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Review Article

Bridging HFpEF Across the Care Continuum: From Screening to Phenotyping and Targeted Management

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Abstract

Heart Failure with preserved Ejection Fraction (HFpEF) has become an important form of Heart Failure (HF), characterized by marked heterogeneity in pathophysiology, clinical presentation, and treatment response. It is an increasingly prevalent form of HF driven by aging populations and comorbidities such as hypertension, diabetes, obesity, and Chronic Kidney Disease (CKD). HFpEF is also associated with high morbidity, frequent hospitalizations, and diagnostic challenges, particularly in resource-limited settings. This manuscript provides a clinically focused overview of HFpEF, integrating current concepts in pathophysiology, diagnosis, phenotyping, and management. Its pathophysiology is multifactorial, involving systemic inflammation, endothelial dysfunction, myocardial stiffness, and contributions from comorbid conditions. Emerging evidence highlights the roles of adiposity and inflammatory pathways, reinforcing the view of HFpEF as a multisystem disorder rather than purely a cardiac condition. The condition is also markedly heterogeneous, with several phenotypes identified, including cardiometabolic, obesity-related, cardiorenal, chronotropic incompetence, and Atrial Fibrillation (AF)–associated HFpEF. These phenotypes influence disease progression and therapeutic response. Additionally, numerous clinical mimics, such as pulmonary disease, valvular heart disease, and infiltrative cardiomyopathies, complicate diagnosis. Diagnosis requires a structured, probability-based approach combining clinical assessment, biomarkers, echocardiography, and, when necessary, stress testing or invasive hemodynamics. However, limited access to advanced diagnostics necessitates pragmatic, tiered approaches, especially in low-resource settings. Management focuses on three pillars: optimization of comorbidities, guideline-directed medical therapy, and phenotype-specific treatment strategies. While no therapy conclusively reduces mortality, recent advances have improved symptom control and hospitalizations. Overall, HFpEF demands a holistic, individualized approach integrating pathophysiology, clinical phenotyping, and healthcare system constraints to improve patient outcomes.

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Keywords: Heart failure, heart failure with preserved ejection fraction, echocardiography, phenotype guided management, comorbidities, guideline-directed medical therapy.

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Introduction

Heart Failure with preserved Ejection Fraction (HFpEF) has emerged as the predominant phenotype of Heart Failure (HF), representing close to half of all cases reported in most modern registries.[1] The number of individuals affected by HFpEF continues to expand globally, largely reflecting an aging population and the increasing prevalence of commonly associated comorbidities, including hypertension, Type 2 Diabetes Mellitus (T2DM), obesity, and Chronic Kidney Disease (CKD).[2-4] Despite modestly better survival rates versus those of Heart Failure with reduced Ejection Fraction (HFrEF), HFpEF continues to be associated with high rates of hospitalization and persistent symptom burden.[2-4]

A nationwide survey involving 160 cardiologists and internists practicing in Indonesia highlighted clear challenges in daily clinical practice of managing HFpEF, with 79% of respondents finding of more complex than that of HFrEF, mainly due to diagnostic ambiguity and limited access to advanced diagnostic tools.[5] There was also significant under-utilization of therapies such as Angiotensin Receptor Neprilysin Inhibitors (ARNI) and Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors, despite robust evidence in their prognostic benefits. These findings highlight the urgent need for a simplified, resource-adapted diagnostic and therapeutic framework that can be applied across the Indonesian healthcare system.

Our review aims to consolidate current evidence surrounding the pathophysiological processes and management of HFpEF, while proposing practical, tier-based diagnostic, phenotyping, and treatment algorithms suited to Indonesia's healthcare structure. This initiative seeks to bridge the gap between global recommendations and pragmatic implementation to improve outcomes in HFpEF care.

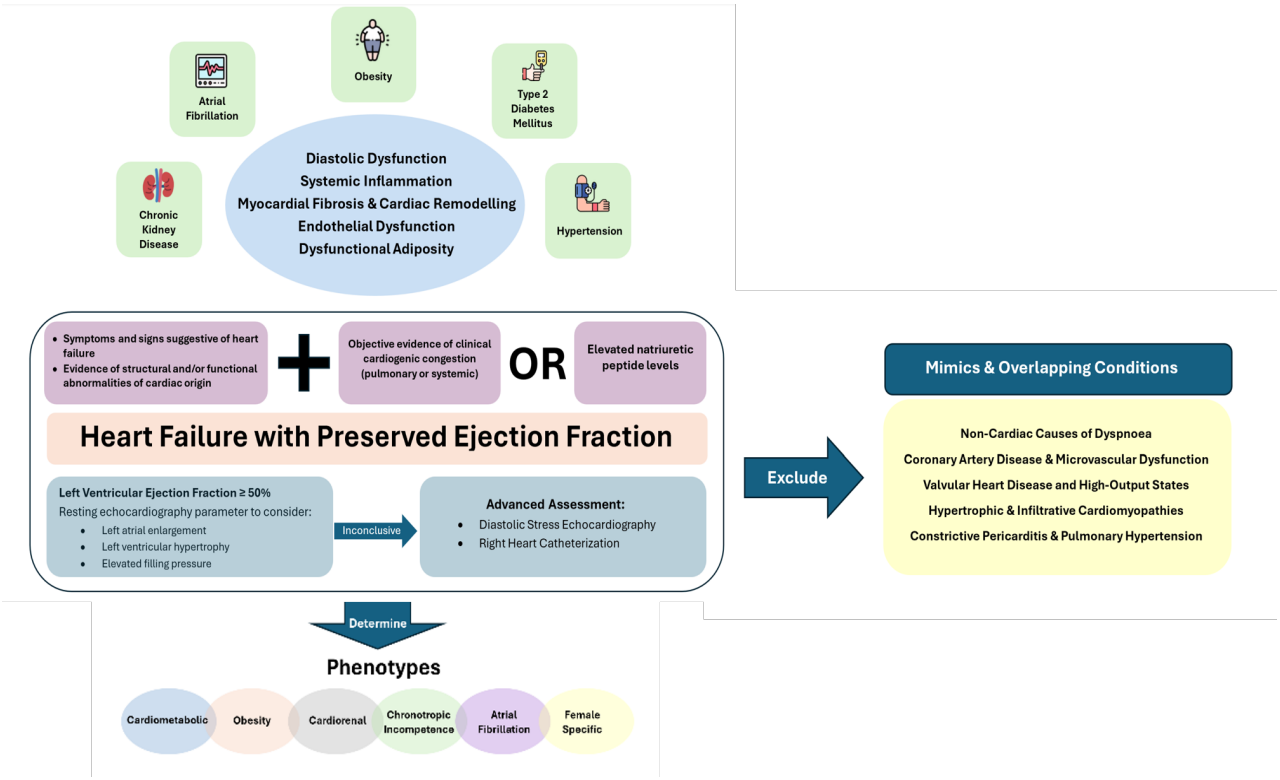

Figure 1. Integrated Diagnostic and Phenotyping Framework for Heart Failure with Preserved Ejection Fraction (HFpEF). Common cardiometabolic comorbidities (obesity, type 2 diabetes mellitus, hypertension, chronic kidney disease, and atrial fibrillation) drive a shared pathophysiological substrate characterized by systemic inflammation, myocardial fibrosis and remodeling, endothelial dysfunction, and diastolic impairment. HFpEF diagnosis requires symptoms and/or signs of heart failure, preserved left ventricular ejection fraction (≥50%), objective structural or functional cardiac abnormalities, and either elevated natriuretic peptide levels or evidence of congestion. Resting echocardiography (e.g., left atrial enlargement, left ventricular hypertrophy, elevated filling pressures) is central, with advanced testing (diastolic stress echocardiography or right heart catheterization) recommended when inconclusive. Mimics and overlapping conditions must be excluded. Following diagnosis, patients are stratified into clinical phenotypes (e.g., cardiometabolic, obesity-related, cardiorenal, chronotropic incompetence, atrial fibrillation-related, and female-specific) to guide targeted management.

Discussion

Pathophysiology of HFpEF – Comorbidities, Inflammation & Adiposity

Alongside the 'Universal Definition of Heart Failure', HFpEF is further defined as HF with a Left Ventricular Ejection Fraction (LVEF) of 50% or more, accompanied by objective evidence of cardiac structural and/or functional abnormalities consistent with diastolic dysfunction and elevated Left Ventricular (LV) filling pressures.[2-4,6-9] These abnormalities may include any combination of left atrial enlargement, LV hypertrophy, abnormal diastolic indices on Transthoracic Echocardiography (TTE), or elevated circulating Natriuretic Peptides (NP) (Figure 1).

Early conceptual models emphasized abnormalities in LV relaxation and increased myocardial stiffness following long-standing comorbidities such as hypertension as a principal mechanism responsible for diastolic dysfunction, elevated LV End-Diastolic Pressure (LVEDP), and subsequent development of HF.[3-4,6] However, subsequent research has demonstrated that HFpEF arises from a broader multi-systemic process, including that of physiological aging and pathological cardiometabolic comorbidities. Furthermore, although diastolic dysfunction is a recognized clinical feature in HFpEF, there is evidence that echocardiographic features commonly used to define and grade diastolic dysfunction may not be present in most cases of HFpEF, as confirmed by invasive hemodynamics.[10] This further supports the rather complex, multifactorial pathophysiology underlying HFpEF (Figure 1).

A landmark paradigm proposed that common comorbidities such as hypertension, obesity, T2DM, and CKD promote systemic inflammation and coronary microvascular endothelial dysfunction, involving inhibition of the cyclic guanosine monophosphate-protein kinase G signaling pathway and resulting in myocardial stiffness and fibrosis.[11-12] Beyond intrinsic myocardial abnormalities, coronary microvasculature, and peripheral endothelial dysfunction commonly co-exist as well. Increased arterial stiffness and enhanced wave reflections augment LV afterload and diminish diastolic suction, further increasing LV wall stress and contributing to pulmonary venous congestion, particularly during exertion. Skeletal muscle dysfunction (linked to reduced capillary density, mitochondrial abnormalities, and impaired oxygen utilization) often adds insult to injury.[3-4,11-12] Increasing attention has also focused on the contribution of atrial myopathy and Atrial Fibrillation (AF) to HFpEF pathophysiology, by eliminating atrial contraction, exacerbating ventricular filling abnormalities, creating a vicious cycle that accelerates disease progression.[13]

Recently, adiposity has been implicated in the development of HFpEF.[14-16] The adipokine-mediated hypothesis centers around visceral adiposity, and it describes the secretion of pro-inflammatory, pro-hypertrophic, and pro-fibrotic adipokines from visceral fat depots. Adipokines act as the molecular mediators for systemic inflammation, myocardial hypertrophy, myocardial fibrosis, and microcirculatory dysfunction.[14-16] An interesting proposition includes the idea that distribution, as opposed to absolute amount or mass, of adiposity may be a more important factor in the pathogenesis of the condition.

