is associated with substantial morbidity, high rates of recurrent hospitalization, and mortality risks comparable to those observed in HFrEF. Although growing recognition of its clinical impact, effective disease modifying therapies remain limited, highlighting the urgent need for individualized, phenotype guided treatment strategies.[22–24] Moreover, HFpEF imposes a considerable economic burden on healthcare systems, driven by frequent hospital admissions, complex diagnostic assessments, and prolonged longitudinal follow up.

The present systematic review aims to critically appraise and synthesize contemporary evidence related to HFpEF, with a focus on epidemiological trends, underlying pathophysiological mechanisms, diagnostic challenges, therapeutic interventions, and long-term management strategies. By providing a comprehensive and clinically relevant synthesis, this review seeks to support the development of more effective, personalized, and multidisciplinary approaches to the care of patients with HFpEF.

Materials and Methods

Search Strategy and Data Sources

A systematic and comprehensive literature search was conducted across four major electronic databases: PubMed, Scopus, Web of Science, and the Cochrane Library. The search covered studies published between January 2015 and June 2025. Relevant keywords and Medical Subject Headings (MeSH) terms, including "heart failure with preserved ejection fraction", "HFpEF", "diastolic dysfunction", "phenotypic heterogeneity", "management", and "long-term outcomes", were combined using Boolean operators (AND, OR, NOT) to optimize search sensitivity and specificity.

To minimize selection bias and enhance methodological rigor, two independent investigators performed the literature searches and screened retrieved records. Any discrepancies regarding study selection or eligibility were resolved through consensus, with arbitration by a third investigator when necessary. Additional relevant studies were identified by manually reviewing the reference lists of included articles, relevant systematic reviews, and contemporary clinical guidelines issued by the European Society of Cardiology (ESC) and the American Heart Association (AHA). Trial registry records were not included, as this review was restricted to peer-reviewed published literature.

Inclusion and Exclusion Criteria

Studies were selected based on the following predefined criteria.

Inclusion Criteria

1. Studies involving adult patients with a confirmed diagnosis of HFpEF, defined as LVEF ≥50%.
2. Studies addressing any aspect of HFpEF, including etiology, pathophysiology, diagnostic approaches, therapeutic strategies, long-term outcomes, or clinical management.
3. Peer-reviewed original research articles, including randomized controlled trials (RCTs), observational cohort studies, meta-analyses, and comprehensive review articles. Studies available in full text and published in English language.

Exclusion Criteria

1. Studies primarily focused on HFrEF or HFmrEF.
2. Studies based exclusively on animal models or in vitro experiments without direct clinical relevance.
3. Editorials, letters to the editor, conference abstracts, and other publications lacking original data.
4. Studies published in languages other than English.

Study Selection Process Based on PRISMA Framework

All records retrieved from the database search were imported into EndNote reference management software (Version 21), where duplicate entries were identified and removed. Approximately 2700 duplicate records were excluded, resulting in

6000 unique titles and abstracts for initial screening by two independent reviewers. Based on the predefined inclusion and exclusion criteria, 900 articles were selected for full-text evaluation. After detailed assessment, 830 studies were deemed potentially eligible and subjected to methodological quality appraisal. Ultimately, 83 studies met all eligibility and quality criteria and were included in the final qualitative synthesis.

The study selection process was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility.[25] Data extraction was performed using a standardized data collection form capturing study design, sample size, diagnostic criteria for HFpEF, interventions, clinical outcomes, and principal findings.

The methodological quality of observational studies was assessed using the Newcastle–Ottawa Scale (NOS),[26] while RCTs were evaluated with the Cochrane Risk of Bias (RoB) tool.[27] The quality of included systematic reviews was assessed using the updated "A MeaSurement Tool to Assess Systematic Reviews 2" (AMSTAR 2) instrument.[28] Studies failing to meet predefined quality thresholds were excluded from the final analysis. The PRISMA flow diagram illustrating the study selection process is presented in Figure 1.

Results

A total of 83 studies fulfilled the predetermined eligibility and quality assessment criteria and were included in this systematic review. Among these, 22 were RCTs, 38 were observational cohort studies, and 23 were systematic reviews or meta-analyses. Collectively, the included studies addressed a broad spectrum of topics relevant to HFpEF. Specifically, 25 studies investigated epidemiology and associated risk factors, 20 explored pathophysiological mechanisms and phenotypic heterogeneity, 15 evaluated diagnostic strategies, 15 examined therapeutic interventions, and 8 focused on long-term clinical outcomes.

Epidemiological Trends and Risk Factors in HFpEF: Demographic Shifts and Clinical Implications

HFpEF is currently recognized as accounting for estimated at half of all HF cases worldwide.[29] In European cohorts, HFpEF represents nearly 50–55% of diagnosed HF cases, with a disproportionately high prevalence among women aged 65 years and older.[30] Comparable epidemiological patterns have been reported in highly urbanized regions of East Asia, where HFpEF prevalence ranges from 30% to 45%, again predominantly affecting older female populations.[31] In the United States (US data from large registries, including the Get With The Guidelines®–Heart Failure (GWTG-HF) program, indicate that HFpEF constitutes approximately 47–50% of HF cases, with notable regional variation influenced by comorbidity burden and disparities in healthcare access.[32]

Advancing age remains the most significant non-modifiable risk factor for HFpEF, with incidence increasing markedly after 65 years of age. Female sex is consistently associated with greater susceptibility, a phenomenon attributed to sex-specific patterns of myocardial remodeling and hormonal alterations, particularly the decline in estrogen levels following menopause.[33,34] Comorbid conditions, such as HTN, DM, obesity, chronic kidney disease (CKD), and AF, are highly prevalent among patients with HFpEF and play a central role in both disease onset and progression.[34,35] These conditions are not merely coincidental but contribute mechanistically to HFpEF pathogenesis through interconnected pathways involving systemic inflammation, endothelial dysfunction, and impaired nitric oxide signaling. Population-based studies have further highlighted the pronounced phenotypic variability characteristic of HFpEF, in contrast to the relatively more homogeneous presentation of HFrEF.[34] One prominent HFpEF phenotype comprises patients with metabolic syndrome (MetS), defined by the coexistence of obesity, insulin resistance, dyslipidemia, and HTN. The metabolic–inflammatory axis has emerged as a dominant driver of HFpEF pathophysiology, especially in Asian populations experiencing rapid increases in the prevalence of type 2 diabetes mellitus (T2DM) and obesity.[10]

In European populations, obesity is increasingly recognized as a key modifiable risk factor, strongly associated with adverse structural cardiac remodeling and impaired diastolic function.[30,36] In contrast, in resource-limited regions of Asia, restricted access to advanced diagnostic modalities contributes to under recognition and misclassification of HFpEF, resulting in an underestimation of disease burden and missed opportunities for timely intervention.[31] These

