ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Maísa-Lopes-de-Menezes/339

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Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 3 & Iss: 3

Review

Current Approach to Heart Failure with Preserved Ejection Fraction: An Updated Review

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Citation: Menezes ML, Goi GA, Schmidt LTS, et al. Current Approach to Heart Failure with Preserved Ejection Fraction: An Updated Review. *Medi Clin Case Rep J* 2025;3(3):1235-1237. DOI: doi.org/10.51219/MCCRJ/Maísa-Lopes-de-Menezes/339

Received: 17 August, 2025; **Accepted:** 19 August, 2025; **Published:** 21 August, 2025

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure cases and presents a high morbidity and mortality rate, similar to the reduced ejection fraction phenotype. It is characterized by signs and symptoms of heart failure, a left ventricular ejection fraction (LVEF) ≥ 50% and evidence of diastolic dysfunction, ventricular hypertrophy or elevated natriuretic biomarkers. Its prevalence increases with age, is more common in women and is associated with hypertension, obesity, diabetes and atrial fibrillation. Diagnosing HFpEF is challenging, as symptoms such as dyspnea and fatigue are nonspecific. Clinical-echo scoring systems, such as the H_2FPEF score, combine risk factors and imaging parameters, showing a sensitivity of 83% and specificity of 92% for HFpEF identification. Biomarkers like B-type natriuretic peptide (BNP) assist in risk stratification and prognosis. Advanced imaging techniques, including cardiac magnetic resonance imaging for quantifying fibrosis and assessing myocardial relaxation, offer greater diagnostic accuracy. Historically, treatment focused on symptom control and comorbidity management diuretics, blood pressure control, atrial fibrillation management and cardiac rehabilitation—without demonstrating clear mortality benefit. In 2019, the PARAGON-HF trial evaluated sacubitril–valsartan versus valsartan in patients with LVEF ≥ 45%, failing to reach statistical significance for the primary endpoint but suggesting benefit in subgroups with borderline EF and in women. A true therapeutic breakthrough came with sodium-glucose co-transporter 2 inhibitors (SGLT2i). In the EMPEROR-Preserved trial, empagliflozin reduced the risk of cardiovascular death or heart failure hospitalization by 21% and in the DELIVER trial, dapagliflozin reduced these events by 18%, regardless of diabetes status. These results led to SGLT2i being recommended as the first pharmacological class to modify outcomes in HFpEF. Future perspectives include therapies targeting fibrosis and myocardial remodeling, myofibril modulators and antifibrotic agents currently under early-phase investigation. Combining different mechanisms of action may offer synergy, but randomized trials are required. An integrated approach including early diagnosis, pharmacological optimization, rehabilitation and multidisciplinary care is essential to improve quality of life and long-term outcomes.

Keywords: Heart failure with preserved ejection fraction; H_2FPEF score; SGLT2 inhibitors; Echocardiographic diagnosis; Multidisciplinary management

Introduction

Heart failure with preserved ejection fraction (HFpEF) is characterized by the presence of typical signs and symptoms of heart failure (HF) in association with a left ventricular ejection fraction (LVEF) ≥ 50%, combined with evidence of diastolic dysfunction, ventricular hypertrophy or elevated levels of natriuretic peptides[1,2]. HFpEF represents approximately half of all HF cases in clinical practice and displays morbidity and mortality rates comparable to those of heart failure with reduced ejection fraction (HFrEF), posing a significant diagnostic and therapeutic challenge[3,2,4]. Epidemiologically, the prevalence of HFpEF increases exponentially with age, being more common in elderly women and patients with multiple metabolic and hemodynamic comorbidities such as systemic arterial hypertension, obesity, type 2 diabetes mellitus and atrial fibrillation[2,1]. These conditions contribute to structural and functional myocardial changes, triggering a complex process of atrial and ventricular remodeling, collagen deposition and interstitial fibrosis, thereby compromising ventricular compliance[3].