This multidimensional pathophysiology explains the marked heterogeneity observed among patients and has led to the recognition of several HFpEF phenotypes, each associated with distinct clinical trajectories and therapeutic responses.[14] Understanding this integrative model helps explain why traditional HF therapies that target only cardiac hemodynamics have shown limited benefit and underscores the need for phenotype-directed treatment strategies that address the broader systemic mechanisms underlying HFpEF. Clinical phenotyping provides a mechanistic framework to stratify patients based on dominant drivers of myocardial dysfunction, systemic comorbidity burden, and hemodynamic patterns. Such classification is not merely descriptive – it has implications for prognosis and therapeutic responsiveness.

Phenotypes, Mimics & Overlapping Conditions in Patients Living with HFpEF (Figure 1)

Cardiometabolic Phenotype

The cardiometabolic phenotype is the most prevalent HFpEF subtype and is characterized by hypertension, T2DM, visceral adiposity, and Metabolically Associated Fatty Liver Disease (MAFLD). An associated inflammatory–microvascular axis leads to concentric remodeling, extracellular matrix expansion, and impaired ventricular–vascular coupling. Hypertension, in particular, plays a central mechanistic role in the

cardiometabolic HFpEF phenotype by promoting arterial stiffening, increased wave reflections, and augmented pulsatile afterload, all of which impair ventricular–vascular coupling and delay myocardial relaxation.[11] In the cardiometabolic phenotype, Renin-Angiotensin-Aldosterone System (RAAS) activation represents a biologically coherent downstream consequence of obesity, insulin resistance, and hypertension rather than an isolated neurohormonal event.[13,15-16] Aldosterone-mediated mineralocorticoid receptor activation promotes myocardial fibroblast proliferation, collagen deposition, extracellular matrix expansion, and microvascular inflammation, directly contributing to ventricular stiffening and impaired diastolic compliance. Mineralocorticoid receptor signaling also amplifies inflammatory pathways central to the cardiometabolic HFpEF paradigm.[17] These mechanistic links provide biological plausibility for RAAS and mineralocorticoid receptor antagonism in this phenotype, and would support the results from pivotal clinical trials such as FINEARTS-HF.[18]

MAFLD, an increasingly recognized comorbidity associated with HFpEF, has been independently associated with subclinical myocardial remodeling and impaired diastolic function, even in asymptomatic individuals. Implicated pathophysiological processes linked to the bidirectional relationship between MAFLD and HFpEF, aside from hepatic congestion, portal hypertension, and cirrhosis, include the presence of systemic inflammation, oxidative stress, insulin resistance, RAAS activation, and atherosclerosis.[19] Thus, several proposed therapeutic nodes have been suggested as potential treatment options, pending clinical trials, including existing drug classes such as RAAS and SGLT2 inhibition, as well as more novel therapeutics involving IL-1/IL-6 inhibition and glucagon-like peptide-1 receptor agonists.[19]

Obesity Phenotype

Obesity functions not merely as a comorbidity but as a pathophysiological amplifier in HFpEF. Adiposity promotes systemic inflammation through adipokine secretion and oxidative stress, leading to endothelial dysfunction and myocardial fibrosis.[16-17,20-22] Epicardial adipose tissue exerts local paracrine effects that impair myocardial relaxation and promote extracellular matrix deposition. Obesity also induces plasma volume expansion and increased preload, resulting in exaggerated rises in filling pressures during exertion. Reduced circulating NP levels in obese individuals, attributed to enhanced neprilysin activity and increased clearance, may mask congestion and delay diagnosis.[17,20-22] Lower NP levels are also associated with enhanced aldosterone signaling, perpetuating sodium retention and ventricular stiffness.[22]

Cardiorenal Phenotype

Renal dysfunction is highly prevalent in HFpEF and represents a central component of disease heterogeneity. CKD contributes not only to sodium retention and volume expansion but also to systemic inflammation, endothelial dysfunction, vascular calcification, and neurohormonal activation. The cardiorenal phenotype is therefore increasingly recognized as a multispecialty disorder involving complex bidirectional heart–kidney interactions.[23-24] Reduced glomerular filtration rate promotes plasma volume expansion and elevated LV filling pressures. Beyond hemodynamic congestion, renal impairment is strongly associated with adverse cardiovascular outcomes, including increased mortality and hospitalization risk in patients with HF.[23-25] Uremic toxins, oxidative stress, and chronic inflammation stimulate fibroblast activation and extracellular matrix deposition, leading to myocardial fibrosis and increased passive stiffness. RAAS activation and sympathetic overactivity further amplify ventricular–vascular uncoupling and arterial stiffening.[23-25] Elevated central venous pressure further impairs renal perfusion, perpetuating a vicious cycle of congestion and renal dysfunction.[23-25]

Chronotropic Incompetence & Exercise Intolerance Phenotype

Chronotropic incompetence and exercise intolerance are frequently observed in HFpEF.[25-27] Pandey et al. demonstrated that reduced heart rate augmentation and exaggerated increases in Pulmonary Capillary Wedge Pressure (PCWP) were strongly associated with reduced Peak Oxygen Consumption (VO_2 max) in HFpEF.[27] Impaired heart rate augmentation limits cardiac output reserve and contributes substantially to exertional intolerance in HFpEF. There is also growing interest in heart rate modulation in managing HFpEF, where clinical trials center around Beta-Blockers (BB) and rate-limiting pharmacotherapy withdrawal, as well as rate-adaptive pacing have been designed in selected phenotypes of HFpEF, to test the theory of personalized heart rate modulation.[28] However, exercise limitation is not solely cardiac in origin. Sarma et al. demonstrated that patients with HFpEF had lower VO_2 max and exercise heart rate than older controls, but sinus node dysfunction could not be entirely attributed to chronotropic incompetence.[26] Initially thought to be mainly driven by impaired

chronotropic reserve and rhythmic disturbances, the phenomenon is now increasingly understood to involve multi-system contributors, including pulmonary vascular remodeling, lung disease, adiposity, renal dysfunction, peripheral factors, and myocardial remodeling.[29] At the tissue level, peripheral abnormalities, including skeletal muscle mitochondrial dysfunction, reduced capillary density, impaired oxidative metabolism, and diminished oxygen extraction, have been shown to contribute to restricted aerobic capacity in HFpEF.[27, 29]

Atrial Fibrillation Phenotype

AF can often mimic HFpEF when sub-optimally managed.[13] Furthermore, loss of atrial contraction, irregular ventricular filling, and altered NP levels complicate the interpretation of both clinical symptoms and investigation findings. In such cases, clinicians should maintain a low threshold in performing advanced imaging or invasive hemodynamic monitoring when diagnostic uncertainty persists.[13,30-31] Left atrial dysfunction itself, however, has also emerged as a key mechanistic and prognostic substrate in HFpEF.[30-31] Atrial cardiomyopathy is defined as structural or functional atrial abnormalities independent of arrhythmia burden, and it may develop as a consequence of elevated filling pressures or exist as a primary substrate. AF has been shown to be both a consequence and a driver of atrial cardiomyopathy and HFpEF progression, in which elevated LV filling pressures lead to progressive left atrial remodeling, fibrosis, and loss of compliance, resulting in impaired reservoir, conduit, and booster-pump function and a predisposition to AF. AF, in itself, induces metabolic and structural remodeling, resulting in poor atrial compliance. More importantly, the co-existence of AF and HFpEF accelerates pulmonary hypertension development and worsens prognosis, and management of concomitant disease remains complex.[30-32]

Special Consideration in Female Patients with HFpEF

A distinct and clinically relevant HFpEF phenotype is the female-predominant cardiometabolic–inflammatory phenotype, typically observed in post-menopausal women.[33-34] This phenotype is characterized by a high burden of obesity, hypertension, and metabolic dysfunction, with a strong interplay between visceral adiposity, systemic inflammation, and Microvascular Dysfunction (MVD). Loss of oestrogen plays a central mechanistic role, leading to endothelial dysfunction, impaired nitric oxide bioavailability, and activation of pro-inflammatory and neurohormonal pathways, including the renin–angiotensin–aldosterone system.[33-34] This results in increased vascular stiffness, concentric remodeling, and diastolic dysfunction. In parallel, adipose tissue–driven inflammation promotes cytokine activation (e.g., IL-6, TNF-α), oxidative stress, and coronary MVD, further impairing myocardial relaxation.[33-34] Clinically, women exhibit smaller ventricular cavities, higher LV stiffness, and greater impairment in diastolic reserve during exercise, contributing to exertional intolerance despite preserved LVEF.[33-34] This phenotype underscores that HFpEF in women represents a distinct biological entity, driven by sex-specific hormonal, metabolic, and inflammatory mechanisms.