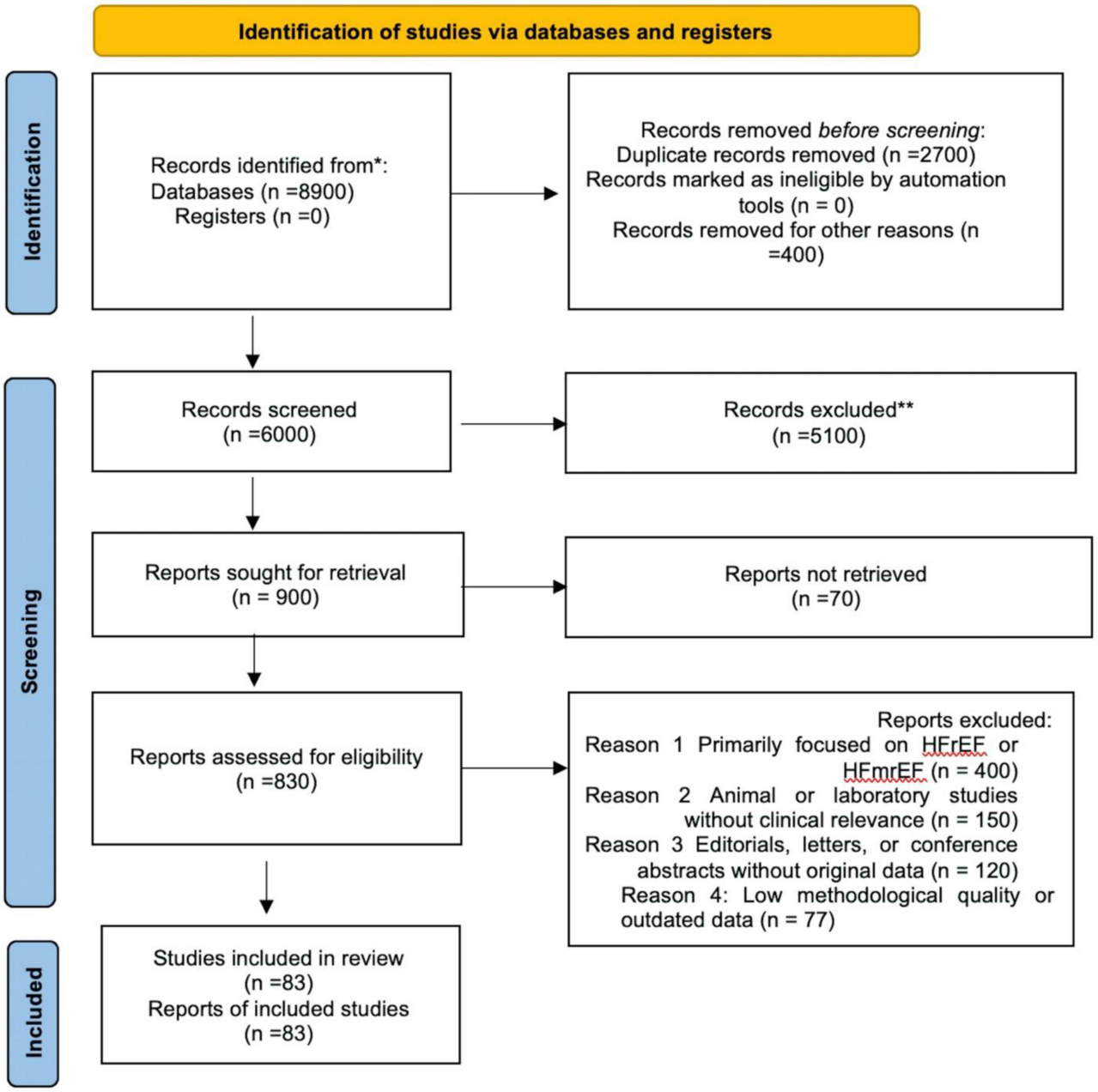

Figure 1 Systematic flow diagram of the study selection process. *Records Identified: Electronic database searches retrieved 8900 records, including PubMed (n = 2800), Scopus (n = 3500), and Web of Science (n = 2600). Additionally, 200 records were identified through manual screening of reference lists in relevant reviews and clinical guidelines. No records were found in trial registers. **Records Excluded: Following deduplication, 2700 duplicate records were removed manually. Records were excluded by human reviewers no automation tools were used during screening for the following reasons: primarily focused on HFrEF or HFmrEF (n = 400), animal or laboratory studies without direct clinical relevance (n = 150), editorials, letters, or conference abstracts lacking original data (n = 120), and studies with low methodological quality or outdated data (n = 77). These exclusions ensured alignment with the review's focus on epidemiology, pathophysiology, diagnostics, and therapeutic strategies for HFpEF.

observations underscore the urgent need for region-specific public health strategies aimed at mitigating modifiable risk factors and improving early detection.

Overall, regional variations in HFpEF prevalence reflect the combined influence of demographic characteristics, comorbidity profiles, and healthcare system factors, emphasizing the importance of preventive and therapeutic frameworks tailored to population-specific needs. Figure 2 illustrates the global epidemiological landscape of HFpEF, highlighting variations in prevalence according to geographic region, age, sex, and comorbidity burden.

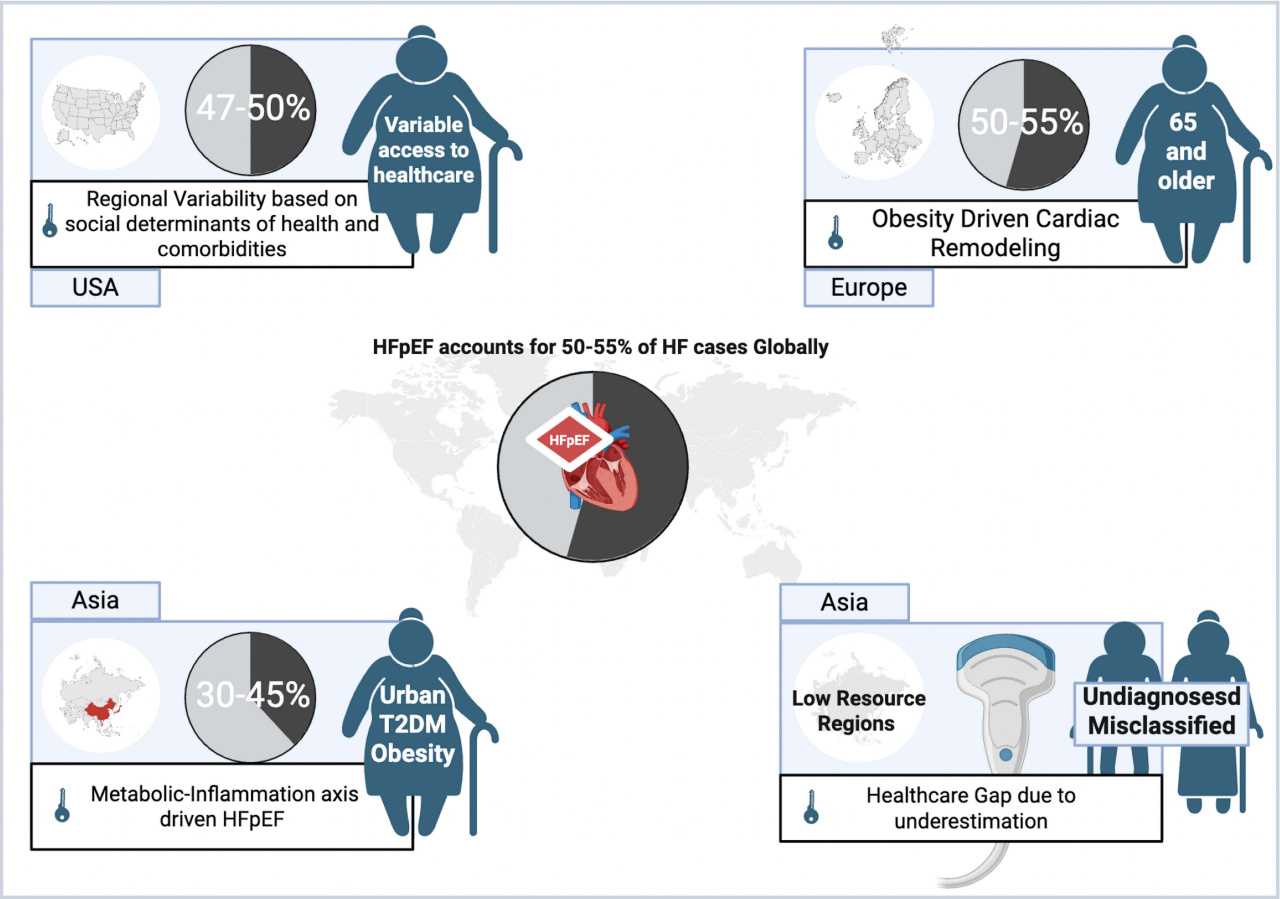

Figure 2 Worldwide distribution of HFpEF, depicting regional variations in prevalence by age group, sex, and associated comorbidities.