In terms of pathophysiology, diastolic dysfunction plays a central role, resulting in delayed relaxation and increased ventricular stiffness, which elevates filling pressures even with a normal ejection fraction. Interstitial fibrosis, linked to inflammatory processes and microvascular endothelial dysfunction, reduces coronary flow reserve and exacerbates exercise intolerance. Additionally, atrial remodeling often manifested as atrial fibrillation contributes to the loss of effective atrial contraction, further worsening volume and pressure overload in the left ventricle. The diagnosis of HFpEF remains challenging due to the nonspecific clinical presentation, which includes exertional dyspnea, fatigue and exercise intolerance symptoms often attributed to pulmonary conditions or aging. To improve diagnostic accuracy, the European Society of Cardiology (ESC) recommends clinical-echo scoring systems such as the H_2FPEF score, which integrates demographic (age > 60 years), comorbidity (hypertension on ≥ 2 medications; BMI > 30 kg/m²; atrial fibrillation) and echocardiographic (E/e' > 9; pulmonary artery velocity > 35 cm/s) parameters, with a sensitivity of 83% and specificity of 92%[5]. Concurrently, BNP and NT-proBNP levels offer prognostic information and help with risk stratification, although values may be reduced in obese individuals and elevated in arrhythmias[6]. In addition to conventional 2D echocardiography, advanced imaging modalities have become indispensable. Cardiac magnetic resonance imaging (CMR) allows quantification of myocardial fibrosis via T1 mapping and assessment of regional diastolic function, helping distinguish HFpEF from infiltrative cardiomyopathies and guiding antifibrotic therapy. Myocardial strain echocardiography detects subclinical mechanical dysfunction, anticipating adverse events even before changes in LVEF occur.

Historically, HFpEF management was limited to symptom control with diuretics to relieve congestion, antihypertensives to reduce afterload, anticoagulation and rate control in atrial fibrillation and cardiac rehabilitation to optimize functional capacity without clear mortality or hospitalization recurrence benefit. However, recent years have witnessed major therapeutic advancements: the PARAGON-HF trial compared sacubitril–valsartan to valsartan, showing benefit in patients with borderline EF (45–57%) and in women and the landmark EMPEROR-Preserved and DELIVER trials demonstrated for the first time a robust reduction in cardiovascular mortality and hospitalization for HF with the SGLT2 inhibitor class.

Objectives

This review aims to detail the underlying pathophysiological mechanisms of HFpEF, describe the currently available diagnostic tools, critically analyze results from the main recent therapeutic trials and discuss future perspectives for managing this complex syndrome, with an emphasis on multidisciplinary integration and treatment personalization.

Materials and Methods

A literature review was conducted using databases including PubMed, SciELO, Google Scholar and ScienceDirect.

Discussion

The therapeutic landscape for HFpEF underwent a paradigm shift with the introduction of SGLT2 inhibitors, which represent the first pharmacological class shown to alter the natural course of the disease. In the EMPEROR-Preserved study, Anker, et al. randomized 5,988 patients with LVEF ≥ 50% to receive 10 mg/day empagliflozin or placebo[4]. After a median follow-up of 26 months, the composite outcome of cardiovascular death or HF hospitalization was reduced by 21% (HR 0.79; 95% CI 0.69–0.90; p < 0.001) in Favor of empagliflozin. Subgroup analyses showed consistent benefit regardless of diabetes status, suggesting mechanisms beyond glucosuria, including osmotic diuresis, reduced ventricular stiffness and anti-inflammatory effects. The DELIVER trial, led by Butler, et al.[7], assessed 10 mg/day dapagliflozin in 6,263 participants with LVEF > 40%. The results confirmed an 18% reduction in the composite risk of HF hospitalization or cardiovascular death (HR 0.82; 95% CI 0.73-0.92; p < 0.001), cementing SGLT2 inhibitors as a first-line recommendation by the ESC[8]. These consistent findings reinforce the pharmacologic pleiotropy of SGLT2i-improving endothelial function, reducing interstitial fibrosis and offering microvascular protection that directly targets HFpEF pathophysiology[7]. Although PARAGON-HF did not meet its primary endpoint (p = 0.06), exploratory analyses showed reduced hospitalization in patients with borderline EF (45–57%) and women[9]. These data support conditional recommendations for sacubitril–valsartan in selected profiles, offering an alternative for patients who cannot tolerate SGLT2i or respond suboptimally[8].

