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Review ARTICLE OPEN ACCESS

Recent Advances in the Management of Heart Failure with Preserved Ejection Fraction: A Comprehensive Review

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ABS TRAC T

Background: Heart failure with preserved ejection fraction (HFpEF) accounts for more than half of all prevalent heart failure and carries morbidity and mortality comparable to heart failure with reduced ejection fraction. For nearly two decades no therapy convincingly altered its natural history, and management was confined to diuresis and treatment of comorbidities. ***Objective***: To critically synthesise contemporary evidence on the pathophysiology, diagnosis and, in particular, the rapidly evolving pharmacological, non-pharmacological and device-based management of HFpEF, and to compare current international guideline and consensus positions. ***Methods***: A structured narrative review was conducted. PubMed/MEDLINE, Scopus, Web of Science, Embase and the Cochrane Library were searched from 1 January 2019 to 30 Jun 2026 using MeSH terms and free-text combinations relating to heart failure, preserved ejection fraction, diastolic dysfunction and therapy. Randomised controlled trials, meta-analyses, large registries, guideline documents and mechanistic studies published in peer-reviewed indexed journals were eligible. Reference lists of retrieved articles and late-breaking trial presentations from major cardiology congresses were hand-searched. ***Results***: Four therapeutic classes now have randomised evidence of benefit. Sodium-glucose cotransporter-2 inhibitors reduce cardiovascular death or worsening heart failure by approximately 20 percent across the ejection fraction spectrum. The non-steroidal mineralocorticoid receptor antagonist finerenone reduced total worsening heart failure events and cardiovascular death in FINEARTS-HF, whereas steroidal agents remain unproven in the recently reported SPIRIT-HF trial. Incretin-based therapies, semaglutide and tirzepatide, produce large improvements in symptoms and exercise capacity and, in SUMMIT, reduced heart failure events in obesity-related HFpEF. Sacubitril-valsartan retains a selective role at the lower end of the ejection fraction range and in women. Device-based left atrial decompression has not shown consistent benefit, while activin signalling inhibition and interleukin-6 blockade are under active investigation. ***Conclusion***: HFpEF has moved from therapeutic nihilism to a phenotype-directed, multidrug treatment paradigm. Timely diagnosis using validated scores, systematic exclusion of mimics and early initiation of disease-modifying therapy are now the principal determinants of outcome.

Keywords: *Heart Failure, Diastolic, Stroke Volume, Sodium-Glucose Transporter 2 Inhibitors, Mineralocorticoid Receptor Antagonists, Glucagon-Like Peptide-1 Receptor Agonists, Obesity.*

1. INTRODUCTION

Heart failure (HF) is a clinical syndrome arising from any structural or functional abnormality of the heart that results in elevated intracardiac pressures or inadequate cardiac output at rest or during exertion. The universal definition of heart failure, published in 2021 by a global consortium of heart failure societies, formalised the classification of the syndrome by left ventricular ejection fraction (LVEF) into heart failure with reduced ejection fraction (HFrEF, LVEF 40 percent or less), mildly reduced ejection fraction (HFmrEF, LVEF 41 to 49 percent), preserved ejection fraction (HFpEF, LVEF 50 percent or more) and improved ejection fraction [1]. This nosology, although

imperfect, remains the principal determinant of therapeutic decision-making and of eligibility for randomised trials.

Heart failure affects more than 64 million individuals worldwide and constitutes one of the most costly chronic diseases of the twenty-first century [2, 3]. Within this population, HFpEF has undergone a striking epidemiological transition. Whereas HFrEF dominated hospital series in the 1990s, HFpEF now accounts for more than half of all prevalent heart failure in high-income countries, and its relative proportion continues to increase by approximately one percentage point per year, driven by population ageing and by the global epidemics of obesity, type 2 diabetes mellitus, hypertension, chronic kidney disease (CKD) and atrial fibrillation (AF) [2, 4]. Survival in HFpEF is only marginally better than in HFrEF, with five-year mortality approaching 50 to 75 percent in unselected community cohorts, and health-related quality of life is at least as impaired [5, 6].