Risk Factors for HFpEF in Younger Populations

Although HFpEF has traditionally been viewed as a disorder primarily of older adults, emerging evidence reveals a notable increase in its incidence among younger populations. This trend largely reflects the escalating prevalence of MetS, a constellation of interrelated conditions encompassing obesity, insulin resistance, HTN, and dyslipidemia, that collectively promote early myocardial dysfunction and predispose individuals to HFpEF.[37] In a large analysis of 264,571 patients with HFpEF in the Veradigm registry (formerly PINNACLE) between 2016 and 2019, 52.5% met criteria for MetS and 55.7% were classified as obese. These results underscore the central role of cardiometabolic comorbidities in HFpEF pathogenesis, particularly among younger populations.[37]

Environmental exposures, such as ambient air pollution and industrial chemical toxins have been implicated in endothelial damage and microvascular inflammation, processes that accelerate the fundamental pathophysiology of HFpEF.[38] Sedentary lifestyles, suboptimal dietary patterns, and substance abuse further amplify CV risk and are increasingly related to early onset HFpEF phenotypes in younger individuals.[39] Moreover, autoimmune diseases such as systemic lupus erythematosus(SLE), rheumatoid arthritis(RA), and autoimmune myocarditis contribute to persistent myocardial inflammation and fibrotic remodeling, both of which are central to the development of HFpEF, even in the absence of traditional risk factors.[40]

The long-term cardiovascular sequelae of coronavirus disease 2019 (COVID-19) are increasingly recognized as significant contributors to HFpEF in younger adults. Cardiovascular magnetic resonance (CMR) imaging has identified persistent myocardial inflammation, interstitial fibrosis, and diastolic dysfunction in as many as 78% of recovered individuals, many of whom were previously healthy and under 50 years of age.[41] A recent systematic review examining COVID-19 sequelae in patients with pre-existing heart failure further delineates the pathophysiological mechanisms and

heightened cardiovascular risk, underscoring the necessity for vigilant post-COVID monitoring in this population.[42] Notably, Parizad et al characterized these multifactorial determinants as a growing public health concern, emphasizing the importance of early risk identification and preventive strategies tailored to younger adults.[43] Mitigating these interrelated risk pathways through comprehensive clinical assessments, lifestyle modification, and regionally adapted public health policies is essential to curbing the rising burden of HFpEF among younger individuals.

Pathophysiological Insights into HFpEF: Mechanisms and Clinical Implications

HFpEF is a complex, multifactorial syndrome defined by preserved LVEF in the setting of impaired diastolic relaxation and increased myocardial stiffness. Unlike HFrEF, HFpEF predominantly manifests as diastolic dysfunction with elevated ventricular filling pressures even a normal LVEF.[44]

The pathophysiology of HFpEF encompasses systemic inflammation, endothelial dysfunction, myocardial fibrosis, and cardiomyocyte (CMC) alterations. Chronic low-grade inflammation, frequently driven by comorbid conditions such as obesity, HTN, and T2DM, initiates endothelial activation and oxidative stress, which in turn fosters interstitial myocardial fibrosis and increased ventricular stiffness.[2,5] Coronary microvascular dysfunction further contributes to myocardial ischemia (MI), further exacerbating fibrotic remodeling and myocardial stiffness.[45]

At the molecular level, reduced bioavailability of nitric oxide (NO) and dysregulation of the cyclic guanosine monophosphate protein kinase G (cGMP PKG) signaling cascade are critical in impairing diastolic function in HFpEF. Moreover, defective calcium (Ca^{2+}) handling and heightened stiffness of the sarcomeric protein titin diminish myocardial compliance, impair diastolic relaxation, and contribute to exercise intolerance.[7,46,47] Extracardiac comorbidities, including pulmonary hypertension (PH), renal impairment, and chronotropic incompetence, are commonly prevalent in HFpEF, amplifying clinical heterogeneity and complicating management These factors exacerbate cardiac impairment and adversely affect prognosis.[48] The broad spectrum of phenotypic manifestations underscores the necessity for individualized treatment approaches and reinforces the concept of HFpEF as a syndrome with multiple pathophysiological pathways rather than a single disease entity. Figure 3 illustrates the principal mechanisms underlying HFpEF.

Economic Burden of HFpEF: Healthcare Costs and Resource Utilization

HFpEF imposes a substantial economic burden on healthcare systems worldwide. Frequent hospital admissions, extended inpatient stays, and ongoing outpatient management are the primary drivers of this burden. Although LVEF is preserved, individuals with HFpEF frequently experience recurrent episodes of decompensation, resulting in repeated utilization of healthcare resources and significant direct medical costs.[49–51] Hospitalization represents the largest component of total costs in this population. Emerging data indicate that more than one third of patients delay seeking care due to financial barriers, and many experience notable economic hardship following hospitalization.[51] In addition to acute care expenditures, long term disease management further escalates financial strain.

Recent evidence suggests that integrating pharmacologic treatments such as sacubitril/valsartan with structured cardiac rehabilitation (CR) may improve patient outcomes and confer potential cost saving benefits by reducing rehospitalization and enhancing functional status.[52] Beyond direct medical costs, HFpEF also incurs significant indirect costs, including loss of productivity, caregiving demands, and reduced health-related quality of life (QoL). These factors collectively intensify the societal and economic impact of the condition.[50,53] The chronic and progressive nature of HFpEF, which necessitates frequent clinical assessments, long-term pharmacologic therapy, and multidisciplinary interventions, results in sustained healthcare resource utilization.[54] Comparative analyses indicate that total healthcare spending for HFpEF is comparable to or may even exceed that of HFrEF, despite the absence of equally effective targeted therapies.[54,55] Figure 4 depicts the complex economic burden of HFpEF, encompassing direct costs such as hospitalization and outpatient care as well as indirect societal costs associated with productivity losses and caregiving responsibilities.

Psychosocial Aspects of HFpEF

HFpEF exerts a substantial psychosocial burden alongside its physical manifestations. Patients commonly report persistent fatigue and dyspnea, which may contribute to social isolation, emotional distress, and marked reductions in