Clinical Mimics in HFpEF (Figure 1)

Non-Cardiac Causes of Dyspnoea

There are various causes of dyspnoea, beyond that of HFpEF. Anemia, Chronic Obstructive Pulmonary Disease (COPD), obstructive sleep apnoea, and thyroid disorders are particularly important mimics as they independently contribute to dyspnoea and other overlapping symptoms, but also remain highly prevalent in HFpEF populations.[14, 35-36] In the case of COPD, it frequently coexists with HFpEF due to shared risk factors. Systemic inflammation and chronic hypoxia promote pulmonary vasoconstriction and right ventricular remodeling. Lung hyperinflation alters ventricular interdependence and impairs diastolic filling, leading to complex hemodynamic interactions that worsen clinical outcomes.[35-36] Targeted treatment of these abnormalities may significantly improve symptoms, regardless of co-existing HFpEF.[14] Therefore, HFpEF should not be diagnosed solely on the basis of symptoms when alternative systemic causes are plausible. When available, cardiopulmonary exercise testing or exercise echocardiography provides additional discriminatory value by distinguishing ventilatory limitation from circulatory impairment, particularly in diagnostically uncertain cases, although accessibility may be an issue, especially in resource-limited settings.[37]

Coronary Artery Disease & Coronary Microvascular Dysfunction

Coronary Artery Disease (CAD) is more prevalent in patients with HFpEF and is independently associated with worse clinical outcomes. Observational analyses have demonstrated that the presence of CAD correlates with greater structural remodeling, higher filling pressures, and increased rates of hospitalization and mortality.[38-39] Evaluation

for ischemic heart disease should be undertaken in patients with suggestive clinical features, including typical angina, high-risk cardiovascular profiles, electrocardiographic abnormalities, or regional wall motion abnormalities on cardiac imaging. Various forms of non-invasive diagnostic tests, including exercise stress testing, stress echocardiography, nuclear-based stress imaging, or coronary computed tomography angiography, may be used depending on patient characteristics and local expertise. Recognition is clinically important, as targeted anti-ischemic therapy or revascularization may alleviate symptoms and improve outcomes when ischemia coexists with HFpEF.[39-41]

Coronary MVD further contributes by impairing subendocardial perfusion and promoting myocardial fibrosis and diastolic dysfunction.[41-42] An important aspect to appreciate includes the high prevalence of MVD among patients affected by HFpEF, which can occur despite normal or mildly diseased epicardial coronary arteries. Guidelines recommend either non-invasive (i.e., positron emission tomography or cardiac MRI to assess myocardial perfusion and flow reserve) and/or invasive testing (i.e., cardiac catheterization measurements of coronary flow reserve and index of microvascular resistance) for coronary MVD, although availability of facilities and expertise remains sparse in our region.[40-42]

Valvular Heart Disease and High-Output States

Valvular heart disease, particularly aortic stenosis and mitral regurgitation, frequently results in congestion with preserved LVEF and may be misclassified as HFpEF if echocardiographic assessment is not performed comprehensively. Both the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) guidelines emphasize TTE as the cornerstone for identifying valvular pathology and determining whether symptoms are primarily valve-mediated or attributable to HFpEF physiology.[6,8,43] Similarly, high-output states, including severe anemia, thyrotoxicosis, and arteriovenous shunts, can present similarly with clinical congestion, despite preserved systolic function. Identification of these conditions is essential because management strategies differ fundamentally from standard HFpEF-directed therapy.

Hypertrophic & Infiltrative Cardiomyopathies

Hypertrophic Cardiomyopathy (HCM) is a well-recognized HFpEF mimic, presenting with exertional dyspnoea, preserved LVEF, and diastolic dysfunction.[45] Distinguishing features include asymmetric or disproportionate LV hypertrophy, dynamic LV outflow tract obstruction, characteristic electrocardiographic abnormalities, family history of cardiomyopathy or sudden cardiac death, and specific patterns of late gadolinium enhancement on Cardiac Magnetic Resonance (CMR) imaging.[45] Misclassification of HCM as HFpEF may delay disease-specific therapies and appropriate family screening.[44-45] In elderly patients, differentiation from hypertensive heart disease may be challenging, and clinicians should carefully assess "red flags," including marked wall thickness, discordant electrocardiogram voltage, unexplained hypertrophy, and history of syncope.[45-46]

Infiltrative cardiomyopathies, particularly cardiac amyloidosis, are increasingly recognized among patients initially labeled as HFpEF and represent an important diagnostic consideration, especially in older individuals with increased wall thickness.[45-46] Transthyretin Cardiac Amyloidosis (ATTR-CM) is increasingly identified in patients previously diagnosed with HFpEF, and accurate diagnosis is critical given the availability of disease-modifying therapies. Clinical and extracardiac "red flags" that may raise suspicion include carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, peripheral neuropathy, and intolerance to conventional HF therapies.[45-46] Imaging findings suggestive of amyloidosis include increased ventricular wall thickness with bi-atrial enlargement, restrictive filling patterns, discordance between low QRS voltage and wall thickness, apical sparing on strain imaging, and characteristic CMR features.[46] Bone tracer scintigraphy enables non-invasive diagnosis of ATTR-CM in the absence of monoclonal protein, thereby reducing the need for endomyocardial biopsy in appropriate cases.[46]

Constrictive Pericarditis & Pulmonary Hypertension

Constrictive pericarditis is a classic mimic of HFpEF, characterized by preserved ejection fraction with symptoms of congestion due to pericardial constraint rather than intrinsic myocardial dysfunction.[47] Key diagnostic features include respiratory variation in Doppler inflow velocities, annulus reversus or paradoxus, pericardial thickening or calcification on computed tomography or CMR imaging, and confirmatory invasive hemodynamic findings when non-invasive evaluation is inconclusive.[47]

Pulmonary hypertension (PH) frequently coexists with HFpEF but may also represent a primary pulmonary vascular disorder.[48] Accurate

classification requires careful measurement and interpretation of PCWP, as misclassification may lead to inappropriate treatment, including the use of pulmonary vasodilators in patients with left heart disease. When available, exercise hemodynamic assessment can reveal exertional elevation in filling pressures, thereby identifying 'masked' HFpEF and distinguishing it from primary pulmonary arterial hypertension.[49-50] This differentiation is clinically crucial, as therapeutic strategies differ substantially between these conditions.

Diagnostic Approach to Heart Failure with Preserved Ejection Fraction

Conceptual Framework for Diagnosis

The diagnostic pathway for HFpEF should be probability-based and stepwise, integrating symptoms and signs with objective evidence of cardiac dysfunction or congestion. Contemporary guidance emphasizes that HF is a clinical syndrome supported by biomarkers and/or objective findings, and that HFpEF requires demonstration of

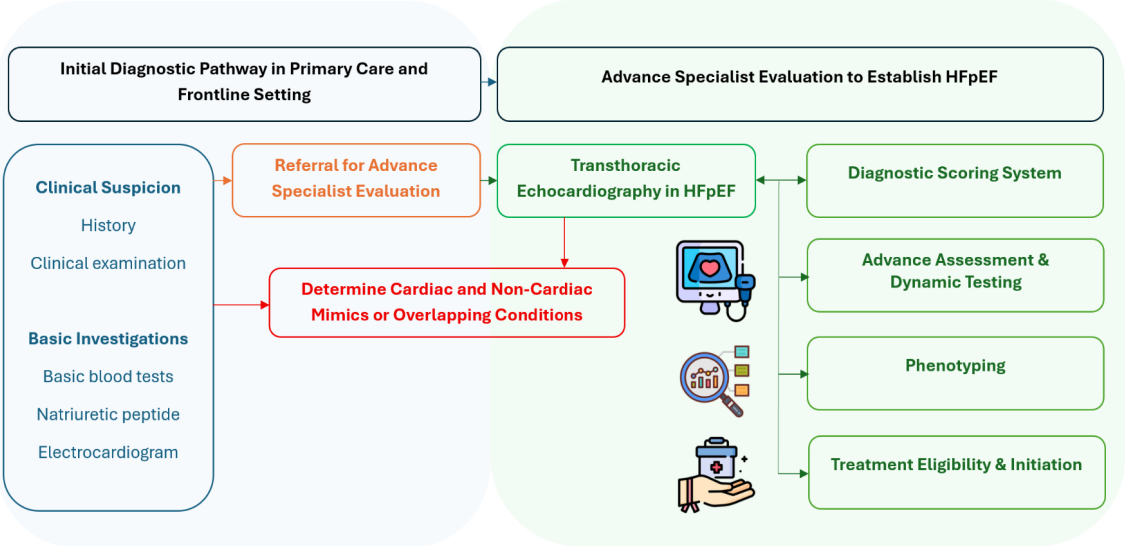

Figure 2. Stepwise Diagnostic Pathway for HFpEF from Primary Care to Specialist Evaluation. In primary care, HFpEF is suspected based on clinical assessment and basic investigations (blood tests, natriuretic peptides, ECG), prompting referral. Specialist evaluation centers on transthoracic echocardiography and exclusion of cardiac and non-cardiac mimics. Diagnosis is supported by scoring systems and advanced testing when needed. Confirmed HFpEF is followed by phenotyping and initiation of targeted therapy.

preserved LVEF together with evidence consistent with elevated filling pressures, either at rest or during physiological stress.[6,50] Because many patients with HFpEF have near-normal resting hemodynamics, contemporary diagnostic strategies increasingly incorporate dynamic functional testing to reveal abnormal reserve and exertional rises in filling pressure.[6,49-52]

The workflow is therefore structured according to tiers of care:

- Primary care and frontline clinicians aim to identify suspected HF and refer patients suspicious of HFpEF, and
- Subspecialists, commonly cardiologists, aim to confirm the diagnosis of HFpEF using TTE and diagnostic scores, and/or perform further investigations to support the clinical suspicion.

Initial Diagnostic Pathway in Primary Care and Frontline Setting (Figure 2)

Clinical suspicion typically arises when patients present with symptoms associated with HF, commonly exertional dyspnoea, reduced exercise tolerance, fatigue, orthopnoea or paroxysmal nocturnal dyspnoea, or peripheral edema.[2-4,6,50] Furthermore, from clinical history, suspicion is heightened further based on the context of having risk factors commonly associated with HFpEF, such as older age, hypertension, obesity, T2DM, CKD, and AF. This is corroborated by clinical examination findings such as an elevated jugular venous pressure, pulmonary crackles, or peripheral edema, although such findings may be absent in early or latent HFpEF.[2-4,6,50]

From here, clinicians should then embark on basic clinical investigations with TWO goals in

mind – to support the possibility of a cardiac etiology, alongside identifying potential alternative diagnoses for the clinical presentation.[2-4,6,50] Routine blood investigations should include a full blood count, renal function and electrolytes, liver function test, glucose or glycated hemoglobin, and thyroid function test to help identify potential mimics such as anemia or thyroid disease, assess comorbidity burden, and provide baseline values for subsequent management. Electrocardiography may reveal AF, LV hypertrophy, past myocardial infarctions, or conduction disease. However, a normal electrocardiogram does not eliminate the likelihood of HF. Chest radiography can demonstrate cardiomegaly, pulmonary congestion, pleural effusion, or alternative pulmonary pathology.

NP levels, however, remain the most useful triage investigation in HF. Cut-off values for NP depend on the clinical setting (i.e., ambulatory outpatient clinics versus emergency department) and age.[53] Other clinical considerations include the presence or absence of obesity, AF, and renal dysfunction, although cut-off values in these settings are yet to be formally established.[53] In addition, it is known that HFpEF can exist even in the absence of elevated NP levels.[54-55] Thus, in patients highly suspicious of the condition, a referral for further investigations is still warranted, regardless of NP levels.