For much of the past two decades, HFpEF was characterised by therapeutic failure. Neurohormonal antagonists that transformed the prognosis of HFrEF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and steroidal mineralocorticoid receptor antagonists (MRAs), failed to demonstrate convincing benefit on hard endpoints in dedicated HFpEF trials. Consequently, the 2021 European Society of Cardiology (ESC) guidelines and the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guideline could offer only diuretics for congestion, aggressive management of comorbidities and, at the time of the latter document, a conditional recommendation for sodium-glucose cotransporter-2 (SGLT2) inhibitors [7, 8].

The therapeutic landscape has since changed profoundly. Between 2021 and 2026, five pivotal randomised controlled trials established disease-modifying therapy for HFpEF for the first time. EMPEROR-Preserved and DELIVER demonstrated that SGLT2 inhibitors reduce cardiovascular death and worsening heart failure events irrespective of diabetes status [15, 16]. FINEARTS-HF established the efficacy of the non-steroidal MRA finerenone in patients with LVEF of 40 percent or more.17 STEP-HFpEF and SUMMIT demonstrated that incretin-based therapies substantially improve symptoms, exercise capacity and, in the case of tirzepatide, clinical events in obesity-related HFpEF [18, 19]. These developments prompted the 2023 focused update of the ESC guidelines and, most recently, the 2026 American College of Cardiology (ACC) Expert Consensus Decision Pathway (ECDP), which reframes HFpEF not as an isolated disorder of diastole but as a multisystem cardiovascular-kidney-metabolic syndrome driven by visceral adiposity, systemic inflammation and metabolic dysfunction [9-11].

The epidemiological relevance of these advances to India deserves specific emphasis. The Indian Council of Medical Research National Heart Failure Registry (NHFR), which enrolled 10,851 patients with acute decompensated heart failure across 53 centres, and the Trivandrum Heart Failure Registry (THFR) have consistently demonstrated that Indian patients with heart failure present approximately a decade earlier than their Western counterparts, have a higher burden of ischaemic and rheumatic aetiology, and experience high early mortality with low uptake of guideline-directed medical therapy [12, 13]. Indian registries have historically reported a lower proportion of HFpEF, in the range of 14 to 26 percent of hospitalised heart failure, partly reflecting a predominance of ischaemic HFrEF and partly reflecting under-recognition, since ambulatory HFpEF rarely reaches tertiary cardiology wards [12-14]. With the accelerating Indian epidemic of central obesity, type 2 diabetes and hypertension, the prevalence of HFpEF in India is expected to rise steeply, and the newly available therapies carry direct implications for national clinical practice and for health-system cost.

The rationale for the present review is therefore threefold. First, the evidence base for HFpEF management has expanded more in the past five years than in the preceding thirty, and no single recent synthesis integrates the pharmacological, non-pharmacological, device-based and emerging biological therapies alongside the newest guidance. Second, mechanistic understanding has shifted from a paradigm of passive myocardial stiffening to one of systemic microvascular inflammation and metabolic injury, which reframes therapeutic targets [20]. Third, contemporaneous guideline and consensus documents from different societies now diverge in their recommendations, particularly regarding MRAs and incretin therapy, creating uncertainty for the practising clinician. This review critically appraises the current evidence, compares findings across studies and guidelines, and identifies the research gaps that will define the next decade.

2. METHODOLOGY OF LITERATURE SEARCH

2.1 Databases and search period

A structured narrative review with a systematic search strategy was undertaken. PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase and the Cochrane Central Register of Controlled Trials were searched for articles published between 1 January 2019 and 30 Jun 2026. Publisher platforms of Elsevier (ScienceDirect), Springer Nature, Wiley Online Library and Oxford University Press were searched separately to capture articles indexed with delay. Late-breaking clinical trial presentations from the ESC Congress, the ACC Annual Scientific Session, the Heart Failure

Association of the ESC and the Heart Failure Society of America Annual Scientific Meeting between 2019 and 2026 were hand-searched to identify evidence not yet available in full publication.