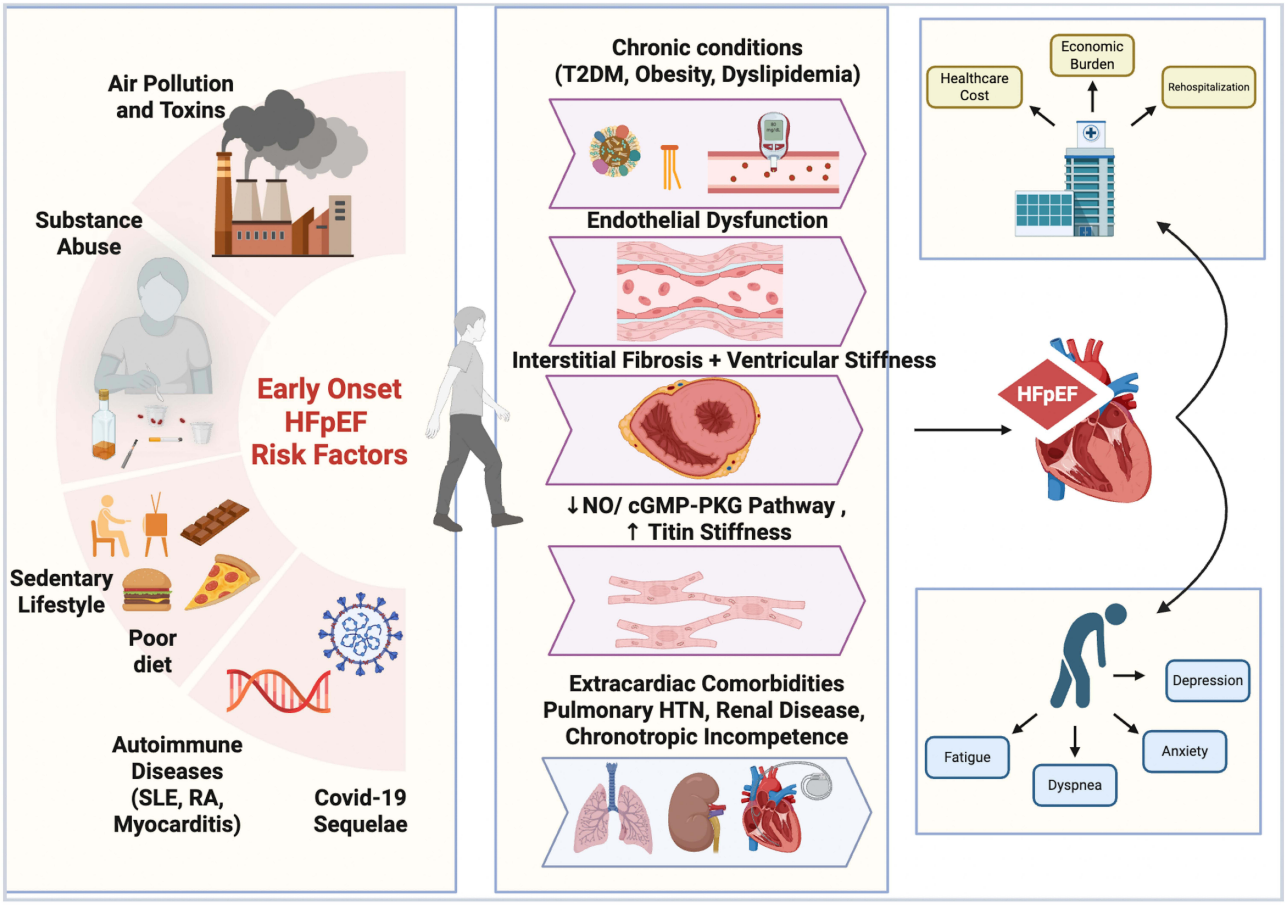

Figure 3 Overview of the major pathophysiological pathways contributing to HFpEF development and progression.

QoL. A multicenter study of hospitalized patients with HFpEF reported substantial levels of anxiety and depression in both sexes, with women demonstrating particularly elevated anxiety symptoms. These results underscore the importance of routine psychological evaluation in clinical practice.[56]

Cognitive impairment is increasingly recognized as a significant non cardiac complication in HFpEF. A scientific statement fromt he Heart Failure Society of America (HFSA) indicates that cognitive deficits, likely resulting from chronic cerebral hypoperfusion and systemic inflammation, can substantially impair patients' ability to adhere to medication regimens, make informed health decisions, and maintain beneficial lifestyle practices.[57]

Psychosocial stressors may further exacerbate HFpEF progression via activation neurohormonal and inflammatory pathways. The Aldosterone in Diastolic Heart Failure (Aldo-DHF) trial identified correlations between elevated anxiety, reduced social support, and increased biomarkers of cardiac stress.[58]

Interventions such as peer support groups, patient education programs, and multidisciplinary care models have demonstrated effectiveness in enhancing coping strategies and emotional wellbeing.

Systematic screening for anxiety, depression, and cognitive dysfunction should be integrated into HFpEF management protocols. Timely referral for cognitive behavioral therapy, psychosocial support, and patient education is essential. Such a comprehensive approach not only alleviates emotional and cognitive burdens but also promotes improved treatment adherence, reduces hospitalization rates, and enhances patient centered outcomes.

Diagnosis and Contemporary Therapeutic Approaches to the Management of HFpEF

The differential diagnosis of HFpEF encompasses conditions that can mimic its hallmark symptoms, including dyspnea, fatigue, and exercise intolerance, as well as signs of congestion. These conditions include chronic obstructive pulmonary

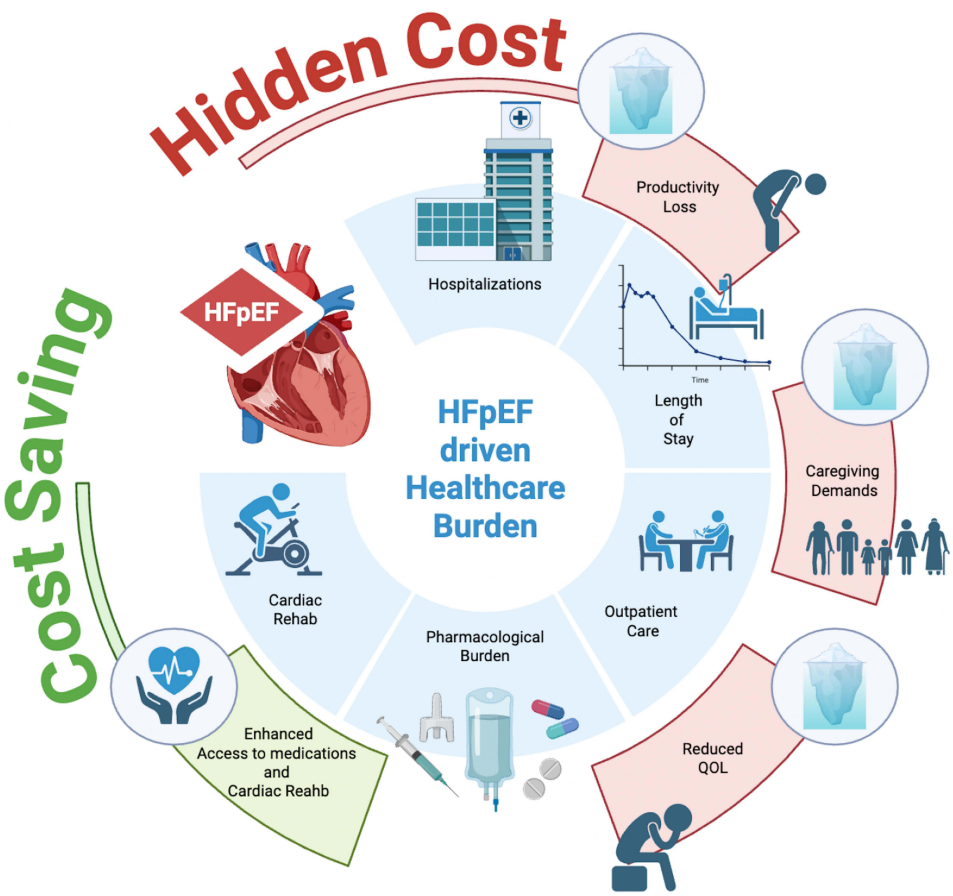

Figure 4 Overview of the economic burden of HFpEF.

disease (COPD), PH, anemia, CKD, obesity-related deconditioning, VHD, constrictive pericarditis, cardiac amyloidosis, and atrial myxoma. Accurate diagnosis requires integration of clinical history, biomarkers, and advanced imaging modalities such as echocardiography and CMR, and, in select cases, invasive hemodynamic assessment to exclude mimics and confirm HFpEF.[59,60]