Although scoring systems to determine the probability of HFpEF would prove to be useful in the community setting as a triage tool, two of the most commonly used scoring tools (i.e., H2FPEF and HFA-PEFF) include parameters requiring TTE, which often remain poorly accessible to most clinicians.[50,56] An alternative tool to help with referral decisions includes the HFpEF-ABA scoring system, derived from the H2FPEF scoring tool, which utilizes only THREE parameters – age, body mass index, and AF, which can easily be determined in the community setting.[57] The HFpEF-ABA score largely demonstrated reasonably strong discrimination and calibration across ambulatory patients with dyspnoea, although validation studies across various populations, including Indonesia, remain limited.

Table 1. Echocardiographic criteria for estimating elevated left ventricular filling pressure in sinus rhythm and atrial fibrillation.

A. Echocardiographic Criteria for Estimating Elevated Left Ventricular Filling Pressure in Sinus Rhythm.				
Mitral E/A ratio ≥2 (as a single strong indicator of elevated filling pressure) OR Mitral E/A ratio between 0.8 and 2.0, in conjunction with at least two of the following: • LAVI >34 mL/m² • TR velocity ≥2.8 m/s or PASP ≥35 mmHg • E/e' ratio ≥15 (septal), ≥13 (lateral), or ≥14 (average) • LASr ≤16% • LV mass index >95 g/m² in women or >115 g/m² in men				
B. Echocardiographic Criteria for Estimating Elevated Left Ventricular Filling Pressure in Atrial Fibrillation.				
Elevated LVFP is suggested when at least three of the following are present: • mitral E velocity ≥100 cm/s • septal E/e' >11 • TR velocity >2.8 m/s or PASP >35 mmHg • deceleration time ≤160 ms				
In the absence of definitive parameters, additional supportive indices may include:				
PR end-diastolic velocity ≥2 m/s	pulmonary artery diastolic pressure ≥16 mmHg	mitral inflow L-wave velocity ≥50 cm/s	Ar–A duration >30 ms*	and/or a decrease in mitral E/A ratio ≥50% with Valsalva manoeuvre*

This table summarizes key echocardiographic parameters used to estimate elevated left ventricular filling pressure (LVFP) in patients with preserved ejection fraction who are in sinus rhythm or atrial fibrillation (AF). In AF, conventional diastolic parameters are less reliable due to beat-to-beat variability and absence of atrial contraction, thus the need for unique parameters. Peak early diastolic mitral inflow velocity (E), peak atrial contraction mitral inflow velocity (A), left atrial volume index (LAVI), tricuspid regurgitation (TR), pulmonary artery systolic pressure (PASP), peak early diastolic mitral annular tissue velocity (e'), left atrial reservoir strain (LASr), left ventricle (LV), pulmonary regurgitation (PR), and pulmonary vein atrial reversal wave to the mitral late diastolic atrial flow wave duration ratio (Ar–A).

Advance Specialist Evaluation to Establish HFpEF (Figure 2)

Upon referral for advanced evaluation, further assessment often begins by performing a TTE, and the utilization of scoring systems to determine the probability of having HFpEF. In certain circumstances, additional investigations (both invasive and non-invasive) may be required depending on clinical context, expertise, and availability.

Transthoracic Echocardiography in HFpEF (Table 1 & Supplementary Table 1)

TTE remains the cornerstone imaging modality in the diagnostic evaluation of HFpEF, providing essential information for confirmation of cardiac involvement, assessment of hemodynamic burden, exclusion of alternative diagnoses, and prognostication.[50,58-59] Furthermore, given the non-specific clinical presentation of HFpEF, TTE is indispensable for differentiating HFpEF from a broad range of cardiac and non-cardiac conditions that may mimic the condition, while also offering insight into the underlying pathophysiological mechanisms driving the syndrome.[50,58-59]

HFpEF is commonly associated with characteristic remodeling of the LV. Structural abnormalities frequently observed include LV hypertrophy, specifically that of concentric remodeling (assessed using LV mass index and relative wall thickness) and left atrial enlargement (assessed using Left Atrial Volume Indexed [LAVI]). In addition, assessment for elevated filling pressure is routinely performed and largely reflects a combination of impaired relaxation, reduced contractile reserve, abnormal atrioventricular coupling, increased ventricular stiffness, relative pericardial restraint, and abnormal ventricular-vascular coupling (Table 1).[50,58-59] It should be remembered that a multiparametric approach rather than reliance on any single variable is often advised when assessing diastolic function.

In AF, assessment for diastolic function may still be performed, although it may be more challenging (Table 1).[58-59] In such cases, elevated filling pressure is suspected when several supportive features are present, including increased mitral E velocity, increased septal E/e', shortened deceleration time, and increased tricuspid regurgitation velocity or pulmonary artery systolic pressure. In addition, these algorithms should not be applied uncritically in certain settings, including left bundle branch block, right ventricular pacing or cardiac resynchronization therapy, severe mitral valve disease or prosthetic mitral valves, heart transplantation, LV assist device support, non-cardiac pulmonary hypertension, and constrictive pericarditis.[58-59] Further staging of HFpEF phenotypes based on echocardiography can also be performed, as per previous studies, with significance in prognostication.[60-61] However, classification based on such phenotypes requires further validation in its clinical utility. An example of echocardiographic-based stratification and classification is listed in Table 2.

However, as previously discussed, echocardiographic-based changes used in diastolic functional assessment may not be present in all cases of confirmed HFpEF.[10] Conversely, many individuals, particularly older adults, may exhibit echocardiographic features of diastolic dysfunction without having clinical features suggestive of HFpEF, underscoring why isolated diastolic dysfunction should not be used as a surrogate for diagnosis.[50,58-59] Contemporary concepts emphasize HFpEF as a syndrome of abnormal pressure-volume responses to physiological stress, in which resting echocardiographic findings may underestimate disease severity. Therefore, in cases of high clinical suspicion where resting TTE is revealed to be non-suggestive of the condition, assessment should move beyond measurements at resting state toward a comprehensive interpretation of cardiac structure, function, and dynamic reserve with physiological stress, which will be discussed in another section.

One of the primary roles of TTE in suspected HFpEF is the exclusion of other conditions that may mimic or overlap with HFpEF, of which may require distinct management strategies.[2-4,6,50] These include restrictive or infiltrative cardiomyopathies, HCM, ischemic heart disease, HF with improved ejection fraction, pulmonary arterial hypertension, constrictive pericarditis, valvular heart disease, high-output states, and primary pulmonary disease. Accurate identification of these entities is critical, as misclassification as HFpEF may delay disease-specific therapy and adversely affect outcomes. Furthermore, depending on clinical suspicion, additional investigations may be required outside of TTE, including ischemia evaluation, CMR imaging for infiltrative disease, invasive hemodynamic assessment for constrictive pericarditis, or targeted pulmonary evaluation.

Diagnostic Scoring Systems, Advanced Assessment & Dynamic Testing (Figure 2)

When clinical investigations performed at rest remain indefinite, validated diagnostic scores may help with the diagnosis and treatment planning in HFpEF management. TWO popular scoring systems are often used – the H2FPEF and HFA-

Table 2. Echocardiography-based staging of heart failure with preserved ejection fraction.

Stage 1: Isolated Left Ventricular Involvement
• Echocardiographic clusters, as per ASIAN-HF registry: ○ normal left ventricular (LV) structure; with elevated filling pressures ○ restrictive; small LV cavities, concentric hypertrophy, and low stroke volume ○ hypertrophic; with concentric LV hypertrophy ○ high-output; with increased stroke volume ○ atrial-dominant; driven by atrial myopathy ○ others (not clearly defined)
LV structural and functional parameters: concentric LV hypertrophy (i.e., LV mass index ≥115 g/m² in men or ≥95 g/m² in women, RWT >0.42), reduced LV compliance, elevated LV filling pressures (E/e' >9), and impaired forward flow with reduced cardiac output.
Stage 2: Left Atrial Myopathy (Isolated or Predominant)
• Left atrial (LA) dysfunction may be disproportionate to the degree of left ventricular diastolic abnormality and can act as an important driver of symptoms, pulmonary hypertension, and atrial fibrillation in HFpEF. • LA dysfunction has been linked to incident atrial fibrillation and progression to permanent arrhythmia, increased pulmonary vascular resistance and right ventricular dysfunction, contributing to worse clinical outcomes.
LA dilatation parameters: LAVI >34 mL/m² in sinus rhythm, or >40 mL/m² in atrial fibrillation LA dysfunction parameters: impaired left atrial reservoir strain (peak atrial longitudinal strain ≤ 24%), and increased left atrial stiffness or reduced atrial compliance.
Stage 3: Pulmonary Vasculature Involvement with Pulmonary Hypertension, with or without Right Atrial & Ventricular Dysfunction
• Pulmonary hypertension (PH) in HFpEF may arise passively from elevated left-sided filling pressures or evolve into a combined pre- and post-capillary process due to pulmonary vasoconstriction and vascular remodelling in chronic disease states. • Right ventricular (RV) dysfunction reflects both load-dependent and intrinsic myocardial impairment. • Right atrial (RA) myopathy is increasingly recognised as part of advanced HFpEF, and it correlates with a higher burden of atrial fibrillation, more severe pulmonary vascular disease, significant tricuspid regurgitation, RV dysfunction, and adverse prognosis.
Pulmonary vasculature abnormalities: tricuspid regurgitation peak velocity >2.8m/s, pulmonary artery systolic pressure > 35mmHg RV dysfunction: reduced RV fractional area change <35%, tricuspid annular plane systolic excursion (TAPSE) <17 mm, or tricuspid annular systolic velocity (RV S') < 9.5cm RA dilatation: RA enlargement (RA volume index >39 mL/m² in men and >33 mL/m² in women) RA dysfunction: reduced RA reservoir strain (≤19.8%),

This table describes the various stages of cardiac abnormalities, and corresponding parameters, that can potentially be observed and measured through cardiac imaging.

PEFF scores.[50-56] An earlier-mentioned scoring system, the HFpEF-ABA, is actually a derivative of the H2FPEF tool and will not be discussed further in this section.

