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# Heart Failure with Preserved Ejection Fraction: A Clinical Reappraisal

**Dedeepya Sree Parna[1*], Panchajanya Kolli[2], Sai Karthic Ananthakrishnan[3*] and Sahithi Reddy Daivamdinne[4]**

[1]Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, Telangana, India
[2]Long Island University, Brooklyn, New York, USA
[3]Indira Gandhi Medical College & Research Institute, Kathirkamam, Puducherry, India
[4]Mamata Academy of Medical Sciences, Hyderabad, Telangana, India

## Abstract

Heart failure with preserved ejection fraction (HFpEF) poses a significant and growing clinical burden, yet its complex pathophysiology and diagnostic challenges hinder effective management, necessitating a comprehensive reappraisal of current knowledge. This review highlights the heterogeneous nature of HFpEF, emphasizing the critical roles of comorbidities such as hypertension, diabetes, and obesity in driving disease progression, while also exploring advancements in diagnostic tools like the HFA-PEFF score and emerging biomarkers. Furthermore, it evaluates the therapeutic potential of SGLT2 inhibitors, anti-inflammatory agents, and personalized treatment strategies, offering insights into their mechanisms and clinical benefits. The review underscores the limitations of current therapies and the need for improved phenotyping to guide precision medicine approaches. Future research should prioritize large-scale trials to validate novel interventions, refine diagnostic criteria, and explore integrative care models that address both cardiac and systemic contributors to HFpEF. By bridging gaps in understanding and treatment, this review aims to inform clinical practice and inspire innovative solutions for improving outcomes in HFpEF patients.

**Keywords:** Biomarkers, Comorbidities, Diagnosis, Heart failure with preserved ejection fraction, Pathophysiology, SGLT2 inhibitors, Treatment strategies

***Correspondence to:*** Dedeepya Sree Parna and Sai Karthic Ananthakrishnan, Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, Telangana, India and Indira Gandhi Medical College & Research Institute, Kathirkamam, Puducherry, India.

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## Introduction

HFpEF is increasingly recognized as a significant clinical syndrome characterized by the presence of heart failure symptoms alongside a normal or near-normal left ventricular ejection fraction (LVEF ≥ 50%) [1-3]. This condition accounts for approximately half of all heart failure cases globally, with its incidence rising by 45% in recent years [1]. Despite this growing prevalence, HFpEF remains poorly understood, with no standardized guidelines for diagnosis or treatment, leading to challenges in patient management and outcomes [1].

The clinical reappraisal of HFpEF has been approached through various perspectives, emphasizing prognostic assessment, pathophysiological mechanisms, therapeutic strategies, and diagnostic challenges. Prognostic tools such as the HFA-PEFF score have demonstrated significant clinical relevance in predicting outcomes in HFpEF patients. Sotomi et al. [4] highlighted the prognostic significance of this scoring system, associating higher scores with increased risks of all-cause mortality and heart failure readmissions, thereby underscoring its utility in clinical risk stratification.

## Pathophysiology of HFpEF

HFpEF is a multifactorial disease influenced by various cardiac and non-cardiac comorbidities, including hypertension, obesity, and diabetes [5]. The pathophysiological mechanisms underlying HFpEF are complex and involve diastolic dysfunction, characterized by impaired left ventricular relaxation and increased stiffness [5]. This dysfunction leads to elevated filling pressures and contributes to the clinical manifestations of heart failure, such as dyspnea and exercise intolerance [5]. Recent studies have highlighted the role of inflammation and neurohormonal activation in the progression of HFpEF, suggesting that targeting these pathways may offer new therapeutic avenues [6, 7].

Pathophysiological heterogeneity remains a central theme in understanding HFpEF. Campos-Martins et al. [8] proposed the 'systemic microvascular paradigm' to explain the presentation variability, emphasizing the role of microvascular dysfunction and adenosine signaling pathways. Pharmacological modulation of these pathways offers potential therapeutic benefits, although side effects must be carefully considered. Systemic inflammation is recognized as a key driver in HFpEF pathophysiology [9-11]. Kittipibul et al. [12] reviewed the efficacy and safety of anti-inflammatory therapies, particularly myeloperoxidase inhibitors like mitiperstat, as explored in the ENDEAVOR trial, emphasizing the potential of targeting inflammatory pathways to modify disease progression.

HFpEF is characterized by the presence of heart failure symptoms despite a normal or nearly normal LVEF [13-15]. It represents a significant and increasing portion of heart failure cases, highlighting the need for better understanding and treatment options. Complex pathophysiology, the underlying mechanisms of HFpEF are multifactorial and complex [16, 17]. They involve a combination of: (i) myocardial fibrosis: this refers to the thickening and stiffening of the heart muscle, which can impair its ability to function properly [18], (ii) ventricular-arterial coupling: this describes the relationship between the heart and the arteries, which can be disrupted in HFpEF [19], and (iii) endothelial dysfunction: this involves the impairment of the inner lining of blood vessels, affecting blood flow and pressure [20]. The significant impact of various comorbidities such as obesity, diabetes, and hypertension on the development and progression of HFpEF. These conditions can exacerbate the heart's structural and functional abnormalities. Systemic inflammatory responses, inflammation plays a crucial role in the pathophysiology of HFpEF, contributing to the overall dysfunction of the cardiovascular system [21-23].

While diastolic dysfunction and ventricular stiffness are central to HFpEF, the condition's complexity is compounded by the interplay of multiple pathophysiological mechanisms and comorbidities [24, 25]. This complexity poses challenges for treatment, as universal therapies remain limited. Further research is needed to unravel the precise mechanisms and develop targeted interventions that address the underlying causes of HFpEF. Understanding the contributions of diastolic dysfunction and ventricular stiffness is a step towards improving outcomes for patients with this challenging condition [26, 27].

Comorbidities such as hypertension, diabetes, and obesity significantly influence the pathophysiology of HFpEF by contributing to various pathophysiological mechanisms that exacerbate cardiac dysfunction [28-30]. These comorbidities are not only prevalent among HFpEF patients but also play a crucial role in the disease's onset and progression [31, 32]. The interplay between these conditions and HFpEF involves complex mechanisms including vascular dysfunction, metabolic alterations, and myocardial remodeling.