Currently, no single pharmacologic therapy is universally recognized as disease-modifying across all HFpEF phenotypes, and management primarily targets comorbidities, symptom relief, and SGLT2 inhibitors, which constitute the principal evidence-based option. Recent advances include the nonsteroidal mineralocorticoid receptor antagonist finerenone. In the Finerenone in Subjects with Heart Failure (FINEARTS-HF) trial, finerenone significantly reduced the composite endpoint of CV death and total worsening HF events, including hospitalizations, by approximately 16% in patients with HFmrEF or HFpEF (LVEF ≥40%). Benefits were consistent across EF ranges, with a favorable safety profile regarding hyperkalemia when appropriately monitored.[61,62] Emerging device-based therapies for select HFpEF patients with resistant HTN include renal sympathetic denervation (RDN), which reduces sympathetic overactivation, improves diastolic function, and lowers blood pressure. While observational studies demonstrate promising outcomes, large-scale randomized data remain limited.[63,64] Baroreflex activation therapy (BAT), via implanted carotid sinus stimulation, has shown potential to improve hemodynamics and symptoms relief in early HFpEF studies with resistant HTN, though its application remains investigational.[65]

Diagnostic Evaluation of HFpEF

Prompt and accurate diagnosis is critical, as effective management depends on distinguishing HFpEF from alternative causes of dyspnea. Initial assessment begins with a comprehensive clinical evaluation identifying HF symptoms in

patients with preserved LVEF (≥50%), supported by echocardiographic evidence of LV enlargement and diastolic dysfunction, as well as elevated natriuretic peptide levels, including B-type natriuretic peptide (BNP) or NT-proBNP.[66]

Contemporary diagnostic algorithms enhance precision by combining clinical features, imaging, and biomarkers. The H2FPEF score incorporates HTN, obesity, AF, age >60 years, PH, and elevated filling pressures to provide a non-invasive rule-in/rule-out tool.[67] The Heart Failure Association Pre-test Assessment, Echocardiography and natriuretic peptides, Functional testing, Final etiological work-up (HFA-PEFF) algorithm follows a stepwise approach using echocardiography and natriuretic peptides, with functional testing reserved for cases with intermediate probability.[60] Both scoring systems demonstrate robust diagnostic and prognostic utility, particularly when applied together.[60,67]

Therapeutic Strategies

Upon confirmation of HFpEF, treatment aims to relieve symptoms and attenuate disease progression. Loop diuretics remain the cornerstone of congestion management; however, they do not improve long-term prognosis and require cautious use to prevent over-diuresis.[53] Neurohormonal modulation is advised for managing comorbidities. Mineralocorticoid receptor antagonists (MRAs) such as spironolactone reduced hospitalizations in specific subgroups of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT), although variable adherence and regional differences have limited their universal recommendation.[68,69] In the Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial, sacubitril–valsartan did not meet the primary efficacy endpoint in the overall study population. However, subgroup analyses indicated potential benefit among women and in patients with LVEF at the lower end of the preserved range.[70]

SGLT2 inhibitors represent a major therapeutic advancement. In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial, empagliflozin reduced the composite endpoint of CV death or HF hospitalization by about 21% in patients with LVEF > 40%. Similarly, in the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial, dapagliflozin exhibited comparable benefits across the spectrum of preserved EF. These findings have supported robust guideline recommendations endorsing the use of SGLT2 inhibitors for the management of HFpEF.[71,72]

Exercise-based rehabilitation improves functional capacity and QoL. The REHAB-HF trial demonstrated that tailored physical training enhanced mobility and psychosocial well-being in older HFpEF patients.[73] Device-based interventions, including percutaneous interatrial shunts, aim to reduce LV filling pressure and improve exercise tolerance in selected patients; however, long-term safety and efficacy data are still limited.[74]

Comprehensive management necessitates the optimal management of prevalent comorbidities, including HTN, DM, CKD, and AF, while individualizing therapy according to metabolic, inflammatory, or fibrotic phenotypes. Such precision medicine approaches hold promise for the development of future personalized therapies for heart failure with preserved ejection fraction.

Follow-Up and Prognosis in HFpEF

HFpEF imposes a substantial long-term clinical burden. Despite diagnostic and therapeutic advances, prognosis remains poor, with mortality rates comparable to HFrEF.[75] Key determinants of outcomes include age, comorbidity burden, sex, and baseline functional status. Rehospitalization serves as a critical marker of disease severity and healthcare utilization. Contemporary registries report 30-day readmission rates of 18–23%, with nearly 50% of patients rehospitalized within one year.[76] Precipitants of recurrent hospitalizations include volume overload, exacerbations of comorbid conditions such as CKD and AF, and non-cardiac complications including infections and frailty-related syndromes.[77] These results underscore the multifactorial and systemic nature of HFpEF pathophysiology, which often limits the effectiveness of therapies targeting a single pathogenic mechanism.[78] Recurrent hospitalizations are independently associated with higher all-cause mortality and progressive functional decline, particularly in older adults.[79] Survival outcomes vary across populations and healthcare systems. Five-year all-cause mortality rates are estimated to range from 50% to 60%, largely driven by advanced age and a high burden of comorbidities.[80] About half of all deaths are attributable to cardiovascular causes, with the remainder related to renal disease, infections, and malignancies.[81]

Structured and proactive follow-up is essential for improving clinical outcomes and preserving QoL. Current guidelines recommend regular outpatient monitoring focused on fluid status, symptom assessment, and optimization of comorbidity management.[15] Multidisciplinary care models that integrate cardiology, nephrology, geriatrics, nursing, and palliative care have been illustrated to reduce hospitalizations and improve patient-centered outcomes.[82] Risk stratification tools, including the H2FPEF score and serial measurement of natriuretic peptides, assist in identifying high-risk patients and tailoring the intensity of follow-up.[67] In addition, telemonitoring and structured rehabilitation programs have been showento enhance treatment adherence and reduce adverse events among elderly populations.[83]

HFpEF remains associated with an unfavorable prognosis, with increased risk of rehospitalization and mortality. Optimizing outcomes requires a multidisciplinary, personalized approach that integrates early risk stratification with evidence-based interventions. Recent studies underscore phenotypic heterogeneity and the influence of comorbidities such as obesity, DM, and AF on disease trajectory. Tailored management strategies addressing these diverse phenotypes are increasingly recognized as essential.[5,24,35] RCTs have demonstrated the efficacy SGLT2 inhibitors, including empagliflozin and dapagliflozin, in reducing the composite endpoint of CV death and HF hospitalization in patients with preserved EF, representing a major therapeutic advance in HFpEF care.[84,85] Angiotensin receptor–neprilysin inhibition with sacubitril/valsartan has shown variable benefits depending on sex and baseline LVEF, further underscoring the need for individualized treatment approaches.[86] Non-pharmacologic interventions, particularly structured rehabilitation and exercise training, consistently improve functional status and QoL and should be integrated into standard HFpEF management.[87,88] Emerging evidence also emphasizes the impact of psychosocial stressors, environmental exposures, and metabolic disturbances in younger populations, supporting the need for early detection and integrative management strategies tailored to this cohort.[43,58] Table 1 provides a chronological overview of selected landmark studies, focusing on those with significant impact on epidemiology, pathophysiology, diagnostics, and therapeutics.

Discussion

This systematic review synthesizes current evidence regarding the epidemiology, diagnosis, treatment approaches, follow-up, and prognosis of HFpEF, emphasizing recent therapeutic advances while also delineating persistent clinical management.