The H2FPEF score combines clinical variables, including obesity and AF, with echocardiographic surrogates of filling pressure to estimate diagnostic likelihood and guide further investigation.[56] The HFA-PEFF algorithm integrates echocardiographic parameters and NP into major and minor criteria to stratify patients into low, intermediate, or high probability of HFpEF, recommending functional testing in intermediate-probability patients.[50]

Comparative analyses support the complementary use of these tools, where high scores have been shown to be useful to support the diagnosis of the condition, whereas intermediate scores help identify patients who would most likely benefit from further investigations, ideally those which are exercise or stress-based.[62] Furthermore, these scores have been shown to assist in functional assessment, outcome prediction, and prognostication when incorporated into daily clinical practice.[63-64]

However, there remain issues with potential misclassification, specifically when using low scores using either of the scoring tools, to confidently rule out a diagnosis of HFpEF.[62] As previously

mentioned, HFpEF is a syndrome of abnormal pressure-volume responses to physiological stress, and therefore, clinical parameters obtained at rest may severely underestimate the presence of the condition. In such cases, where a diagnostic scoring system demonstrates an intermediate probability of having the condition, it is recommended that either a non-invasive diastolic stress test or invasive hemodynamic testing be performed.

Diastolic Exercise Stress Echocardiography

When resting TTE is unremarkable or inconclusive, particularly in patients with suggestive symptoms like exertional dyspnoea, exercise stress echocardiography can be performed to unmask latent HFpEF. Exercise stress echocardiography is typically performed using a supine bicycle, with a fixed protocol reminiscent of a treadmill exercise stress test for ischemia evaluation.[65-67] However, parameters measured during the test are specific to those of diastolic function and reserve, as well as pulmonary pressure response to exercise or stress. Key parameters include mitral inflow velocities, E/e' ratio, tricuspid regurgitation velocity, and left atrial functional indices. Abnormal exercise filling pressures are suggested by either a raised E/e' and/or raised tricuspid regurgitation velocity during exercise.[65-67]

Right Heart Catheterization

Alternatively, or if stress echocardiography remains non-diagnostic or inaccessible, invasive hemodynamic testing can be considered. Invasive testing is particularly valuable in patients with obesity, AF, unexplained exertional dyspnoea, or coexisting pulmonary disease, where non-invasive indices may be less reliable.[65,67-69] Right Heart Catheterization (RHC) allows direct measurement of PCWP to help confirm a diagnosis of HFpEF, where PCWP of >15 mmHg at rest is fairly suggestive of the disease.[68-70] Some may opt for direct catheter-based measurement of LVEDP to support the diagnosis of HFpEF. However, there continues to be uncertainty with regard to which measurements (i.e., PCWP versus LVEDP) are most diagnostic for HFpEF, although the former has been shown to be a better predictor of prognosis in the condition.[71]

Similar to exercise stress echocardiography, there is added value in performing RHC with exercise, most commonly through the use of a supine bicycle. Following exercise, a PCWP of ≥25 mmHg would be suggestive of HFpEF and remains the gold standard in diagnosing the condition.[65,68-70] In the event that a supine bicycle is unavailable, various other methods have been employed in the past, including the use of passive leg raises, direct volume challenge using saline, and complex use of conductance catheterization to assess pressure-volume loops of the right ventricle and pulmonary artery, which go beyond the scope of this review.[65,68-70] There also remains contention with regard to performing RHC in either an upright or supine position, which are beyond the aims of this article.[71]

Common Pitfalls and Diagnostic Errors

One of the most common pitfalls in the diagnosis of HFpEF is over-reliance on resting echocardiographic indices, which can lead to both under- and misdiagnosis in routine clinical practice. Various cardiac conditions may exhibit similar echocardiographic features, including structural abnormalities and hemodynamic changes suggestive of diastolic dysfunction, including both hypertrophic and infiltrative cardiomyopathies, as well as valvular heart disease.[2-4,6,50] As the treatment for each of these conditions differs greatly from that of HFpEF phenotypes, it would be prudent to identify features that would help distinguish these mimics early through TTE, so as to not delay further investigations, such as cardiac MRI or nuclear imaging, that are required to diagnose these conditions, specifically cardiomyopathies such as cardiac amyloidosis.

In addition, the use of diagnostic scoring systems may not necessarily be helpful in distinguishing HFpEF from its mimics.[72] Conversely, many patients with HFpEF may also demonstrate no symptoms at rest, and their resting estimates of filling pressure may be normal or of borderline significance even after perturbation of their hemodynamic system.[10] This is particularly problematic in early-stage disease and in obesity-related phenotypes, where NP levels may also be suppressed and resting congestion may be very minimal.[54-55] Therefore, in cases of clinical conundrum, we would recommend more invasive hemodynamic testing, as opposed to non-invasive alternatives, to ensure that a diagnosis of HFpEF is not missed.

However, the biggest issue contributing to an underdiagnosis of the condition remains clinical inertia, which often amounts to missed opportunities in referrals.[2-4,6,50] HFpEF is often overlooked in the presence of mimicking non-cardiac comorbidities such as obesity, deconditioning, chronic lung disease, or anemia. In fact, these conditions frequently coexist with HFpEF and can even amplify the symptoms faced by patients, highlighting the need to address both HFpEF and comorbidities simultaneously.

Table 3. Treatment strategy for heart failure with preserved ejection fraction.

Treatment Domain	Therapy/ Intervention	Mechanism / Target	Clinical Benefit	Key Evidence
Comorbidity Management	Hypertension control	↓ afterload, ↓ vascular stiffness	↓ HF incidence, disease progression	SPRINT, HYVET
	Diabetes management	Metabolic modulation	Improves outcomes	SGLT2i preferred
	CKD management	Cardiorenal protection	↓ progression, improved outcomes	SGLT2i, finerenone
	CAD management	Anti-ischemic therapy	Symptom relief	No HFpEF-specific RCT
	AF management (rate/ rhythm control)	Improve filling & haemodynamics	↓ symptoms, potential ↓ hospitalization	CABANA, ATHENA (post-hoc)
Foundational GDMT	Loop diuretics	Volume control (decongestion)	Symptom relief, ↓ congestion	No mortality benefit; careful titration required
	SGLT2 inhibitors (empagliflozin, dapagliflozin)	Osmotic diuresis, improved energetics, anti-inflammatory, renal protection	↓ HF hospitalization, improved outcomes	EMPEROR-Preserved, DELIVER; cornerstone therapy
	MRA (spironolactone, finerenone)	Anti-fibrotic, anti-inflammatory, RAAS modulation	↓ HF hospitalization (selected patients)	TOPCAT, FINEARTS-HF
Phenotype-Specific Therapy	Cardiometabolic phenotype	SGLT2i, MRA, blood pressure control	Target inflammation, fibrosis	RAAS-driven phenotype
	Obesity phenotype (semaglutide, tirzepatide)	Weight loss, ↓ inflammation	↑ quality of life, ↑ exercise capacity	STEP-HFpEF, SUMMIT
Non-Pharmacological Therapy	Cardiorenal phenotype	SGLT2i ± MRA	Renal protection, ↓ congestion	Strong benefit across CKD spectrum
	AF phenotype	Rhythm control, anticoagulation	Improve symptoms, prevent stroke	Individualized approach

This table summarizes a practical, phenotype-oriented approach to HFpEF management, integrating comorbidity optimization, guideline-directed medical therapy, and phenotype-specific interventions. Heart failure (HF), chronic kidney disease (CKD), coronary artery disease (CAD), atrial fibrillation (AF), sodium-glucose cotransporter 2 (SGLT2), mineralocorticoid receptor antagonist (MRA), renin-angiotensin-aldosterone system (RAAS), angiotensin receptor neprilysin inhibitors (ARNI).

Treatment of Heart Failure with Preserved Ejection Fraction (Table 3)

Therapeutic Goals in HFpEF

Unfortunately, unlike HFrEF, there are no proven pharmacological therapies that have demonstrated a definitive reduction in cardiovascular mortality across clinical trials in the HFpEF population.[2-4,6,50] However, there has been a paradigm shift in the landscape of treatment surrounding HFpEF, moving from symptom management and comorbidities optimization, to now include pharmacotherapies with evidence in reducing HF-related events such as hospitalization, symptom improvement, functional capacity, and quality of life.

We encourage a structured approach in terms of management of HFpEF, which includes:

1. treatment of comorbidities and co-existing conditions,
2. guideline-directed medical therapy targeting shared neurohormonal and metabolic pathways, and
3. phenotype-based therapy tailored to dominant comorbid and pathophysiologic drivers.

1. Treatment of Comorbidities and Coexisting Conditions

Optimal management of comorbidities is fundamental in the management of HFpEF because they contribute to the underlying pathophysiology of the condition, as highlighted in an earlier section.[11-12,14,73] For example, evidence has shown that optimization in blood pressure

control improved cardiac remodeling and diastolic dysfunction, although the exact impact of treatment on LV remodeling largely depended on the extent of regression in hypertrophy, changes in LV loading conditions, the direct effect of the antihypertensive medication on the myocardium, and potentially alterations in coronary reserve.[73-75] There is also growing evidence in the use of therapeutic agents such as ARNI and Mineralocorticoid Receptor Antagonist (MRA) for the concomitant treatment of HFpEF and resistant hypertension, which would potentially help clinicians in prioritizing choice of anti-hypertensive therapies.[74-75] There has also been similar levels of benefit seen in HFpEF outcomes following optimal glycaemic control, management of ischemic heart disease, rhythm control strategies in AF, treatment of obesity and management of sleep apnoea in patients living with HFpEF.[14]

2. Fundamental Therapy Diuretics

Various therapeutic agents have now been shown to be beneficial in the management of HFpEF, which in fact have superseded previously developed treatments. Nevertheless, evidence for the use of diuretics, despite lacking randomized controlled trials, is unquestionable in the face of cardiac congestion, and diuretics remain the cornerstone of symptomatic management in HFpEF. Loop diuretics are recommended as first-line therapy for relief of both pulmonary and systemic congestion, with careful assessment and titration of the dose to avoid risk of renal dysfunction and electrolyte imbalances.[6,8-9,43] Interestingly, HFpEF patients may exhibit differential responses to diuresis, with predominant interstitial rather than intravascular fluid retention, necessitating individualized dosing strategies.[76] There is also emerging evidence surrounding the use of novel therapies, such as semaglutide, that led to lower use of decongestive therapies in the long term. These findings highlight the evolving role of decongestion beyond conventional diuretics, supporting a more integrated and phenotype-specific approach.[77]