Hypertension is a well-established risk factor for HFpEF, contributing to increased arterial stiffness and altered ventricular-vascular coupling. This results in elevated left ventricular filling pressures and diastolic dysfunction, which are hallmark features of HFpEF [33, 34]. Over time, hypertension leads to cardiac hypertrophy and fibrosis, further exacerbating diastolic dysfunction and increasing the risk of HFpEF development [35]. Despite its prevalence, recent trends indicate a decrease in the severity of hypertension in HFpEF patients, possibly due to improved management strategies, although the prevalence of hypertension itself has increased (Figure 1) [34].

Diabetes contributes to HFpEF through mechanisms such as endothelial dysfunction, increased systemic inflammation, and metabolic disturbances [36, 37]. These factors lead to myocardial stiffness and impaired relaxation, which are critical in HFpEF pathophysiology [38, 39]. The presence of diabetes is associated with

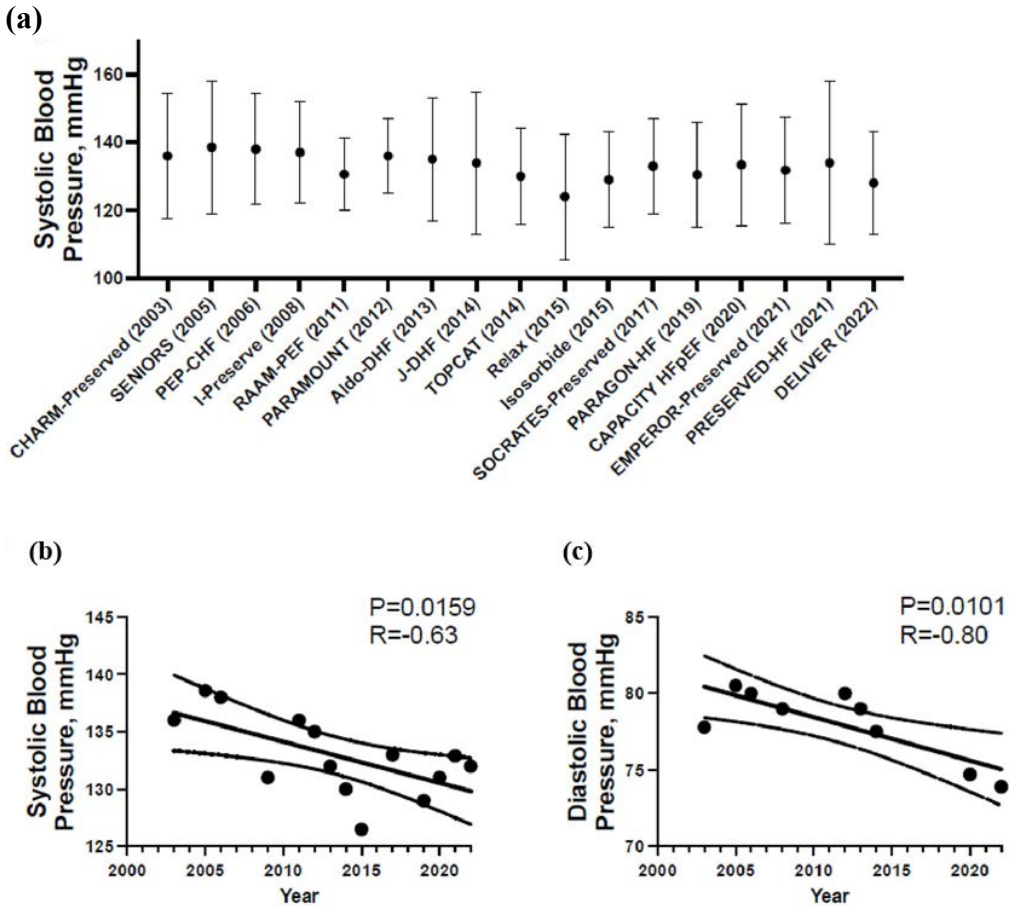


**Figure 1:** Systolic blood pressure trends, analysis of enrolment of systolic blood pressure and diastolic blood pressure in HFpEF clinical trials [34].

increased cardiac lipid accumulation, which exacerbates diastolic dysfunction, particularly in female patients [40]. Diabetes also promotes microvascular dysfunction and chronic low-grade inflammation, further contributing to myocardial remodeling and dysfunction in HFpEF [39].

Obesity is a significant contributor to HFpEF, primarily through its effects on systemic inflammation, adiposity-related metabolic changes, and increased cardiac workload [38, 40]. It independently drives cardiac hypertrophy and alters mitochondrial metabolism, leading to structural and functional cardiac changes characteristic of HFpEF [35]. Obesity-related comorbidities, such as sleep apnea and metabolic syndrome, further compound the risk and severity of HFpEF by promoting adverse cardiovascular remodeling [41].

The combination of these comorbidities often results in a cumulative effect on arterial stiffness, which is a critical determinant of HFpEF. This cumulative effect is independent of age and other factors, highlighting the importance of managing these comorbidities to prevent HFpEF progression [33]. The pathophysiological interactions between these comorbidities and HFpEF are complex and multifactorial, involving changes in myocardial structure, function, and metabolism. These interactions underscore the need for a tailored therapeutic approach that addresses the specific comorbidities present in each patient [41, 42].

While the influence of comorbidities on HFpEF is well-documented, the exact mechanisms remain incompletely understood, and the heterogeneity of HFpEF poses challenges for treatment [43, 44]. The interplay between comorbidities and HFpEF suggests that a one-size-fits-all approach may not be effective, and personalized treatment strategies that consider individual comorbidity profiles could improve outcomes [45-47]. Additionally, the role of non-cardiac factors, such as chronic kidney disease and systemic inflammation, further complicates the pathophysiological landscape of HFpEF, indicating the need for comprehensive management strategies [48].

## Diagnosis of HFpEF

Diagnosing HFpEF poses significant challenges due to its heterogeneous nature and the overlap of symptoms with other conditions [49]. Traditional diagnostic criteria often fail to capture the complexity of HFpEF, leading to underdiagnosis and misclassification [49]. Recent advancements in echocardiographic techniques, such as speckle tracking and the assessment of diastolic function, have improved diagnostic accuracy [5]. Additionally, biomarkers like Galectin-3 and N-terminal pro-B-type natriuretic peptide are being explored for their prognostic value in HFpEF [7, 50].