The accumulated data reinforce HFpEF as a complex, heterogeneous syndrome characterized by diverse clinical presentations and a high burden of comorbidities. Accurate diagnosis remains essential, increasingly supported by algorithms such as the H2FPEF score and the HFA-PEFF algorithm, which integrate clinical, imaging, and biomarker data to enhance diagnostic precision and prognostic stratification.[60,67]

Therapeutically, SGLT2 inhibitors, including empagliflozin and dapagliflozin, have transformed HFpEF management by significantly reducing CV mortality and HF hospitalizations across a broad spectrum of preserved EF.[84,85] Other pharmacologic agents, including MRAs and sacubitril/valsartan, demonstrate more selective or subgroup-specific benefits.[68,87]

While SGLT2 inhibitors now constitute the foundational pillar of HFpEF therapy with robust guideline recommendations (Class I, ESC/AHA), recent landmark trials have expanded therapeutic options targeting metabolic, inflammatory, and fibrotic pathways in specific phenotypes. The FINEARTS-HF trial (2024) established finerenone as the first nonsteroidal MRA to significantly reduce total worsening HF events—including hospitalizations—and CV death in patients with HFmrEF, with consistent benefits across EF ranges and favorable hyperkalemia risk under monitoring.[61,62] In obesity-related HFpEF, the STEP-HFpEF program demonstrated that semaglutide improved symptoms, physical function, exercise capacity, and reduced inflammation/weight, with pooled analyses showing lower risks of CV death or HF events.[102] Similarly, the SUMMIT trial (2024–2025) reported that tirzepatide, a dual GLP-1/GIP receptor agonist, reduced the composite of CV death or HF worsening by about 38%, improved patient-reported health status, and mitigated circulatory overload and inflammation, achieving greater weight loss compared with semaglutide.[103,104] These findings underscore the heterogeneity of HFpEF and the potential for targeted metabolic and anti-fibrotic interventions, although no single agent is universally disease-modifying across all phenotypes. Integration with existing foundational therapies, such as SGLT2 inhibitors, requires careful consideration of comorbidities and vigilant monitoring.

Despite these therapeutic advances, rehospitalization rates remain high, and long-term outcomes are often poor, especially among patients with multimorbidity or frailty. These challenges highlight the critical role of multidisciplinary care models integrating cardiology, geriatrics, nephrology, and palliative care to optimize outcomes and reduce healthcare

https://doi.org/10.2147/VHRM.S578698

Table 1 Chronological Overview of Selected Landmark Clinical Investigations in Heart Failure with Preserved Ejection Fraction (HFpEF)

Author & Year	Study Focus	Study Type	Sample Size	Population	Main Outcome	Clinical Implication
Parizad R et al (2025)[43]	Emerging risk factors in younger populations	Observational study	Not specified	Younger HFpEF patients	Identified metabolic syndrome, environmental exposures, and post-COVID effects as drivers of early-onset HFpEF	Called for early risk recognition and prevention strategies in younger adults
Ilonze OJ et al (2025)[89]	Nonpharmacologic management	Review	Not specified	HFpEF patients	Highlighted role of physical activity and weight control	Recommends lifestyle modifications to reduce rehospitalization and mortality
Forsyth FJ et al (2024)[90]	Blended lifestyle intervention	Interventional study	Not specified	Multi-morbid older HFpEF patients	Designed to improve physical function, diet, and QoL	Supports combined lifestyle interventions in HFpEF
Gao M et al (2024)[91]	Effects of SGLT2 inhibitors on exercise ability and well-being in HF	Systematic review and meta-analysis	Total N=23,523	Symptomatic heart failure patients with either reduced or preserved ejection fraction	Enhanced peak oxygen uptake by 1.61 mL/kg/min, walking distance by 13 m, and gains in symptom, clinical, and overall KCCQ scores by 2–2.3 points.	Reinforces SGLT2 inhibitors as key for boosting daily function and life satisfaction in heart failure, irrespective of heart function type, gender, or blood sugar issues.
Paitazoglou C et al (2024)[74]	Atrial Flow Regulator (AFR) device for interatrial shunting (PRELIEVE)	Prospective non-randomized pilot study	N=53	Symptomatic patients with HFrEF or HFpEF (NYHA class II–IV)	Device remained patent in 92% at 1 year, reduced pulmonary capillary wedge pressure (PCWP) by 5 mmHg at 3 months, improved NYHA class, 6-minute walk distance, and KCCQ scores in some patients.	Suggests atrial shunt device is feasible and safe, with potential to improve functional outcomes, particularly in HFpEF; larger randomized trials needed to confirm efficacy.
Zafeiropoulos S et al (2024)[92]	Pharmacological treatments in HFmrEF/HFpEF	Systematic review and network meta-analysis	29,875 (from 13 RCTs)	Patients with HF and LVEF >40% (mean 56.3%)	SGLT2i, ARNI, MRA reduced CV death/HHF composite vs placebo; quadruple therapy (ARNI+BB+MRA+SGLT2i) most effective (HR 0.47)	Supports SGLT2i (and combinations including ARNI/MRA) as key for reducing composite CV/HF outcomes in HFpEF/HFmrEF; SGLT2i benefit consistent across LVEF subgroups.
Böhm M et al (2023)[93]	Empagliflozin efficacy across systolic blood pressure levels (EMPEROR-Preserved)	RCT	N=5988	Patients with HFpEF (EF >40%)	Empagliflozin reduced cardiovascular death or heart failure hospitalization consistently across baseline systolic blood pressure groups, with no significant impact on adverse events like hypotension.	Supports the use of empagliflozin as an effective and safe treatment in HFpEF patients, regardless of baseline blood pressure.
Wilke MR et al (2023)[58]	Links between NT-proBNP, anxiety symptoms, and social support over time	Post-hoc analysis of multicenter randomized controlled trial	N=422	Patients with HFpEF (mean age 66.8 years, 47.6% male, mostly NYHA class II)	NT-proBNP showed small inverse link to anxiety at start, stronger in males; baseline anxiety tied to lower NT-proBNP after one year; ties weakened after adjusting for support and other factors; support fully explained NT-proBNP-anxiety connection.	Points to complex ties where social support explains NT-proBNP effects on anxiety; hints at two-way influence; suggests exploring roles of gender, oxytocin, and nerve tone in future work.