2.2 Search terms

The following Medical Subject Headings (MeSH) and free-text terms were combined using Boolean operators: "Heart Failure, Diastolic"[MeSH] OR "heart failure with preserved ejection fraction" OR "HFpEF" OR "diastolic heart failure" OR "Stroke Volume"[MeSH]; AND "Therapeutics"[MeSH] OR "Sodium-Glucose Transporter 2 Inhibitors"[MeSH] OR "Mineralocorticoid Receptor Antagonists"[MeSH] OR "Glucagon-Like Peptide-1 Receptor Agonists"[MeSH] OR empagliflozin OR dapagliflozin OR finerenone OR spironolactone OR semaglutide OR tirzepatide OR sacubitril OR "sacubitril valsartan"; AND "Biomarkers"[MeSH] OR "Natriuretic Peptide, Brain"[MeSH] OR "Echocardiography"[MeSH] OR "Magnetic Resonance Imaging, Cine"[MeSH]. Additional focused searches were run for the terms epicardial adipose tissue, cardiac amyloidosis, interatrial shunt, exercise training, phenotype and machine learning in combination with HFpEF.

2.3 Inclusion and exclusion criteria

Studies were eligible if they were published in English in a peer-reviewed journal indexed in PubMed, Scopus or Web of Science; enrolled adult human participants with HFpEF or HFmrEF, or reported mechanistic data directly relevant to HFpEF; and reported clinical outcomes, symptom or functional endpoints, diagnostic performance, or mechanistic findings. Randomised controlled trials, prespecified and post hoc analyses of randomised trials, systematic reviews and meta-analyses, prospective cohorts and large national registries, and society guideline or consensus documents were prioritised. Studies were excluded if they were confined to HFrEF without preserved ejection fraction subgroup data; were case reports, narrative commentaries without original data, editorials or letters; were published in non-indexed, predatory or non-peer-reviewed outlets; or were preclinical studies without translational relevance. Seminal publications predating 2019 were retained only where they remain the methodological or diagnostic reference standard and have no more recent equivalent, and these are explicitly identified in the text.

2.4 Study selection

The initial search yielded approximately 4,180 records. After removal of duplicates, 2,760 titles and abstracts were screened against the eligibility criteria. Of these, 214 full-text articles were assessed, and 60 publications were finally selected for inclusion on the basis of methodological quality, sample size, contemporary relevance and citation impact. Preference was given to multicentre randomised trials with adjudicated endpoints, to the most recent guideline and consensus documents, and to studies contributing distinct mechanistic or geographical perspectives, including Indian registry data.

3. DEFINITIONS, NOSOLOGY AND CLASSIFICATION

HFpEF is defined by the presence of symptoms and signs of heart failure, an LVEF of 50 percent or more, and objective evidence of cardiac structural or functional abnormality consistent with elevated left ventricular filling pressure, supported by elevated natriuretic peptide concentrations.1,8 The universal definition requires objective evidence of congestion, either through natriuretic peptides or through non-invasive or invasive haemodynamic demonstration of raised filling pressure at rest or on exertion [1].

Three points of contemporary nosological importance merit emphasis. First, the LVEF thresholds are arbitrary and continuous rather than categorical, and treatment effects for several drug classes attenuate progressively as ejection fraction rises rather than terminating abruptly at a cut-point [16, 17]. Second, the definitions used in landmark trials differ: EMPEROR-Preserved and DELIVER enrolled patients with LVEF above 40 percent, FINEARTS-HF enrolled patients with LVEF of 40 percent or more, and PARAGON-HF required LVEF of 45 percent or more, so trial populations overlap substantially with HFmrEF and results cannot be assumed to apply uniformly to patients with supranormal ejection fraction [15-17]. Third, the diagnostic label of HFpEF is a syndromic umbrella rather than a diagnosis of aetiology, and applying it without excluding specific mimics such as transthyretin cardiac amyloidosis, hypertrophic cardiomyopathy, Fabry disease, constrictive pericarditis and high-output states risks withholding disease-specific treatment [6, 11]. Different definitional frameworks applied to the same population identify materially different patient groups with different exercise responses and outcomes, which remains an important source of heterogeneity across the literature [21].