SGLT2 Inhibitors

SGLT2 inhibitors are now considered fundamental and a foundational disease-modifying therapy for Heart Failure with mildly reduced Ejection Fraction (HFmrEF) and HFpEF, irrespective of T2DM status.[78-79] This was mainly based on consistent reductions in worsening HF events driven mainly by fewer HF hospitalizations in clinical trials such as EMPEROR-Preserved and DELIVER.[78-79] These studies led to guideline positioning in the 2022 AHA/ACC/HFSA guideline, where SGLT2 inhibitors received a Class IIa recommendation for both HFmrEF and HFpEF to reduce HF hospitalizations and cardiovascular events.[43] The 2023 Focused Update of the ESC HF Guidelines similarly recommends SGLT2 inhibitors for patients with HFmrEF/HFpEF to reduce HF hospitalization and cardiovascular death, with a higher Class Ia level of recommendation.[9]

Aldosterone Targeted Therapies

In the TOPCAT trial, spironolactone reduced HF hospitalizations following subgroup analysis, which differentiated patients from 'the Americas' from those randomized in Russia and Georgia.[80-81] However, it should be highlighted that the overall trial remains largely neutral in its primary outcomes. Nevertheless, the 2022 AHA/ACC/HFSA guidelines have provided a Class IIb recommendation for the use of steroidal MRAs in HFpEF, reflecting earlier mixed evidence and heterogeneity of benefit across HFpEF populations.[43] More recently, the FINEARTS-HF trial demonstrated evidence in the use of the non-steroidal MRA, finerenone, in significantly reducing composite endpoints of worsening HF events and cardiovascular death in patients with HFmrEF/HFpEF.[18,80-81] These results strengthen the biological and clinical rationale for aldosterone targeted therapies as potential disease-modifying therapy in HF, and have led to many more clinical trials being conducted in this space involving other agents such as vicadrostat and balcirenone in treating HF, agnostic to LVEF values.[80-81]

3. Phenotype-Based Treatment Cardio-Kidney-Metabolic (CKM) Syndrome and Obesity

The American Heart Association has since introduced a framework in the management of Cardio-Kidney-Metabolic (CKM) syndrome, owing to its exponential rise among communities globally.[82-83] It remains uncanny how treatment options available for the management of HFpEF greatly resemble those of diabetic and non-diabetic CKD, which emphasizes the large overlap in pathophysiological processes, centered around inflammation, fibrosis, hemodynamic and metabolic disturbances. As previously described, SGLT2 inhibitors and MRAs, specifically non-steroidal variants, have been shown to be beneficial in CKD, T2DM, and now HFpEF and should be prioritized when managing patients with such HFpEF phenotypes.

Obesity and adiposity, a progenitor in most cases of CKM syndrome, are equally important in HFpEF phenotypes. In the STEP-HFpEF trial, the use of semaglutide 2.4 mg weekly was shown to significantly improve symptoms and functional capacity in obese HFpEF patients.[83] There was improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores by 16.6 points in the intervention group, versus 8.7 points using placebo ($p<0.001$), with equally significant weight reduction (−13.3% versus −2.6% ($P<0.001$)) and 6-minute walk distance (21.5m versus 1.2m ($P<0.001$)). Another trial focused on T2DM patients, with HFpEF and obesity, confirmed similar benefits as well, and findings from both trials were further reinforced through a pooled analysis.[83] More recently, the SUMMIT trial demonstrated a significant reduction in composite endpoints of cardiovascular death and worsening HF (HR 0.62; 95% CI 0.41–0.95; P=0.026), alongside significantly improved KCCQ score (between-group difference 6.9 points; $P<0.001$) in HFpEF patients with obesity following the use of tirzepatide, a dual-incretin receptor agonist containing GLP1-RA and glucose-dependent insulinotropic polypeptide (GIP).[83]

These trials provide compelling evidence that obesity is a modifiable pathophysiologic driver rather than merely an associated condition. Alongside pharmacotherapeutics, patients living with HFpEF and obesity should also be considered for bariatric surgery, where limited data have shown improvements in symptoms, reverse LV remodeling, and lipidomic changes in HFpEF patients, albeit in a small cohort.[84] In addition, structured, supervised aerobic exercise training to improve functional capacity and quality of life should also be integrated into the holistic management of the disease.[85]

Coronary Artery Disease & Microvascular Dysfunction

Despite a plethora of evidence proving how prevalent both CAD and MVD are in patients living with HFpEF, there remains no strong evidence to support the routine use of coronary revascularization, anti-anginal, and microvascular-targeted therapies to confer benefit.[38-39,41-42] However, concomitant ischemia and chronic coronary syndrome can exist and should still be managed according to guidelines.[40]

Chronotropic Incompetence & Exercise Intolerance

Chronotropic incompetence is common in HFpEF and contributes to exercise intolerance.[26-27] Excessive heart rate reduction with BB or non-dihydropyridine calcium channel blockers may worsen exercise capacity in selected patients, and as alluded to in an earlier section, withdrawal of such therapies, specifically that of BB, has been shown to be beneficial in selected populations.[28] However, the role of rate-adaptive pacing in symptomatic HFpEF patients with chronotropic incompetence remains uncertain, following publication of opposing results from trials such as RAPID-HF and myPACE.[86] As such, we are unable to recommend routine pacemaker-based chronotropic therapy in HFpEF outside of established pacing indications.

Cardiac Rehabilitation (CR) is a clinically meaningful non-pharmacological intervention in HFpEF, addressing the core limitations of exercise intolerance and functional impairment.[87] Comprehensive CR programs, including structured exercise training, education, and lifestyle modification, have been shown to significantly improve exercise capacity, functional status, and health-related quality of life, while also providing effective symptom relief, particularly dyspnoea and fatigue. These benefits are highly relevant in HFpEF, where reduced physical capacity and poor quality of life are dominant clinical features. Supervised exercise-based CR further enhances adherence and outcomes, leading to greater improvements in peak oxygen uptake and daily functional performance.[87] Therefore, CR should be incorporated as an essential component of holistic HFpEF management, particularly in patients with exercise limitation and deconditioning.

Atrial Fibrillation

The CABANA trial demonstrated the effectiveness of catheter ablation in reducing all-cause mortality and improving quality of life compared with pharmacotherapy in patients with concomitant HF and AF.[88] However, insight from CABANA focusing on HFpEF revealed that patients with the condition experienced higher rates of recurrence post-procedure. This has been similarly demonstrated in other studies as well.[89-90] Rhythm control strategies should, thus, be individualized, and this further highlights the importance of adopting a holistic, multi-prong approach in the management of concomitant HFpEF and AF – tackling underlying comorbidities that can potentially drive both conditions while attempting to restore sinus rhythm.

HFpEF in Women

Recognition of the female-predominant HFpEF phenotype has important therapeutic implications, particularly surrounding neurohormonal

modulation. Among available therapies, ARNI appears especially relevant in this subgroup.[33-34] Although the PARAGON-HF trial did not meet its primary endpoint, prespecified subgroup analyses demonstrated a significant sex-specific benefit, with a substantial reduction in HF hospitalization among women, compared to men.[33-34] This differential response is biologically plausible as women, particularly post-menopausal, exhibit relative NP deficiency, heightened RAAS activation, and increased neprilysin activity related to adiposity, all of which can potentially be modulated by ARNI.[33-34] Therefore, ARNI may be preferentially considered in women with HFpEF, particularly those with cardiometabolic features such as obesity, hypertension, and elevated NP.

Implementation of HFpEF Diagnostic Pathways in Resource-Limited Settings

A common issue faced by many healthcare systems, particularly in low- and middle-income countries, includes poor accessibility to NP testing, diastolic stress echocardiography, and invasive hemodynamic assessment. It is therefore pivotal that our review article addresses potential diagnostic strategies for HFpEF that are adaptable, pragmatic, and grounded in clinical probability rather than dependence on advanced technologies. We highlight some common dilemmas and possible solutions, as follows.

Primary Care & Frontline Services Without Natriuretic Peptide Testing

In healthcare institutions where NP testing remains unavailable, clinical gestalt and probability assessment become paramount. Good history-taking remains important, especially in such circumstances, and primary care clinicians should recognize symptom patterns alongside features suggestive of high-risk clinical risk. Presence of older age, long-standing hypertension, obesity, T2DM, AF, and CKD in particular should alert clinicians regarding a high likelihood of HFpEF in the appropriate clinical context, especially when present together. This should also prompt an early referral for advance evaluation, even in the absence of biomarker confirmation.

In addition, basic clinical investigations remain valuable in this context to support clinical suspicion for the diagnosis. An abnormal electrocardiogram with features of LV hypertrophy, or a chest radiograph demonstrating pulmonary congestion or pleural effusion, supports a likely cardiac etiology and strengthens the case for referral, even without NP testing or an echocardiogram. Unremarkable baseline tests may lower suspicion but do not exclude HFpEF, particularly in patients with persistent or progressive symptoms. In such scenarios, this should still trigger a referral for specialist evaluation rather than prolonged observation in the ambulatory community setting.

Cardiology Evaluation Without Stress Echocardiography

Hesitance among cardiologists to perform stress echocardiography is often not due to a lack of equipment (stress echocardiography can be performed using a conventional exercise treadmill if a semi-supine bicycle is unavailable) but rather to a lack of awareness and expertise in performing and interpreting the test comprehensively. Furthermore, stress echocardiography using an exercise treadmill can be more cumbersome and time-consuming, requiring back-and-forth transfers between the bedside and the treadmill throughout the test. It is thus important to highlight that stress echocardiography for HFpEF diagnosis is not meant to be performed in all cases suspicious of HFpEF, but only in those with intermediate probability for the condition, and that probability-based diagnostic scores, as discussed above, are especially useful in this context. Patients with scores suggestive of a high probability of the disease may be diagnosed with HFpEF with reasonable confidence, without further testing.

However, in clinical settings where stress echocardiography is truly unavailable, cardiologists should maximize the diagnostic yield of the resting echocardiography performed and, when paired with diagnostic scoring tools, can reasonably follow patients with scores suggestive of intermediate risk for HFpEF closely in the ambulatory setting for changes in clinical context. It is also reasonable to consider pharmacotherapies that already have a clear indication in individual patients, especially in those with T2DM, CKD, or obesity, which may also be beneficial in patients who might have HFpEF. In settings where invasive hemodynamic testing is readily available, this is a reasonable alternative to aid the diagnosis of HFpEF in patients suspected of the condition.