Electrocardiographic (ECG) characteristics have been explored to better understand the electrophysiological profile of HFpEF [51, 52]. Bhattarai et al. [53] identified specific ECG features in hospitalized patients with different heart failure types, which may aid in future diagnostic and research efforts. Diagnostic challenges are exemplified by cases where initial HFpEF diagnoses are reconsidered. Vysočanský et al. [54] presented an elderly patient with an initial HFpEF diagnosis that was later revised, highlighting the importance of comprehensive evaluation in this population. Hemodynamic parameters such as systolic blood pressure and pulse pressure have prognostic implications. Lu et al. [55] analyzed pooled trial data, demonstrating that baseline systolic blood pressure and pulse pressure are associated with cardiovascular outcomes, with specific thresholds correlating with increased risk.

HFpEF is characterized by heart failure symptoms with a LVEF of at least 50%, but the diagnosis remains challenging due to the lack of a universal gold standard and the presence of multiple comorbidities that can mimic HFpEF symptoms [56-58]. Various diagnostic algorithms and tools have been developed to aid in the diagnosis, but their effectiveness and applicability can vary (Table 1).

### Diagnostic criteria and algorithms

- LVEF and structural abnormalities: HFpEF is defined by an LVEF of ≥50% along with symptoms of heart failure and evidence of cardiac structural or functional abnormalities, such as left ventricular hypertrophy or left atrial enlargement, and elevated natriuretic peptide levels [59, 60].

- HFA-PEFF and H2FPEF scores: The HFA-PEFF algorithm involves a stepwise approach using clinical evaluation, ECG, and natriuretic peptide levels to diagnose HFpEF. The H2FPEF score uses demographic, clinical, and ECG measures to estimate HFpEF probability. Both scores have shown moderate accuracy and are used to guide further diagnostic testing [60, 61].

- ECG: This is a key tool in diagnosing HFpEF, assessing diastolic function, left atrial size, and myocardial motion. It helps exclude other causes of symptoms and provides a comprehensive view of cardiac function [60, 62].

**Table 1:** Key diagnostic tools and algorithms for HFpEF.

| Tool/Algorithm | Components | Purpose | Strengths | Limitations |
|---|---|---|---|---|
| HFA-PEFF score | Clinical evaluation, natriuretic peptides, echocardiography (diastolic function, LA size) | Diagnose and stratify HFpEF risk | Validated, comprehensive | Moderate specificity requires advanced imaging |
| H2FPEF score | Obesity, AF, age, hypertension, pulmonary hypertension, filling pressure | Estimate HFpEF probability | Simple, bedside use | Lower sensitivity in comorbid populations |
| NT-proBNP | Blood biomarker (cutoff: >125 pg/mL) | Rule out HFpEF | High negative predictive value | Affected by obesity, renal dysfunction |
| Galectin-3 | Fibrosis biomarker | Prognostic assessment | Predicts disease progression | Limited diagnostic utility alone |
| Speckle-tracking ECG | LV global longitudinal strain | Detect subclinical systolic dysfunction | Early fibrosis detection | Limited availability, expertise-dependent |
| Cardiac magnetic resonance imaging | T1 mapping, ECV quantification | Assess myocardial fibrosis | Gold standard for tissue characterization | Expensive, limited access |
| Exercise stress ECG | Dynamic assessment of filling pressures | Confirm HFpEF in ambiguous cases | Provokes latent dysfunction | Invasive, resource-intensive |
| Invasive hemodynamics | Right heart catheterization (PCWP, LVEDP) | Gold standard for filling pressures | Definitive pressure measurements | Invasive, not routine |
| AI/NLP algorithms | Electronic health record analysis | Identify undiagnosed HFpEF | High-throughput screening | Requires validation |

## Challenges and limitations

- Comorbidities and overlapping symptoms: Conditions such as atrial fibrillation, diabetes, and chronic kidney disease can complicate the diagnosis due to overlapping symptoms and effects on biomarkers like natriuretic peptides [60, 63].

- Lack of consensus: There is no clear consensus on the definition of HFpEF, and diagnostic criteria can vary between guidelines and clinical trials, leading to potential overdiagnosis or underdiagnosis [59, 60].

- Biomarkers and imaging: While natriuretic peptides are commonly used, their levels can be influenced by other conditions, reducing specificity. Advanced imaging techniques and novel biomarkers are being explored to improve diagnostic accuracy [60].

Emerging approaches like AI and phenotyping are being investigated to improve HFpEF detection by analyzing electronic health records and identifying phenotypic clusters. This could lead to more personalized treatment approaches [64, 65]. Exercise testing, in cases where resting tests are inconclusive, exercise stress echocardiography or right heart catheterization can be used to assess diastolic function and filling pressures under stress conditions [60, 66].

A study by Wu et al. [65] focused on improving the detection of undiagnosed HFpEF using natural language processing (NLP) methods. The researchers identified a total of 9004 patients with a clinical diagnosis of heart failure from the Electronic Health Record data collected between 2010 and 2022. This large cohort provided a solid foundation for the analysis. Among the identified patients, 3915 had a LVEF of 50% or higher. This group was crucial for understanding the prevalence of HFpEF. Only 8.3% of the patients with LVEF ≥ 50% had a clinician-assigned diagnosis of HFpEF. This indicates a significant gap in the formal diagnosis of HFpEF among patients who are likely to meet the criteria. A substantial 75.3% of the patients who did not have a formal diagnosis of HFpEF still met the European Society of Cardiology (ESC) diagnostic criteria for HFpEF. This finding highlights the potential for NLP methods to identify patients who are at risk but remain undiagnosed. Patients with confirmed HFpEF experienced more frequent hospitalizations. Interestingly, those who met the ESC criteria but were not formally diagnosed had a higher 5-year mortality rate, despite having fewer comorbidities and experiencing fewer acute cardiovascular events. This suggests that undiagnosed patients may be at a higher risk than previously understood. The study concludes that NLP can effectively identify patients with likely HFpEF from electronic health record data, which could lead to better clinical reviews and the use of diagnostic algorithms to improve patient outcomes. These results underscore the importance of accurate diagnosis and the potential of technology to enhance patient care in heart failure management [65].