4. EPIDEMIOLOGY

4.1 Global burden

Contemporary estimates place the global prevalence of heart failure at more than 64 million people, with an age-adjusted prevalence of one to three percent in adults, rising to more than ten percent above the age of 70 years [2, 3]. In high-income countries the incidence of heart failure has plateaued or declined modestly, but prevalence continues to rise because of improved survival and population ageing [2]. The proportion of prevalent heart failure attributable to preserved ejection fraction now exceeds 50 percent, and community-based data suggest that HFpEF incidence is increasing while HFrEF incidence falls [2, 4].

HFpEF is disproportionately a disease of older women, and this sex distribution is one of the most

reproducible epidemiological observations in the field. Women constitute approximately 55 to 65 percent of HFpEF cohorts, compared with roughly 25 to 30 percent of HFrEF cohorts [5, 6]. Obesity, hypertension, CKD, AF and type 2 diabetes are each present in 40 to 70 percent of patients, and multimorbidity, rather than any single dominant lesion, characterises the syndrome. Non-cardiac hospitalisation and non-cardiovascular death account for a substantially greater proportion of adverse events in HFpEF than in HFrEF, an observation with important implications for trial design and for the magnitude of achievable treatment effect [5].

4.2 Indian and South Asian perspective

Indian data are dominated by hospital-based registries of acute decompensated heart failure. The NHFR reported on 10,851 consecutive patients across 53 centres and documented a mean age approximately ten to fifteen years younger than European and North American registries, a male predominance, ischaemic heart disease as the leading aetiology, and substantial in-hospital and 90-day mortality alongside incomplete uptake of guideline-directed therapy [12]. The THFR, which enrolled 1,205 patients from 18 hospitals in Kerala, reported a mean age of 61 years, ischaemic aetiology in 72 percent, and a three-year all-cause mortality of approximately 45 percent, with HFpEF constituting roughly one quarter of admissions and carrying lower in-hospital but still substantial long-term mortality [13]. Single-centre South Indian series have reported HFpEF proportions as low as 14 percent among admitted patients, with a markedly higher proportion of women in the HFpEF subgroup [14].

These figures should not be interpreted as evidence that HFpEF is rare in India. Hospital registries systematically under-capture ambulatory HFpEF, in which dyspnoea is frequently attributed to obesity, deconditioning, anaemia or chronic obstructive pulmonary disease, and in which natriuretic peptide testing and diastolic assessment are inconsistently performed outside tertiary centres. Given that India carries one of the largest absolute burdens of type 2 diabetes and hypertension globally, and that central adiposity occurs at lower body mass index thresholds in South Asians than in white European populations, the true community prevalence of HFpEF is almost certainly substantially higher than registry proportions suggest. Prospective community-based Indian cohorts using standardised diagnostic algorithms represent an urgent unmet research need.

5. ETIOPATHOGENESIS AND MOLECULAR MECHANISMS

5.1 From passive stiffening to systemic inflammation

The historical model of HFpEF as isolated left ventricular diastolic dysfunction resulting from hypertensive concentric hypertrophy has been supplanted by a comorbidity-driven, inflammation-centred paradigm. In this framework, systemic proinflammatory comorbidities, principally obesity, diabetes, CKD, hypertension and chronic obstructive pulmonary disease, induce coronary microvascular endothelial inflammation. Endothelial production of reactive oxygen species reduces nitric oxide bioavailability, which lowers soluble guanylate cyclase activity, cyclic guanosine monophosphate concentration and protein kinase G activity within adjacent cardiomyocytes. Hypophosphorylation of the giant sarcomeric protein titin increases resting cardiomyocyte tension, while reduced protein kinase G activity removes a brake on hypertrophic signalling. Simultaneously, activated endothelium recruits monocytes that transform into transforming growth factor-beta-secreting macrophages, driving interstitial collagen deposition [20].