Limited Access to Right Heart Catheterization

RHC with exercise remains the 'gold standard' for the diagnosis of HFpEF. However, the authors are cognizant that this service is largely unavailable

in many centers. As mentioned previously, non-invasive stress testing remains a reasonable alternative, and many do not pursue it mainly due to a lack of awareness and knowledge, which can largely be addressed through improved nationwide training. If RHC can be performed sans exercise, several methods to 'perturb the system' have been tested, including direct saline loading or passive leg raises, which can also be attempted. However, clinicians should be aware of the limited evidence supporting their use. It is also reasonable to consider a longitudinal diagnostic approach, with repeated clinical assessments, serial TTEs, evaluation of response to empiric therapy, such as cautious diuretic use, and monitoring of symptom trajectories, which can provide indirect confirmation over time, although this is often less than ideal. It should also be remembered that in certain clinical mimics, such as pulmonary hypertension or constrictive pericardial disease, invasive hemodynamic assessment can at times be crucial for confirmation of the diagnosis, and patients should be referred early to tertiary centers with capabilities to perform invasive hemodynamic testing, so as not to delay treatment.

Referral Networks and Stepwise Escalation

An effective strategy in resource-limited systems is the development of tiered referral networks, whereby primary and secondary care hospitals are encouraged to identify cases of suspected HFpEF early, and are also encouraged to refer complex or inconclusive cases to regional centers with the appropriate echocardiography or catheterization facilities and expertise. The path forward should include the development of a spoke-and-hub model, with clear referral criteria based on symptom burden, comorbidity profile, and resting echocardiographic findings, which could reduce referral delays and avoid redundant requests for investigations, thereby optimizing the use of limited resources.

Conclusion

HFpEF has evolved from a poorly defined clinical entity into one that is both heterogeneous and complex, driven by a diverse range of pathophysiological processes and associated with multimorbidity clusters. Although initial phenotyping exercises have been unnecessarily complicated, clinical phenotyping of HFpEF over the past decade has largely helped reshape the management paradigm of the condition by identifying key clinical manifestations of the disease. The existence of such phenotypes has also been largely supported by successful treatment options that have demonstrated consistent benefits in the HFpEF space.

As the evidence surrounding successful therapeutic agents expands, the importance of improving diagnostic accuracy to ensure patients are identified early and precisely so they can derive benefit from treatment grows. Accurate diagnosis requires a structured, probability-based approach that integrates clinical assessment, biomarker utilization, multimodality imaging, and hemodynamic assessment. Our review will hopefully provide guidance and a framework for managing HFpEF for clinicians in various clinical settings by bridging the gap between the pathophysiological complexity surrounding HFpEF and its effective clinical management.

List of Abbreviations

ACC	American College of Cardiology
AF	Atrial Fibrillation
ARNI	Angiotensin Receptor Neprilysin Inhibitors
ATTR-CM	Transthyretin Cardiac Amyloidosis
BB	Beta-Blockers
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
CMR	Cardiac Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CR	Cardiac Rehabilitation
CKM	Cardio-Kidney-Metabolic
ESC	European Society of Cardiology
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVI	Left Atrial Volume Index
LV	Left Ventricular
LVEDP	Left Ventricular End-Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
MAFLD	Metabolic-Associated Fatty Liver Disease
MRA	Mineralocorticoid Receptor Antagonist

MVD	Microvascular Dysfunction
NP	Natriuretic Peptides
PCWP	Pulmonary Capillary Wedge Pressure
RAAS	Renin-Angiotensin-Aldosterone System
RHC	Right Heart Catheterization
SGLT2	Sodium-Glucose Cotransporter 2
T2DM	Type 2 Diabetes Mellitus
TTE	Transthoracic Echocardiography
VO_2Max	Peak Oxygen Consumption

Ethical Clearance

No ethics approval was required in view of the nature of the article (i.e, review article). All tables and figures are the work of the main author and the co-authors and have not been previously published elsewhere or adapted from other materials previously or currently published.

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References

1. Valente V, Laborante R, Abdin A, et al. The Global Epidemiology of Heart Failure: A Comprehensive and Contemporary Review. Eur J Heart Fail 2026: xuag121.
2. Cannata A & McDonagh TA. Heart Failure with Preserved Ejection Fraction. N Engl J Med 2025; 392(2):173-84.
3. Gevaert AB, Kataria R, Zannad F, et al. Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management. Heart 2022; 108(17):1342-50.
4. Borlaug BA, Sharma K, Shah SJ, et al. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. J Am Coll Cardiol 2023; 81(18):1810-34.
5. Nauli SE, Prima Putri VK, Arifianto H, et al. Heart Failure With Preserved Ejection Fraction: Current Status of Daily Clinical Practice in Indonesia. Cureus 2023; 15(4):e38086.
6. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set

Oversight Committee. J Am Coll Cardiol 2023; 81(18):1835-78.
7. Bozkurt B, Coats AJ, Tsutsui H, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail 2021; 27(4):387-413.
8. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021; 42(36):3599-726.
9. McDonagh TA, Metra M, Adamo M,, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2023; 44(37):3627-39.
10. Dhont S, Moura-Ferreira S, Bekhuis Y, et al. Comparative Value of HFpEF Scores for Risk Stratification in Patients with Unexplained Dyspnea. Eur J Heart Fail 2026: xuag072.
11. Paulus WJ & Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodelling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013; 62(4):263-71.
12. Packer M. Evolutionary History of the Comorbidity-Driven Coronary Microvascular Endothelial Inflammation Hypothesis and Its Metamorphosis to the Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction. JACC Heart Fail 2026; 14(2):102822.
13. Kotecha D, Lam CS, Van Veldhuisen DJ, et al. Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins. J Am Coll Cardiol 2016; 68(20):2217-28.
14. Anker SD, Usman MS, Anker MS, et al. Patient phenotype profiling in heart failure with preserved ejection fraction to guide therapeutic decision making. A scientific statement of the Heart Failure Association, the European Heart Rhythm Association of the European Society of Cardiology, and the European Society of Hypertension. Eur J Heart Fail 2023; 25(7):936-55.
15. Packer M. The Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction: A Novel Framework to Explain Pathogenesis and Guide Treatment. J Am Coll Cardiol 2025; 86(16):1269-373.
16. Packer M. Causal role of adipose tissue-derived adipokines in the pathogenesis of heart failure with preserved ejection fraction: experimental demonstration as the basis for clinical targeting. Eur Heart J 2026: ehag029.
17. Packer M & Kitzman DW. Obesity-Related Heart Failure With a Preserved Ejection Fraction: The Mechanistic Rationale for Combining Inhibitors of Aldosterone, Neprilysin, and Sodium-Glucose Cotransporter-2. JACC Heart Fail 2018; 6(8):633-9.
18. Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction N Engl J Med 2024; 391(16):1475-85.
19. Tun HN, Rahal O, Figueroa Baez IR, et al. Heart failure with preserved ejection fraction beyond the heart: exploring the heart-liver-pancreas axis. ESC Heart Fail 2026; 13(2): xvag040.
20. Verma S, Petrie MC, Borlaug BA, et al. Inflammation in Obesity-Related HFpEF: The STEP-HFpEF Program. J Am Coll Cardiol 2024; 84(17):1646-62.
21. Borlaug BA, Jensen MD, Kitzman DW, et al. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res 2023; 118(18):3434-50.
22. Sindone AP, Abhayaratna WP, Chan A, et al. Heart Failure With Preserved Ejection Fraction in Patients With Obesity: A Growing Cardiometabolic Concern. Heart Lung Circ 2025; 34(10):1033-40.
23. Patel RN, Sharma A, Prasad A, et al. Heart Failure With Preserved Ejection Fraction With CKD: A Narrative Review of a Multispecialty Disorder. Kidney Med 2023; 5(12):100705.
24. Méndez AB, Azancot MA, Olivella A, et al. New aspects in cardiorenal syndrome and HFpEF. Clin Kidney J 2022; 15(10):1807-1815.
25. Khandait H, Sodhi SS, Khandekar N, et al. Cardiorenal Syndrome in Heart Failure with Preserved Ejection Fraction: Insights into Pathophysiology and Recent Advances. Cardiorenal Med 2025; 15(1):41-60.
26. Sarma S, Stoller D, Hendrix J, et al. Mechanisms of Chronotropic Incompetence in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail 2020; 13(3):e006331.
27. Pandey A, Khera R, Park B, et al. Relative Impairments in Hemodynamic Exercise Reserve Parameters in Heart Failure With Preserved Ejection Fraction: A Study-Level Pooled Analysis. JACC Heart Fail 2018; 6(2):117-26.