While the diagnosis of HFpEF remains challenging, ongoing research and technological advancements hold promise for improving diagnostic accuracy and patient outcomes. The use of AI and phenotype-specific approaches may offer new pathways for identifying and managing HFpEF more effectively. However, the variability in diagnostic criteria and the influence of comorbidities continue to pose significant challenges in clinical practice.

## Treatment Strategies for HFpEF

HFpEF is a complex and heterogeneous condition that presents significant challenges in treatment due to its diverse pathophysiology and limited effective therapies. Current strategies for managing HFpEF focus on symptom relief, improving quality of life, and reducing hospitalizations, as no treatments have been definitively proven to improve survival (Table 2). The management of HFpEF involves a combination of pharmacological and nonpharmacological approaches, with an emphasis on individualized care tailored to the patient's specific phenotype and comorbidities.

Pharmacological treatments such as (i) Sodium-glucose cotransporter 2 inhibitors, like dapagliflozin and empagliflozin, have shown promise in reducing cardiovascular death and hospitalizations for heart failure in patients with HFpEF. These drugs are now recommended as first-line treatments for HFpEF patients with an ejection fraction greater than 40% [66]. (ii) Angiotensin receptor-neprilysin inhibitors (ARNI) like sacubitril/valsartan and mineralocorticoid receptor antagonists (MRAs) such as finerenone have demonstrated modest benefits in reducing hospitalizations and improving outcomes in certain HFpEF populations, particularly those with mildly reduced ejection fractions [67, 68]. (iii) Diuretics and beta-blockers, where diuretics remain a cornerstone for managing fluid overload, while beta-blockers are used for rate control in patients with atrial fibrillation, although their role in HFpEF is less clear compared to heart failure with reduced ejection fraction [69].

Nonpharmacological interventions such as regular physical activity and lifestyle changes, including dietary modifications, are crucial for improving functional capacity and quality of life in HFpEF patients. These interventions are often recommended alongside pharmacotherapy [68, 69]. Emerging device-based treatments, such as inter-atrial shunts and cardiac contractility modulation, offer potential benefits by addressing specific pathophysiological mechanisms in HFpEF. These devices aim to reduce left ventricular filling pressures and improve cardiac function [70]. Effective management of comorbid conditions like hypertension, diabetes, and obesity is essential in the treatment of HFpEF. Addressing these conditions can help alleviate symptoms and improve overall patient outcomes [71]. Furthermore, improved phenotyping of HFpEF patients may allow for more

**Table 2:** Current and emerging therapies in HFpEF - evidence and challenges.

| Therapy | Mechanism | Outcomes | Challenges |
|---|---|---|---|
| SGLT2 inhibitors | Metabolic modulation, diuresis, anti-inflammatory | ↓ Heart failure hospitalizations (HR ~ 0.8) | Modest effect on symptoms |
| ARNIs (sacubitril/valsartan) | Neprilysin inhibition, vasodilation | Neutral for mortality, ↓ Heart failure admissions in EF >45% | Cost, renal effects |
| MRAs (spironolactone/finerenone) | Aldosterone antagonism, anti-fibrotic | ↓ Hospitalizations (select populations) | Hyperkalemia risk |
| Anti-inflammatory agents | Target IL-6, myeloperoxidase | Under investigation | Safety, heterogeneous responses |
| Guanylate cyclase stimulators | Enhance NO-sGC-cGMP pathway | Neutral for quality of life/exercise capacity | Limited efficacy |
| Interatrial shunt devices | Reduce LA pressure | ↓ PCWP, mixed symptom relief | Invasive, patient selection |
| Exercise rehabilitation | Improve endothelial function, fitness | ↑ $VO_2$ peak (pending results) | Adherence barriers |
| Weight loss interventions | Caloric restriction, metabolic improvement | ↑ Diastolic function in obese HFpEF | Long-term sustainability |
| Digoxin | Inotropy, rate control | ↑ Systolic function in atrial fibrillation-HFpEF | Narrow therapeutic window |
| Diuretic strategies | Volume management | Intermittent bolus superior to infusion | Renal function risks |

personalized treatment strategies, targeting specific pathophysiological mechanisms and comorbidities unique to each patient [71, 72].

Currently, treatment for HFpEF primarily focuses on symptom management and the management of comorbidities, as no specific therapies have been proven to improve outcomes [5]. Diuretics are commonly used to alleviate volume overload, while the management of conditions such as hypertension and atrial fibrillation is crucial [5]. Recent studies have investigated the role of MRAs in HFpEF, with some evidence suggesting they may reduce hospitalizations [73]. However, the overall efficacy of MRAs and other pharmacological interventions remains uncertain, highlighting the need for further research [7, 73]. Renal function alterations following pharmacological interventions are also of interest. Rastogi et al. [74] examined early changes in estimated glomerular filtration rate after empagliflozin initiation, providing insights into renal outcomes and their implications for cardiovascular health in HFpEF.

While significant progress has been made in understanding and managing HFpEF, challenges remain due to the condition's complexity and heterogeneity. The lack of universal treatment strategies necessitates a personalized approach, considering the individual patient's clinical presentation and comorbidities. Future research should focus on identifying novel therapeutic targets and refining existing treatments to enhance patient outcomes. Additionally, the integration of pharmacological and nonpharmacological strategies, along with a focus on comorbidity management, holds promise for improving the care of HFpEF patients.