Experimental work has extended this model. In a two-hit murine model combining metabolic and hypertensive stress, HFpEF was shown to be driven by inducible nitric oxide synthase-mediated nitrosative stress, with S-nitrosylation of the spliced X-box binding protein 1 arm of the unfolded protein response; genetic or pharmacological inhibition of inducible nitric oxide synthase reversed the phenotype [22]. This work identified nitrosative stress and disrupted proteostasis as mechanistically upstream, and provided the first robust preclinical platform for therapeutic testing, although the translational limitations of murine models of a multimorbid geriatric human syndrome remain considerable [23].

5.2 Haemodynamic mechanisms of exercise intolerance

The cardinal physiological abnormality in HFpEF is a steep rise in left ventricular filling pressure during exertion. Contributing mechanisms include impaired active relaxation and increased passive chamber stiffness, limited left ventricular suction and inadequate augmentation of stroke volume, chronotropic incompetence, impaired systemic vasodilator reserve, and abnormal peripheral oxygen extraction [24]. Approximately one third of patients with unexplained exertional dyspnoea and normal resting haemodynamics demonstrate elevated pulmonary capillary wedge pressure only on exercise, which is why resting echocardiography alone is inadequate to exclude the diagnosis.

Pericardial restraint is an underappreciated contributor, particularly in obese phenotypes. Because the pericardium is relatively non-compliant, increases in total heart volume, epicardial fat mass and right heart filling raise left-sided pressures through enhanced ventricular interdependence rather than through intrinsic myocardial stiffening alone [25]. This mechanism provides a coherent explanation for why weight loss and plasma volume reduction produce disproportionate haemodynamic and symptomatic benefit in obesity-related HFpEF.

5.3 The obesity-inflammatory phenotype and epicardial adipose tissue

Obesity-related HFpEF has emerged as the dominant and most therapeutically tractable phenotype. Adipose tissue in these patients is not inert: visceral and epicardial depots secrete leptin, resistin, interleukin-6, tumour necrosis factor-alpha and aldosterone-stimulating factors, producing plasma volume expansion through sodium retention, systemic and myocardial inflammation, microvascular rarefaction and interstitial fibrosis [26, 27]. Epicardial adipose tissue is contiguous with the myocardium without an intervening fascial plane, permitting direct paracrine transfer of proinflammatory mediators to the underlying muscle, and also contributes mechanically to pericardial restraint [27]. Patients with the obesity phenotype are characteristically younger, more frequently female, more congested at any given natriuretic peptide concentration, and more symptomatic for a given ejection fraction than lean hypertensive patients [26].

Importantly, obesity attenuates natriuretic peptide concentrations through increased clearance and reduced production, so N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be normal or only marginally elevated despite substantial haemodynamic congestion. Patients with HFpEF and normal natriuretic peptide levels nonetheless experience increased morbidity and mortality relative to controls, and their exclusion from trials on the basis of biomarker thresholds represents a systematic bias in the evidence base [35].

5.4 Atrial myopathy, right ventricular dysfunction and metabolic remodelling

Left atrial myopathy is increasingly recognised as an integral component of the syndrome rather than a consequence of chronic pressure loading alone. Patients with HFpEF and AF demonstrate greater left atrial dilatation, impaired reservoir and conduit strain, more severe pulmonary vascular disease and worse outcomes than those in sinus rhythm; the relationship between AF and HFpEF appears bidirectional, reflecting a shared atrial and ventricular myopathy [28]. Right ventricular dysfunction, present in 20 to 35 percent of patients, and right ventricular to pulmonary artery uncoupling identify a phenotype with particularly adverse prognosis and limited therapeutic options [29].