Strict control of comorbidities remains essential. Resistant hypertension accelerates adverse remodelling via pressure overload; normalization of blood pressure improves arterial stiffness and diastolic parameters[1]. In atrial fibrillation, restoring sinus rhythm or rate control prevents tachycardia-induced cardiomyopathy and optimizes diastolic filling, reducing

admissions[8]. Multidisciplinary cardiac rehabilitation including aerobic exercise, resistance training and nutritional education improves functional capacity, quality of life and adherence, although mortality impact remains to be confirmed. On the diagnostic front, advanced methods allow for phenotypic stratification. CMR with native T1 mapping quantifies interstitial fibrosis, identifying patients at high risk of progression and potential candidates for antifibrotic agents under investigation[10]. Strain echocardiography detects subclinical mechanical dysfunction and can monitor early therapeutic response[11]. The use of "phenomapping," which combines clinical, biochemical and imaging profiles, distinguishes HFpEF subgroups with varying patterns of inflammation, fibrosis and microvascular dysfunction, paving the way for personalized treatment.

In translational research, myofibril modulators and inhibitors of profibrotic pathways (e.g., TGF-β, MMPs) have demonstrated reduced ventricular stiffness in preclinical models. Phase II trials are testing agents such as pirfenidone and alagebrium, aiming to reduce collagen deposition and restore myocardial compliance[12]. The combination of SGLT2i, ARNI in selected profiles, comorbidity control and novel antifibrotic therapies may offer synergy, but phase III randomized trials are needed. Finally, the adoption of telemonitoring strategies and home-based multidisciplinary programs shows promise in reducing readmissions, enabling early detection of subclinical congestion and adjustment of therapy. The integration of cardiologists, radiologists, physiotherapists, nutritionists and HF nurses forms the core of a patient-centred care model that can optimize adherence and outcomes.

Conclusion

The management of HFpEF has evolved from a therapeutic void to a model grounded in high-level evidence. Sodium-glucose co-transporter 2 inhibitors (empagliflozin and dapagliflozin) have emerged as the first drug class to significantly reduce HF hospitalizations and cardiovascular mortality, regardless of diabetes status, as demonstrated in the EMPEROR-Preserved and DELIVER trials. These pleiotropic benefits stem from a combination of osmotic diuresis, reduced ventricular stiffness, anti-inflammatory effects and improved microvascular function. Although sacubitril–valsartan did not reach statistical significance in the PARAGON-HF primary endpoint, subgroup benefits in women and patients with borderline EF suggest a complementary role for ARNI in selected profiles. Rigorous comorbidity control (hypertension, atrial fibrillation), along with cardiac rehabilitation programs, remains indispensable for optimizing symptoms, functional capacity and quality of life-though more evidence is needed on mortality outcomes. Early diagnosis using clinical-echo scores (H_2FPEF), natriuretic biomarkers and advanced imaging (CMR, strain echo) supports risk stratification and treatment personalization, identifying phenotypes suited for antifibrotic and myofibril-modulating therapies. The rise of phenomapping reinforces the promise of precision medicine in HFpEF. Future directions include phase III trial completion of antifibrotic agents, refinement of telemonitoring algorithms and implementation of integrated multidisciplinary care, which may reduce readmissions and improve long-term outcomes. The combination of precise diagnosis, proven therapies and a patient-centered approach now defines the new HFpEF management paradigm aimed at slowing disease progression, lowering hospital burden and improving survival and quality of life.

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