## Literature review

Clinical studies on HFpEF have explored various aspects, including the impact of systemic inflammatory markers, the significance of myocardial infarction, and the effectiveness of different therapeutic interventions. These studies often report clinical outcomes such as mortality, cardiovascular events, and hospitalizations, with confidence intervals (CI) providing a measure of the precision of these estimates. The inclusion criteria for clinical trials in HFpEF often exclude certain patient populations, such as obese individuals. Vaishnav et al. [75] found that obese HFpEF patients, whether included or excluded from trials, exhibited similar risks of hospitalization and death, suggesting that trial populations may not fully represent the broader HFpEF demographic. Emerging pharmacotherapies are being evaluated for their potential to improve clinical outcomes. Montero-Pérez-Barquero et al. [76] projected benefits of dapagliflozin based on data from the DELIVER trial, indicating promising therapeutic avenues. Similarly, the ENDEAVOR trial, as described by Lund et al. [77], investigates the effects of myeloperoxidase inhibition on symptoms and exercise capacity, reflecting ongoing efforts to target inflammatory pathways in HFpEF.

A study by Ariyaratnam et al. [61] evaluated the performance of the HFA-PEFF and H2FPEF scoring systems in diagnosing HFpEF in patients with symptomatic atrial fibrillation. A total of 120 patients with symptomatic atrial fibrillation and preserved ejection fraction were recruited for the study. These patients were scheduled for an atrial fibrillation ablation procedure, which served as the basis for the invasive diagnosis of HFpEF. Out of the 120 participants, HFpEF was diagnosed invasively in 88 patients, which accounts for 73.3% of the cohort. The remaining 32 patients (26.7%) did not have HFpEF. HFA-PEFF score results, 38 participants (31.7%) had a high probability of HFpEF based on the HFA-PEFF score and 82 participants (68.3%) had a low or intermediate probability of HFpEF. The HFA-PEFF score demonstrated a sensitivity of 40% and a specificity of 91% for diagnosing HFpEF when a high score (≥5 points) was achieved. H2FPEF score results: 72 participants (60%) had a high probability of HFpEF according to the H2FPEF scoring system and 48 participants (40%) had an intermediate probability. The H2FPEF score showed a sensitivity of 69% and a specificity of 66% for diagnosing HFpEF with a high score (≥6 points). The overall diagnostic accuracy of both scoring systems was similar, with the area under the curve (AUC) being 0.663 for HFA-PEFF and 0.707 for H2FPEF. The difference in accuracy was not statistically significant ($p = 0.636$). In conclusion, both the HFA-PEFF and H2FPEF scores demonstrated moderate accuracy in diagnosing HFpEF in patients with atrial fibrillation, indicating that these tools should be used with caution in this specific patient population [61].

A study by Fu et al. [78] conducted a systematic review and meta-analysis to evaluate the relationship between systemic inflammatory markers and clinical outcomes in patients with HFpEF. The meta-analysis included eight observational studies, comprising a total of 9,744 participants from six different countries. These studies focused on HFpEF patients aged 18 and older, examining the impact of systemic inflammatory markers on adverse clinical outcomes. The analysis revealed that systemic inflammatory markers were significantly associated with an increased risk of all-cause mortality. The hazard ratio (HR) was found to be 1.43, with a 95% CI of 1.19 to 1.72, indicating a statistically significant relationship ($p < 0.05$). There was also a significant association between systemic inflammatory markers and cardiovascular mortality. The HR for this outcome was 2.04, with a 95% CI of 1.33 to 3.12, again showing a significant correlation ($p < 0.05$). The study found that systemic inflammatory markers were linked to cardiovascular rehospitalization, with an HR of 2.83 and a 95% CI of 0.92 to 8.67. This result was also statistically significant ($p < 0.05$). The quality of the studies included was assessed using the Newcastle-Ottawa Scale, and low heterogeneity was observed across the studies ($I^2 = 0.00\%$). This suggests that the results are consistent and reliable. Sensitivity analyses and publication bias assessments indicated that the findings were robust, reinforcing the predictive value of systemic inflammatory markers for adverse clinical outcomes in HFpEF patients. In conclusion, the study highlights the significant role of systemic inflammatory markers in predicting adverse outcomes in patients with HFpEF, suggesting that monitoring these markers could be beneficial for clinical management [78].

An analysis by Cunningham et al. [79] pooled data from three clinical trials, including CHARM preserved, I-preserve, and the Americas region of TOPCAT, involving a total of 8,916 patients. This large sample size enhances the reliability of the findings. At the beginning of the study, 30% of the patients (2,668 individuals) had a history of myocardial infarction. This indicates that a significant portion of the HFpEF population has experienced myocardial infarction prior to enrollment. The study found that prior myocardial infarction was independently associated with an increased risk of cardiovascular death. Specifically, the rate of cardiovascular death was 4.7 events per 100 patient-years (PY) for those with a history of myocardial infarction, compared to 3.5 events per 100 PY for those without. The adjusted HR for this association was 1.42, with a 95% CI of 1.23 to 1.64, indicating a statistically significant increase in risk. While prior myocardial infarction was linked to a higher risk of cardiovascular death, the study found that it did not significantly increase the risk of heart failure hospitalization. This suggests that while myocardial infarction impacts overall cardiovascular mortality, it may not have the same effect on heart failure-related outcomes. The findings underscore the importance of both primary and secondary prevention strategies

for myocardial infarction in patients with HFpEF. Given the high risk of subsequent cardiovascular death and heart failure hospitalization in those with a history of myocardial infarction, targeted interventions are crucial for this patient population. In summary, the study highlights the significant relationship between prior myocardial infarction and increased cardiovascular mortality in patients with HFpEF, while also indicating that it does not necessarily lead to a higher risk of heart failure hospitalization (Figure 2) [79].

A meta-analysis by Lin et al. [80] included 14 randomized controlled trials with a total of 19,573 patients, divided into intervention (n = 9,954) and control groups (n = 9,619). The analysis found no significant correlation between the therapeutic drugs and all-cause mortality. This indicates that the treatments studied did not lead to a reduction in overall death rates among patients with HFpEF. Similar to all-cause mortality, there was no significant impact on cardiovascular mortality from the treatments. The ARNI and angiotensin-converting enzyme inhibitor (ACEI) were found to significantly reduce heart failure hospitalizations compared to placebo. The hazard ratios were HR 0.73 (95% CI 0.60 to 0.87) for ARNI and HR 0.64 (95% CI 0.43 to 0.96) for ACEI. No significant differences were noted in worsening heart failure events among the therapeutic drugs and placebo. The ARNI was shown to be superior to angiotensin receptor blockers in reducing heart failure hospitalizations, with a hazard ratio of HR 0.80 (95% CI 0.71 to 0.91). Additionally, vericiguat 10 mg was ranked worse than beta-blockers for reducing all-cause mortality, with a hazard ratio of HR 3.76 (95% CI 1.06 to 13.32). In conclusion, while no therapeutic drugs significantly reduced mortality in HFpEF patients, the ARNI and ACEI were associated with a lower risk of heart failure hospitalizations, highlighting their potential benefit in managing this condition. These results underscore the complexity of treating HFpEF and suggest that while certain medications may help reduce hospitalizations, they do not necessarily improve survival rates [80].