28. Dhont S & Bertrand PB. Heart rate modulation in heart failure with preserved ejection fraction: lessons from nature. Eur J Heart Fail 2026: xuag016.
29. Landsteiner I, Verwerft J, Belov D, et al. Heart failure and preserved ejection fraction: pathophysiology, clinical assessment, and management of exercise intolerance. Eur Heart J 2026: ehag175.
30. Goette A, Corradi D, Dobrev D, et al. Atrial cardiomyopathy revisited-evolution of a concept: a clinical consensus statement of the European Heart Rhythm Association (EHRA) of the ESC, the Heart Rhythm Society (HRS), the Asian Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS). Europace 2024; 26(9):euae204.
31. Weerts J, Țica O, Aranyo J, et al. Atrial cardiomyopathy: From healthy atria to atrial failure. A clinical consensus statement of the Heart Failure Association of the ESC. Eur J Heart Fail 2025; 27(11):2173-94.
32. Omote K & Borlaug BA. Left Atrial Myopathy in Heart Failure With Preserved Ejection Fraction. Circ J 2023; 87(8):1039-46.
33. Radakrishnan A, Agrawal S, Singh N, et al. Underpinnings of Heart Failure With Preserved Ejection Fraction in Women - From Prevention to Improving Function. A Co-publication With the American Journal of Preventive Cardiology and the Journal of Cardiac Failure. J Card Fail 2025; 31(9):1460-75.
34. Sotomi Y, Hikoso S, Nakatani D, et al. Sex Differences in Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc 2021; 10(5):e018574.
35. Magrì D, Fiori E, Agostoni P, et al. Heart failure and chronic obstructive pulmonary disease. A combination not to be underestimated. Heart Fail Rev 2025; 30(6):1525-38.
36. Ramalho SHR & de Albuquerque ALP. Chronic Obstructive Pulmonary Disease in Heart Failure: Challenges in Diagnosis and Treatment for HFpEF and HFrEF. Curr Heart Fail Rep 2024; 21(3):163-73.
37. Verwerft J, Bertrand PB, Claessen G, et al. Cardiopulmonary Exercise Testing With Simultaneous Echocardiography: Blueprints of a Dyspnea Clinic for Suspected HFpEF. JACC Heart Fail 2023; 11(2):243-9.
38. Rush CJ, Berry C, Oldroyd KG, et al. Prevalence of Coronary Artery Disease and Coronary Microvascular Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction. JAMA Cardiol 2021; 6(10):1130-43.
39. John JE, Claggett B, Skali H, et al. Coronary Artery Disease and Heart Failure With Preserved Ejection Fraction: The ARIC Study. J Am Heart Assoc 2022 Sep; 11(17):e021660.
40. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J 2024; 45(36):3415-537.
41. Tzoumas A, Tapp D, Crousillat D, et al. The Role of Coronary Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction. JACC Adv 2025; 4(12 Pt 2):102345.
42. Bond RM, Ivy K, Crumbs T, et al. Coronary microvascular dysfunction and its role in heart failure with preserved ejection fraction for future prevention and treatment. Am J Prev Cardiol 2025; 22:100983.
43. Heidenreich PA, Bozkurt B, Aguilar D et al. 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America Guideline for the Management of Heart Failure: Executive Summary. J Card Fail 2022; 28(5):810-30.
44. Meder B, Coats CJ, Leinwand LA, et al. EJHF expert consensus statement on the diagnosis and management of hypertrophic cardiomyopathy. Eur J Heart Fail 2026: xuaf008.
45. Moura B, Aimo A, Al-Mohammad A, et al. Diagnosis and management of patients with left ventricular hypertrophy: Role of multimodality cardiac imaging. A scientific statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2023; 25(9):1493-506.
46. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2023; 81(11):1076-126.
47. Al-Kazaz M, Klein AL, Oh JK, et al. Pericardial Diseases and Best Practices for Pericardiectomy: JACC State-of-the-Art Review. J Am Coll Cardiol 2024; 84(6):561-80.
48. Khan MS, Borlaug BA, Butler J, et al. Pulmonary Hypertension Associated With Left Heart Disease: Challenges, Emerging Strategies, and Future Directions. J Am Coll Cardiol 2026: S0735-1097(26)00134-8.
49. O'Sullivan JF, Pugliese NR, Wilcox I, et al.

Exercise echocardiography is a useful tool in the diagnosis of HFpEF. Eur J Heart Fail 2026: xuag045.
50. Pieske B, Tschope C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019; 40(40):3297-317.
51. Zeder K, Mak S, Galie N, et al. Right heart catheterization in heart failure: indications, interpretation, and pitfalls. Eur Heart J 2025; 46(34):3354-72.
52. Rajagopalan N, Borlaug BA, Bailey AL, et al. Practical Guidance for Hemodynamic Assessment by Right Heart Catheterization in Management of Heart Failure. JACC Heart Fail 2024; 12(7):1141-56.
53. Tsutsui H, Albert NM, Coats AJS, et al. Natriuretic peptides: role in the diagnosis and management of heart failure: a scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society. Eur J Heart Fail 2023; 25(5):616-31.
54. Verbrugge FH, Omote K, Reddy YNV, et al. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. Eur Heart J 2022; 43(20):1941-51.
55. Shah SJ. BNP: Biomarker Not Perfect in heart failure with preserved ejection fraction. Eur Heart J 2022; 43(20):1952-4.
56. Reddy YNV, Carter RE, Obokata M, et al. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation 2018; 138(9):861-70.
57. Reddy YNV, Carter RE, Sundaram V, et al. An evidence-based screening tool for heart failure with preserved ejection fraction: the HFpEF-ABA score. Nat Med 2024; 30(8):2258-64.
58. Nagueh SF, Sanborn DY, Oh JK, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography and for Heart Failure With Preserved Ejection Fraction Diagnosis: An Update From the American Society of Echocardiography. J Am Soc Echocardiogr 2025; 38(7):537-69.
59. Robinson S, Ring L, Oxborough D, et al. The assessment of left ventricular diastolic function: guidance and recommendations from the British Society of Echocardiography. Echo Res Pract 2024; 11(1):16.
60. Teramoto K, Ouwerkerk W, Tay WT, et al. Clinical Features of Heart Failure With Normal Ejection Fraction: Insights From the ASIAN-HF Registry. JACC Asia 2023; 3(5):739-51.
61. Shchendrygina A, Giverts I, Tokmakova M, et al. Staging Heart Failure with Preserved Ejection Fraction by Assessing Cardiac Chamber Involvement. Eur Cardiol 2024; 19:e20.
62. Churchill TW, Li SX, Curreri L, et al. Evaluation of 2 Existing Diagnostic Scores for Heart Failure With Preserved Ejection Fraction Against a Comprehensively Phenotyped Cohort. Circulation 2021; 143(3):289-91
63. Ibe T, Reddy YNV, Harada T, et al. Utility of HFpEF Diagnostic Scores to Stratify Cardiac Reserve Among Patients With Dyspnea. JACC Heart Fail 2025; 13(10):102526.
64. Verbrugge FH, Reddy YNV, Sorimachi H, et al. Diagnostic scores predict morbidity and mortality in patients hospitalized for heart failure with preserved ejection fraction. Eur J Heart Fail 2021; 23(6):954-63.
65. Obokata M, Kane GC, Reddy YN, et al. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation 2017; 135(9):825-38.
66. Tani Y, Reddy YNV, Verbrugge FH, et al. Variability in approach to exercise stress echocardiography for diagnosis of heart failure with preserved ejection fraction: an international survey on real-world practice. Eur Heart J Imaging Methods Pract 2024; 2(1):qyae059.
67. Verwerft J, Stassen J, Falter M, et al. Clinical Significance of Exercise Pulmonary Hypertension With a Negative Diastolic Stress Test for Suspected Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc 2024; 13(15):e032228.
68. Huis In 't Veld AE, de Man FS, van Rossum AC, et al. How to diagnose heart failure with preserved ejection fraction: the value of invasive stress testing. Neth Heart J 2016; 24(4):244-51.
69. Andersen MJ & Borlaug BA. Invasive hemodynamic characterization of heart failure with preserved ejection fraction. Heart Fail Clin 2014; 10(3):435-44.
70. Mascherbauer J, Zotter-Tufaro C, Duca F, et al. Wedge Pressure Rather Than Left Ventricular

End-Diastolic Pressure Predicts Outcome in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail 2017; 5(11):795-801.
71. Fudim M, Kittipibul V, Swavely A, et al. Discrepancy in the Diagnosis of Heart Failure With Preserved Ejection Fraction Between Supine Versus Upright Exercise Hemodynamic Testing. Circ Heart Fail 2024; 17(12):e012020.
72. Raja Shariff RE & Ibrahim KS. Discrepancies in Heart Failure With Preserved Ejection Fraction Scoring Systems: A Case Series. Sonography 2025; 12(4): 595–603
73. Sorop O, Heinonen I, van Kranenburg M, et al. Multiple common comorbidities produce left ventricular diastolic dysfunction associated with coronary microvascular dysfunction, oxidative stress, and myocardial stiffening. Cardiovasc Res 2018; 114(7):954-64.
74. Ottosen CI, Nadruz W, Inciardi RM, et al. Diastolic dysfunction in hypertension: a comprehensive review of pathophysiology, diagnosis, and treatment. Eur Heart J Cardiovasc Imaging 2024; 25(11):1525-36.
75. Hiraiwa H, Okumura T & Murohara T. Drug Therapy for Acute and Chronic Heart Failure with Preserved Ejection Fraction with Hypertension: A State-of-the-Art Review. Am J Cardiovasc Drugs 2024; 24(3):343-69.
76. He X, Dong B, Xue R, et al. Effect of aggressive diuresis in acute heart failure with reduced and preserved ejection fraction. ESC Heart Fail 2021; 8(4):3248-56.
77. Riccardi M, Ostrominski JW, Chatur S, et al. Effect of contemporary HFpEF therapies on diuretic management: Decongestive Role or Disease Modification? Eur J Heart Fail 2026: xuag074.
78. Peikert A & Solomon SD. Contemporary treatment options in heart failure with preserved ejection fraction. Eur Heart J Cardiovasc Imaging 2024; 25(11):1517-24.
79. SGLT2 inhibitors for the prevention and treatment of heart failure/ A scientific statement of the HFA and the HFAI
80. Ferreira JP, Pitt B & Zannad F. Mineralocorticoid Receptor Antagonists in Heart Failure: An Update. Circ Heart Fail 2024; 17(12):e011629.
81. Harrington JL, Canonico ME, El Rafei A, et al. Nonsteroidal and Steroidal Mineralocorticoid Antagonists: Rationale, Evidence, and Unanswered Questions. JACC Heart Fail 2025; 13(10):102637.
82. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. Circulation 2023; 148(20):1606-35.
83. Reframing obesity-related HFpEF as a multiorgan syndrome/ incretin- based therapies and imaging endpoints
84. Mikhalkova D, Holman SR, Jiang H, et al. Bariatric Surgery-Induced Cardiac and Lipidomic Changes in Obesity-Related Heart Failure with Preserved Ejection Fraction. Obesity 2018; 26(2):284-90.
85. Sachdev V, Sharma K, Keteyian SJ, et al. Supervised Exercise Training for Chronic Heart Failure With Preserved Ejection Fraction: A Scientific Statement From the American Heart Association and American College of Cardiology. Circulation 2023; 147(16):e699-e715.
86. Packer M. The Ideal Heart Rate for Heart Failure and Ejection Fraction > 40%: Both Myth and Magic? J Card Fail 2024; 30(6):863-5.
87. Hirashiki A & Shimizu A. Cardiac Rehabilitation and Heart Failure With Preserved Ejection Fraction. Circ Rep 2025; 7(10):837-41.
88. Martens P, Augusto SN Jr, Erzeel J, et al. Effects of Atrial Fibrillation Ablation for Heart Failure With Preserved Ejection Fraction: Insights From CABANA. JACC Heart Fail 2025; 13(5):785-94.
89. Younis A, Tabaja C, Santangeli P, et al. Outcomes of Atrial Fibrillation Ablation in Heart Failure Subtypes. Circ Arrhythm Electrophysiol 2024; 17(9):e012926.
90. Zylla MM, Leiner J, Rahm AK, et al. Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure and Preserved Ejection Fraction. Circ Heart Fail 2022; 15(9):e009281.