Chen X, Wu M (2023)[1]	Overview of HF cases where EF improves	Narrative review	Not specified	Individuals with HF who show EF recovery	Discussed definitions, frequency, causes, clinical paths, and ongoing treatment needs for recovered case.	Stresses continued drug therapy to avoid relapse, highlights gaps in knowledge, and suggests future studies on tailored care and monitoring.
De Luca et al (2023)[35]	Endothelial Dysfunction and HFpEF – Updated Review	Narrative Review	N/A (synthesis of literature)	HFpEF patients with comorbidities	Comorbidities (e.g., hypertension, diabetes mellitus, hypercholesterolaemia) induce endothelial dysfunction → impaired NO bioavailability, oxidative stress, inflammation, microvascular dysfunction → contributes to myocardial stiffness, diastolic dysfunction, elevated filling pressures, and HFpEF progression	Endothelial dysfunction as central link between comorbidities and HFpEF pathogenesis; potential therapeutic targets include SGLT2 inhibitors, antioxidants, exercise to improve ED and outcomes
Hamo et al (2024)[29]	HFpEF epidemiology, pathophysiology, diagnosis, management	Narrative Review (Primer)	N/A (synthesis)	Aging global populations	HFpEF accounts for nearly half (~50%) of all HF cases worldwide; prevalence rising with aging and comorbidities (HTN, DM, obesity)	Predominant HF subtype; need for targeted therapies (SGLT2i) and improved diagnostics
Bjarnason-Wehrens B et al (2022)[88]	Effectiveness and safety of resistance training in cardiac patients, focusing on elderly and frail individuals.	Narrative review	Not specified	Patients with coronary artery disease, heart failure (including HFpEF), and valvular heart disease, with emphasis on older and frail adults.	Resistance training is beneficial and safe for improving muscle strength and function in CAD and HFrEF; limited data exist for HFpEF and VHD, especially in frail elderly.	Suggests tailored resistance training programs for older cardiac patients to enhance physical function, highlighting the need for more research on HFpEF and frail populations in rehabilitation settings.
Ferreira JP et al (2022)[68]	Impact of empagliflozin on heart failure outcomes based on mineralocorticoid receptor antagonist use	RCT (subgroup analysis)	N=5988	Patients with HfpEF, 37.5% using MRAs at baseline	Empagliflozin reduced the primary outcome similarly in MRA nonusers and users; stronger effect on HF hospitalizations in nonusers; lowered hyperkalemia risk regardless of MRA use.	Suggests empagliflozin is effective across MRA use groups, with potential added benefit in preventing hospitalizations for non-MRA users; supports its use to manage hyperkalemia in HFpEF.
Solomon SD et al (2022)[85]	Effect of dapagliflozin on HF outcomes in mildly reduced or preserved ejection fraction	RCT	N=6263	Patients with HF and EF >40%, including those with or without diabetes	Dapagliflozin reduced the risk of worsening HF or cardiovascular death by 18%, with consistent benefits across EF levels and diabetes status.	Supports dapagliflozin as an effective treatment to lower HF events in patients with mildly reduced or preserved EF, broadening therapeutic options.
Anker SD et al (2022)[94]	Efficacy of empagliflozin in HF across preserved and mid-range EFs	Pre-specified analysis of randomized controlled trial	N=5988	Patients with HF and EF >40% (66.9% with LVEF ≥50%, 33.1% with LVEF 41–49%)	Empagliflozin reduced cardiovascular death or HF hospitalization by 17% in LVEF ≥50% and 29% in LVEF 41–49%, with consistent benefits in kidney function and QoL across both group	Supports empagliflozin use across the full EF spectrum HF, enhancing outcomes in both preserved and mid-range cases.

(*Continued*)

https://doi.org/10.2147/VHRM.S578698

https://doi.org/10.2147/VHRM.S578698

Table 1 (Continued).

Author & Year	Study Focus	Study Type	Sample Size	Population	Main Outcome	Clinical Implication
Abdin et al (2024)[30]	HFpEF epidemiology, pathophysiology, diagnosis, treatment	Narrative Review	N/A (synthesis)	Global populations with comorbidities	Prevalence of HFpEF increasing across populations; high hospitalization (up to 80%) and mortality (up to 50%) in 5 years; linked to cardiometabolic factors	Poor outcomes and QoL; promising emerging therapies (SGLT2i, incretin-based) for cardiometabolic phenotypes
Martin N et al (2021)[95]	Effects of beta-blockers and renin-angiotensin-aldosterone system inhibitors on HFpEF	Systematic review and meta-analysis	N=23,492	Adults with HFpEF, defined by LVEF >40%	Beta-blockers may reduce cardiovascular mortality, MRAs likely reduce HF hospitalization, while ACEIs, ARBs, and ARNIs show little to no effect on mortality or hospitalization.	Suggests potential benefits of beta-blockers and MRAs in HFpEF, though evidence quality varies, indicating a need for further high-quality trials.
Mishra S, Kass DA (2021)[9]	Cellular and molecular mechanisms underlying HFpEF	Narrative review	Not specified	Patients with HFpEF, focusing on cardiac, lung, kidney, and skeletal muscle involvement	HFpEF involves multisystem dysfunction beyond diastolic issues, with overlapping metabolic, inflammatory, and structural changes also seen in obesity and diabetes, suggesting new therapeutic targets.	Highlights the need for therapies addressing multisystem pathology and metabolic-inflammatory pathways, potentially leading to personalized treatments for improved HFpEF outcomes.
Monte MJ, Eaton CB, (2021)[96]	Role of physical activity in managing and preventing HF	Narrative review	Not specified	Individuals at risk of or with HF	Physical activity improves cardiovascular health, reduces HF risk, and enhances QoL in affected patients.	Supports integrating tailored physical activity programs into HF prevention and treatment strategies.
Packer M et al (2021)[97]	Impact of empagliflozin on worsening HF events in preserved EF	RCT	N=5988	Patients with HF and EF >40%, class II–IV	Empagliflozin reduced the risk of cardiovascular death, HF hospitalization, or urgent visits by 23%, with early benefits and fewer outpatient diuretic intensifications.	Suggests empagliflozin as an effective early intervention to lessen severity and frequency of HF events in patients with preserved EF.
Backhaus SJ et al 2021)[98]	Use of real-time cardiac MRI during exercise to diagnose HF with preserved EF	Prospective cohort study	N=75	Patients with diastolic dysfunction and exertional dyspnea (E/e'>8, NYHA class ≥II)	Real-time cardiac MRI exercise stress identified impaired LA emptying and strain as key markers, outperforming rest measures in diagnosing HFpEF.	Suggests real-time cardiac MRI as a noninvasive, accurate alternative to catheterization for HFpEF diagnosis, pending further multicenter validation.
Kitzman DW et al (2021)[87]	Effect of a tailored rehabilitation program on physical function in older HF patients	RCT	N=349	Older patients hospitalized for acute decompensated HF, mostly frail or prefrail	Rehabilitation improved physical function by 1.5 points on the Short Physical Performance Battery at 3 months compared to usual care, with no significant difference in 6-month rehospitalization rates.	Supports early rehabilitation to enhance recovery in frail older patients with HF, though further research is needed on rehospitalization impact
Anker SD et al (2021)[84]	Effect of empagliflozin on cardiovascular outcomes HFpEF	RCT	N=5988	Patients with class II–IV HF and EF >40%, with or without diabetes	Empagliflozin reduced the combined risk of cardiovascular death or HF hospitalization by 21%, primarily due to a 29% lower risk of hospitalization.	Indicates empagliflozin as a valuable treatment option to reduce HF hospitalizations in patients with preserved EF, regardless of diabetes status.
Wohlfahrt P et al (2021)[99]	Quality of life assessment in patients with recovered ejection fraction	Observational cohort study	Not specified	Patients with a history of HFrEF that improved to recovered EF	Improved quality of life scores observed in patients with recovered EF compared to those without recover	Suggests that recovery of EF may enhance patient well-being, supporting the need for targeted follow-up to sustain these gains