A study by Sotomi et al. [4] aimed to evaluate the prognostic significance of the HFA-PEFF score in patients with HFpEF. The research was conducted as part of the prospective multicenter observational study of patients with HFpEF (PURSUIT-HFpEF). A total of 871 patients were enrolled from 26 hospitals, with a mean follow-up duration of 399 days. Ultimately, 804 patients were analyzed after excluding those with HFA-PEFF scores of 0 or 1. HFA-PEFF score distribution, among the analyzed patients, 487 (59.1%) were diagnosed with HFpEF (HFA-PEFF score ≥ 5), while 317 (38.5%) had an intermediate score. This indicates a significant portion of the

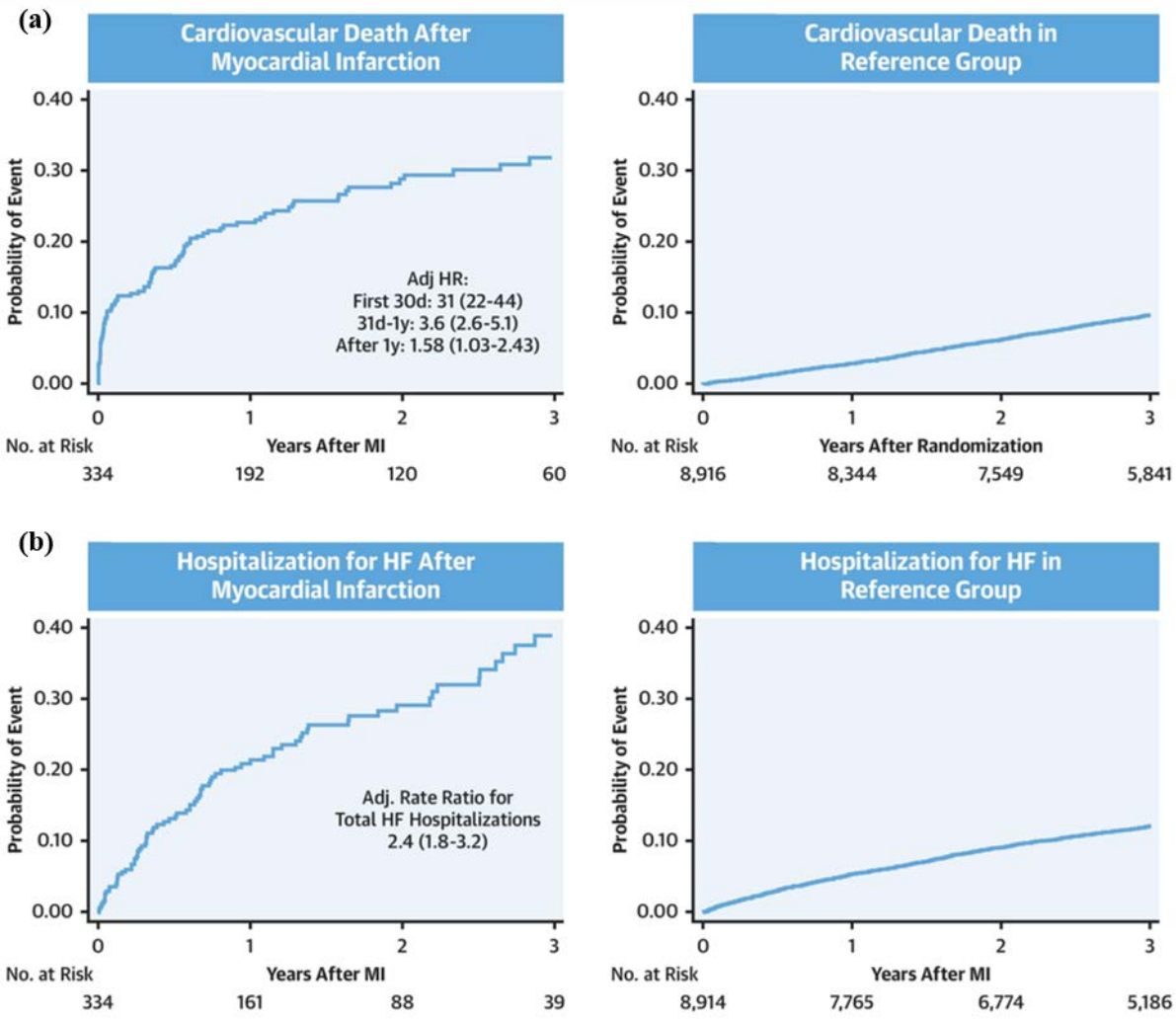


**Figure 2:** Risk of **(a)** cardiovascular death and **(b)** hospitalization for heart failure before and after post-enrollment myocardial infarction [79].

cohort had a higher risk profile based on the HFA-PEFF score. The primary endpoint of the study was a composite of all-cause death and heart failure readmission. The Kaplan-Meier analysis showed that the HFA-PEFF score effectively stratified patients regarding this primary endpoint. Specifically, patients with a low score (2 - 5) versus a high score (6) demonstrated significant differences in outcomes (log-rank test $p < 0.001$). Cox proportional hazard model, the analysis revealed that the HFA-PEFF score was significantly associated with the primary endpoint. The adjusted HR for patients with a high score compared to those with a low score was 1.446, with a 95% CI of 1.099 to 1.902 and a p-value of 0.008. This suggests that a higher HFA-PEFF score correlates with an increased risk of adverse outcomes. The study concluded that the HFA-PEFF score at discharge is not only a useful diagnostic tool but also a practical prognostic tool for predicting post-discharge clinical outcomes in patients with acute decompensated HFpEF. These results highlight the importance of the HFA-PEFF score in clinical practice for managing patients with HFpEF [4].

While these studies provide valuable insights into HFpEF, they also highlight the complexity and heterogeneity of the condition. The variability in patient profiles and treatment responses suggests that a one-size-fits-all approach may not be effective. Future research should focus on personalized treatment strategies and the development of robust surrogate outcomes to improve clinical management and patient outcomes in HFpEF.

## Clinical Trials

HFpEF is a complex and heterogeneous condition that presents significant challenges in clinical management and treatment. Despite its high prevalence, effective therapies remain limited, and clinical trials have yielded mixed results.

The FUNNEL+ study by Cuesta-Vargas et al. [81] (NCT05393362) is designed to evaluate the effectiveness of a cardiac rehabilitation program specifically for elderly patients with HFpEF. The main measure of effectiveness will be the peak oxygen uptake ($VO_2$peak), which is a critical indicator of functional capacity in patients with heart failure. This will be measured at baseline, 12 weeks, and 24 weeks to determine the impact of the rehabilitation program on physical fitness. In addition to $VO_2$peak, the study will evaluate various biomechanical, imaging, and physiological biomarkers. These secondary outcomes aim to provide a comprehensive understanding of how the cardiac rehabilitation program affects different aspects of health in patients with HFpEF. The study employs a randomized crossover clinical trial design, involving participants over the age of 70 diagnosed with HFpEF. This design allows for a comparison between the experimental group receiving the rehabilitation intervention and the control group, which will only receive educational sessions about HFpEF and healthy lifestyle habits. The study aimed to identify objective functional parameters that can help stratify patients based on their functional impairment, referred to as 'biomechanical phenotypes.' This stratification may assist clinicians in identifying which patients are likely to respond to cardiac rehabilitation, thereby improving future treatment decisions and potentially enhancing quality of life while reducing hospital readmissions and healthcare costs. In summary, while the results of the FUNNEL+ study are not yet available, the protocol outlines a comprehensive approach to evaluating the effectiveness of a cardiac rehabilitation program in elderly patients with HFpEF, focusing on both primary and secondary outcomes that could significantly impact patient care [81].

A study by Armstrong et al. [82] (NCT03547583) involved 789 patients with HFpEF who were recently hospitalized or treated with intravenous diuretics. These patients were randomly assigned to receive either vericiguat (at dosages of 10 mg or 15 mg daily) or a placebo for 24 weeks. The primary outcome measured was the change in the physical limitation score (PLS) of the Kansas City cardiomyopathy questionnaire (KCCQ), which assesses how heart failure affects daily activities. The results showed that the mean changes in KCCQ PLS after 24 weeks were: 5.5 points for the 15 mg/day vericiguat group, 6.4 points for the 10 mg/day vericiguat group, and 6.9 points for the placebo group. However, these differences were not statistically significant, indicating that vericiguat did not improve the KCCQ PLS compared to placebo. The secondary outcome was the 6-min walking distance (6MWD), which measures exercise capacity. The mean changes in 6MWD were: 5.0 meters for the 15 mg/day vericiguat group, 8.7 meters for the 10 mg/day vericiguat group, and 10.5 meters for the placebo group. Again, the differences between the vericiguat groups and the placebo were not statistically significant. Adverse events were reported in 65.2% of patients in the 15 mg/day vericiguat group, with symptomatic hypotension occurring in 6.4% of these patients, compared to 4.2% in the 10 mg/day group and 3.4% in the placebo group. Overall, the study concluded that treatment with vericiguat at either dosage did not lead to significant improvements in quality of life or exercise capacity in patients with HFpEF after recent decompensation [82].

The ROPA-DOP trial by Sharma et al. [83] investigated the effects of different diuretic strategies and low-dose dopamine on renal function in patients with HFpEF who were hospitalized with acute heart failure. The trial was a prospective, randomized clinical study involving 90 HFpEF patients. Participants were randomized within 24 h of admission to one of four treatment groups: intravenous bolus furosemide every 12 h, continuous infusion of furosemide, intermittent bolus furosemide with low-dose dopamine, and continuous infusion furosemide with low-dose dopamine. The primary endpoint was the percent change in creatinine levels from baseline to 72 h after treatment. This measure was used to assess renal function. The continuous infusion strategy resulted in a higher percentage increase in creatinine (16.01%) compared to the intermittent bolus strategy (4.62%). This difference was statistically significant ($p = 0.02$). The continuous infusion strategy was also associated with a greater risk of worsening renal function, with an odds ratio of 4.32 ($p = 0.02$) compared to the intermittent bolus strategy. The addition of low-dose dopamine did not have a significant effect on the percentage change in creatinine levels. The percent change with low-dose dopamine was 12.79%, while it was 8.03% without dopamine, with no significant difference ($p = 0.33$). There was no significant interaction observed between the diuretic strategy and low-dose dopamine ($p > 0.10$), indicating that the effects of dopamine did not vary with the type of diuretic used. In conclusion, the trial found that in HFpEF patients hospitalized with acute heart failure, a continuous infusion diuretic strategy was linked to renal impairment, while low-dose dopamine did not significantly impact renal function [83].

The RATE-AF trial by Bunting et al. [84] investigated the effects of digoxin compared to beta-blockers in patients with permanent atrial fibrillation and HFpEF. A total of 160 patients were randomized, with 145 completing the 12-month follow-up. The median age of participants was 75 years, and 44% were women. The median baseline heart rate was 96 beats/min, and the mean NYHA class was 2.4, indicating moderate heart failure symptoms. Blinded ECGs were performed at baseline and after 12 months to assess both systolic and diastolic cardiac function. Key parameters measured included LVEF, systolic tissue Doppler

velocity (s'), stroke volume, and various diastolic measures. In patients with LVEF ≥50% at baseline (119 patients), those treated with digoxin showed significant improvements in systolic function compared to those on beta-blockers: higher LVEF at follow-up (adjusted mean difference of 2.3%, p = 0.021), increased systolic tissue Doppler velocity (s') by 1.1 cm/s (p = 0.003), and greater stroke volume increase of 6.5 ml (p = 0.037). No significant differences were observed in diastolic parameters between the two treatment groups, indicating that digoxin primarily benefited systolic function rather than diastolic function. In patients with LVEF 40 to 50% (16 patients), s' significantly increased with digoxin compared to beta-blockers (adjusted mean difference of 1.5 cm/s, p = 0.001). However, no differences were noted in other systolic or diastolic parameters. For patients with LVEF < 40% (10 patients), there were no significant differences in echocardiographic measures between the two groups. The study concluded that digoxin significantly improves multiple parameters of systolic function in patients with permanent atrial fibrillation and heart failure symptoms, particularly in those with preserved LVEF, compared to conventional treatment with beta-blockers. These results highlight the potential of digoxin as an effective treatment option for improving systolic function in specific heart failure populations [84].