McMurray JJ et al (2020)[86]	Comparison of sacubitril-valsartan versus valsartan effects by sex in HFpEF	Subgroup analysis of randomized controlled trial	N=4822	Patients with HF and EF ≥45%, including men and women.	Sacubitril-valsartan showed a greater reduction in Hf hospitalization or cardiovascular death in women than men, with a hazard ratio of 0.73 versus 0.93.	Suggests sacubitril-valsartan may be more beneficial for women with preserved EF, warranting sex-specific treatment considerations.
Silverman DN, Shah SJ (2019)[100]	Phenotype-guided treatment strategies for HFpEF	Narrative review	Not specified	Patients with HFpEF, considering various phenotypes	Proposed tailored therapies based on phenotypes (eg, metabolic, hypertensive) improve symptom management and outcomes.	Supports a personalized approach to HFpEF treatment, potentially enhancing efficacy by targeting specific patient subgroups.
Pfeffer MA, Shah AM, Borlaug BA (2019)[2]	Overview of HFpEF, including epidemiology and therapeutic advances	Narrative review	Not specified	Patients with HF and non-markedly reduced ejectionEF, including normal levels	Recognition of HFpEF as a significant condition has driven clinical research, with potential for improved outcomes through phenotyping and genotyping in future trials.	Emphasizes the need for targeted research and personalized approaches to enhance treatment efficacy for patients with HFpEF.
Reddy YN et al (2018)[67]	Development of a noninvasive diagnostic score for HfpEF	Retrospective cohort study	N=514 (414 derivation, 100 validation)	Patients with unexplained dyspnea undergoing hemodynamic exercise testing	The H2FPEF score (based on obesity, AF, age, antihypertensives, E/e′ ratio, and PAH) effectively discriminates HFpEF from noncardiac dyspnea with an AUC of 0.841–0.886.	Supports the use of the H2FPEF score as a practical tool to guide diagnosis and further testing for HFpEF in clinical practice.
Zheng SL et al (2018)[101]	Impact of drug treatments on outcomes in HFpEF	Systematic review and meta-analysis	N=18,101	Patients with HF and LV EF ≥40%	Beta-blockers reduced all-cause mortality (RR: 0.78) and cardiovascular mortality, while other drug classes showed no significant effect on mortality or HF hospitalization.	Suggests beta-blockers may benefit HFpEF patients, warranting further trials, while other therapies require additional research to establish efficacy.
Dunlay SM et al, (2017)[80]	Epidemiology of HfpEF	Narrative review	Not specified	Community-dwelling patients with HF	Approximately 50% of HF cases are HFpEF, with increasing age, HTN, obesity, and CAD as key risk factors; mortality is predominantly cardiovascular but includes more noncardiac deaths than HFrEF.	Highlights the need for targeted prevention and management strategies for HFpEF, considering its high prevalence and unique risk profile in the community.
Shah SJ et al (2016)[5]	Phenotype-specific treatment strategies for heart failure with preserved ejection fraction	Narrative review	Not specified	Patients with HFpEF, considering diverse phenotypes	Proposed targeted therapies address systemic inflammation, endothelial dysfunction, and organ-specific issues, tailored to individual HFpEF phenotypes.	Suggests a personalized, multiorgan treatment approach to improve outcomes in HFpEF by addressing its heterogeneous nature.

Abbreviations: AHA, American Heart Association; AF, Atrial Fibrillation; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; BMI, Body Mass Index; CMD, Coronary Microvascular Dysfunction; CMR, Cardiovascular Magnetic Resonance; COVID-19, Coronavirus Disease 2019; cGMP, Cyclic Guanosine Monophosphate; CKD, Chronic Kidney Disease; DM, Diabetes Mellitus; ED, Endothelial Dysfunction; eNOS, Endothelial Nitric Oxide Synthase; ESC, European Society of Cardiology; FMD, Flow-Mediated Dilation; GBD, Global Burden of Disease; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; GWTG-HF, Get with The Guidelines®–Heart Failure; HF, Heart Failure; HFmrEF, Heart Failure with Mid-Range Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction; HFrEF, Heart Failure with Reduced Ejection Fraction; HTN, Hypertension; LVEF, Left Ventricular Ejection Fraction; LV, Left Ventricular; MeSH, Medical Subject Headings; MetS, Metabolic Syndrome; MI, Myocardial Ischemia; NO, Nitric Oxide; NOS, Newcastle–Ottawa Scale; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL, Quality of Life; RCTs, Randomized Controlled Trials; RoB, Risk of Bias; SGLT2, Sodium–Glucose Cotransporter 2; SGLT2i, Sodium–Glucose Cotransporter 2 Inhibitor; T2D, Type 2 Diabetes; VOP, Venous Occlusion Plethysmography.

utilization.[6] Additionally, nonpharmacologic interventions, notably structured exercise rehabilitation as demonstrated in the Rehabilitation Therapy in Older Acute Heart Failure Patients(Patients (REHAB HF) trial, improve physical function, QoL, and psychosocial well-being, emphasizing their integral role in routine care.[87]

Knowledge Gaps and Future Directions

Notwithstanding significant progress, important gaps remain. The absence of a universally effective pharmacologic therapy across all HFpEF phenotypes underscores its conceptualization as a spectrum of overlapping pathophysiological processes rather than a single disease entity. Future research should focus on identifying reliable biomarkers and advanced imaging modalities to enable phenotype-driven stratification and targeted therapeutic interventions.

Emerging therapies include cellular approaches, epigenetic modifiers, and regulatory RNAs targeting maladaptive remodeling. The Phase 1b/2 trial of the microRNA132 inhibitor CDR-132L(CDR-132L (Phase 1b/2 trials of CDR-132L), a synthetic antisense oligonucleotide inhibiting miR-132, have demonstrated safety, sustained miR-132 suppression, and potential to prevent or reverse post-MI cardiac remodeling, with ongoing evaluation in the HF-REVERT trial (primarily HFrEF-focused, but potentially relevant to HFpEF fibrosis).[105,106] Fibroblast-targeted approaches, such as Fibroblast Activation Protein(FAP) imaging, antifibrotic strategies and, C-C Chemokine Receptor type 2(CCR2) inhibitors (targeting monocyte/macrophage recruitment in inflammation-driven HFpEF) are under investigation in preclinical and early-phase studies for anti-inflammatory and anti-fibrotic effects.[107,108] Pirfenidone, a Transforming Growth Factor-beta (TGF-β) inhibitor approved for idiopathic pulmonary fibrosis, has demonstrated preclinical card ioprotective effects by reducing cardiac fibroblast proliferation, myofibroblast differentiation, and myocardial fibrosis in animal models, supporting its potential rationale for HFpEF trials like PIROUETTE (though clinical data remain limited to modest changes in extracellular volume).[109–111]

Sex-specific differences in treatment response, as observed in PARAGON-HF subgroup analyses, suggest hormonal and structural factors may confer differential benefit in women, warranting further investigation.[86] Moreover, frailty, sarcopenia, and cognitive impairment likely influence therapeutic outcomes but remain underexplored in clinical trial design and care pathways.

Device-based therapies, including interatrial shunt devices, represent a promising symptom-relief strategy in select patients. Early feasibility studies report favorable safety profiles and functional improvement at six months, while REDUCE LAP-HF II suggests potential benefit in carefully selected subgroups despite the trial not meeting its primary endpoint.[112] Furthermore, global disparities in HFpEF outcomes and access to care further emphasize the need for inclusive research encompassing low- and middle-income populations.

The future of HFpEF care will increasingly depend on precision medicine, integrating individualized treatment strategies guided by pathophysiology, comorbidity profiles, and patient preferences.

Limitations

This review has several limitations. Despite a comprehensive literature search, studies published in non-English languages or indexed outside the selected databases may have been inadvertently excluded. In addition, substantial heterogeneity in diagnostic criteria and outcome measures across the included studies limits direct comparisons and may reduce the generalizability of the findings. Given the rapidly evolving therapeutic landscape of heart failure with preserved ejection fraction, evidence published after completion of this review may not have been captured. Finally, although efforts were made to include data from diverse global populations, most available evidence originates from high-income countries, potentially limiting the applicability of the findings to low- and middle-income settings.

Conclusion

HFpEF represents a growing clinical and public health challenge due to its rising prevalence, diagnostic complexity, and limited availability of evidence-based therapies. Although recent advances have enhanced understanding of its heterogeneous pathophysiology, current management remains predominantly symptom-directed, with relatively few pharmacologic interventions demonstrating meaningful effects on hospitalization or mortality. The introduction of SGLT2 inhibitors represents a pivotal milestone, delivering clinically significant improvements in patient outcomes.

Optimal HFpEF management requires a comprehensive, individualized approach that addresses comorbidities, promotes lifestyle modification, and integrates emerging device-based therapies in carefully selected patients. Continued research into phenotype-specific pharmacologic and non-pharmacologic strategies is essential to improve long-term outcomes and reduce the societal and economic burden of HFpEF.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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