An analysis by Wang et al. [85] focused on 1,767 participants from the Americas enrolled in the TOPCAT trial. This subset was specifically chosen to evaluate recurrent heart failure hospitalization events in HFpEF patients. Recurrent heart failure hospitalization was defined as two or more hospitalizations for heart failure during the follow-up period. This definition helped in identifying patients who were at higher risk for repeated hospitalizations. Over a median follow-up period of 3.4 years, 72.2% of the total 751 hospitalizations (542 events) occurred in just 9.4% of the patients (163 individuals) who experienced recurrent heart failure hospitalization. This indicates that a small proportion of patients accounted for the majority of hospitalizations. Patients in the recurrent heart failure hospitalization group exhibited significantly higher mortality rates. The cardiovascular mortality rate was 6.2 per 100 PY compared to 3.8 per 100 PY in the non-recurrent group (p = 0.016). Similarly, the all-cause mortality rate was 10.0 per 100 PY in the recurrent group versus 6.8 per 100 PY in the non-recurrent group (p = 0.015). A risk prediction model was developed using nine predictors, which demonstrated moderate predictive power for recurrent heart failure hospitalization events, with an AUC of 0.75 and a Brier score of 0.08. This model can help identify patients at high risk for recurrent heart failure hospitalization. The findings suggest that the majority of heart failure hospitalization events occur in a small subset of patients with multiple comorbidities, who are at a higher risk of mortality. The predictive model offers a tool for clinicians to identify and manage these high-risk patients effectively. These results highlight the critical need for targeted interventions in patients with HFpEF who are at risk for recurrent hospitalizations [85].

While CIs provide valuable insights into the precision of effect estimates, they also highlight the variability and uncertainty inherent in HFpEF trials. The heterogeneity of patient populations, treatment responses, and trial designs can influence the width and interpretation of these intervals. Therefore, while CIs are essential for understanding trial results, they should be considered alongside other factors such as study design, sample size, and clinical context to draw comprehensive conclusions about treatment efficacy and safety in HFpEF.

## Prognosis and Future Directions

The prognosis for patients with HFpEF is often poor, with high rates of morbidity and mortality [49]. Factors such as age, comorbidities, and the presence of diastolic dysfunction significantly influence outcomes [49, 86]. As the understanding of HFpEF evolves, there is a pressing need for large-scale clinical trials to evaluate novel therapeutic strategies and refine diagnostic criteria [75, 87]. HFpEF remains a significant clinical challenge, with a prognosis that is often poor and comparable to that of heart failure with reduced ejection fraction. Despite advances in cardiovascular care, mortality and hospitalization rates for HFpEF remain high, with limited effective therapies currently available. The heterogeneous nature of HFpEF, involving multiple comorbidities such as hypertension, diabetes, obesity, and renal dysfunction, complicates both prognosis and treatment. Patients often experience progressive functional decline, reduced quality of life, and high rates of recurrent hospitalizations. Identifying high-risk subgroups through biomarkers, imaging, and clinical phenotypes may help refine prognostic assessments and guide personalized management strategies.

Future research should also focus on the development of targeted therapies that address the underlying pathophysiological mechanisms of HFpEF, particularly in populations that have been historically underrepresented in clinical trials [75, 87]. Future directions in HFpEF research are focused on unraveling its complex pathophysiology to develop targeted therapies. Recent insights into systemic inflammation, microvascular dysfunction, and metabolic disturbances have opened new avenues for investigation, including anti-inflammatory agents, SGLT2 inhibitors, and novel metabolic modulators. The success of SGLT2 inhibitors in reducing heart failure hospitalizations, even in HFpEF, marks a significant breakthrough, but further studies are needed to optimize their use and explore additional mechanisms. Precision medicine approaches, leveraging advanced imaging, omics technologies, and artificial intelligence, may help identify distinct HFpEF endotypes and tailor therapies accordingly. Additionally, large-scale clinical trials are essential to evaluate emerging therapies, such as guanylate cyclase stimulators, MRAs, and advanced device-based interventions.

Beyond pharmacotherapy, holistic management strategies emphasizing comorbidity control, lifestyle modifications, and multidisciplinary care are critical in improving HFpEF outcomes. Weight loss, exercise training, and dietary interventions have shown promise in alleviating symptoms and enhancing functional capacity. Future research should also explore the role of targeted rehabilitation programs and patient-centered care models to address the multifactorial nature of HFpEF. Collaborative efforts among researchers, clinicians, and policymakers will be key to advancing our understanding of HFpEF, refining risk stratification, and developing effective therapies to improve the long-term prognosis for this growing patient population.

## Conclusion

HFpEF represents a complex and growing clinical challenge, yet advancements in understanding its pathophysiology, diagnosis, and treatment offer promising avenues for improving patient outcomes. The development of standardized diagnostic tools like the HFA-PEFF score, alongside emerging therapies such as SGLT2 inhibitors and targeted anti-inflammatory agents, has begun to address the heterogeneity of HFpEF, providing hope for more personalized and effective management. While significant gaps remain, the integration of precision medicine, lifestyle interventions, and multidisciplinary care underscores a transformative shift toward holistic and patient-centered approaches. Collaborative research and innovative clinical

trials will continue to refine risk stratification and therapeutic strategies, ultimately enhancing quality of life and prognosis for individuals with HFpEF. These efforts highlight the potential for meaningful progress in combating this prevalent and debilitating condition.

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## Conflict of Interest

None.

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