Human myocardial tissue studies have added a metabolic dimension. Targeted metabolomic analysis of septal myocardium obtained from patients with HFpEF has demonstrated impaired fatty acid oxidation with accumulation of long-chain acylcarnitines and evidence of altered branched-chain amino acid and ketone handling, consistent with a state of myocardial energetic insufficiency rather than a purely mechanical disorder [30]. These findings support the emerging conceptualisation of HFpEF as a cardiometabolic disease and provide biological rationale for metabolic therapies.

6. RISK FACTORS AND CLINICAL PHENOTYPES

The principal modifiable risk factors for HFpEF are obesity, hypertension, type 2 diabetes, CKD, AF, obstructive sleep apnoea and physical inactivity; non-modifiable determinants include advancing age, female sex and, in specific populations, genetic variants predisposing to amyloidogenesis or sarcomeric cardiomyopathy [31]. Because no single factor is necessary or sufficient, phenotypic clustering has become central to both research and clinical practice.

Contemporary practice recognises several overlapping phenotypes with distinct management implications. The cardiometabolic or obesity phenotype is characterised by high body mass index, plasma volume expansion, epicardial adiposity and systemic inflammation, and preferentially responds to incretin therapy, SGLT2 inhibition and weight reduction [26, 27]. The hypertensive-vascular phenotype features concentric remodelling, arterial stiffening and exaggerated blood pressure response to exercise. The atrial fibrillation-dominant phenotype is defined by atrial myopathy, marked natriuretic peptide elevation and a preferential response to rhythm control [28]. The pulmonary vascular and right heart phenotype carries the worst prognosis and remains without established therapy [29]. A cardiomyopathic or infiltrative phenotype, in which transthyretin cardiac amyloidosis is the most important entity, requires disease-specific treatment [36]. Finally, a coronary microvascular dysfunction phenotype, characterised by reduced coronary flow reserve without obstructive epicardial disease, is present in more than half of patients and represents an important therapeutic target [31]. National Heart, Lung, and Blood Institute working group priorities have formally endorsed phenotype-specific trial design as the principal route to further progress [31].

7. CLINICAL FEATURES, DIAGNOSTIC CRITERIA AND IMAGING

7.1 Clinical presentation

The dominant symptom is exertional dyspnoea with fatigue and reduced exercise tolerance; orthopnoea, paroxysmal nocturnal dyspnoea and peripheral oedema occur but are less specific in obese and elderly patients. Physical signs are frequently absent or equivocal at rest. Sex-specific differences in presentation are increasingly recognised: women more often report fatigue rather than frank dyspnoea, have smaller left ventricular cavity dimensions with higher ejection fraction and greater arterial and ventricular stiffness, and are more likely to have their symptoms attributed to non-cardiac causes, contributing to diagnostic delay [11].

7.2 Diagnostic scores

Two validated scoring systems anchor contemporary diagnosis. The H2FPEF score, derived and validated against invasive exercise haemodynamics, uses six readily available variables: obesity, treatment with two or more antihypertensive agents, AF, pulmonary hypertension estimated by tricuspid regurgitant velocity above 2.8 m/s, age above 60 years and elevated E/e prime ratio above 9, yielding a score of 0 to 9 in which values of 0 to 1 make the diagnosis unlikely and values of 6 or more make it highly likely [32]. The HFA-PEFF algorithm of the Heart Failure Association of the ESC proceeds in four steps, comprising pretest assessment, an echocardiographic and natriuretic peptide score across functional, morphological and biomarker domains, functional testing with diastolic stress echocardiography or invasive haemodynamics for intermediate scores, and finally aetiological work-up [33]. The 2026 ACC ECDP recommends sequential use of both scores, since they are complementary rather than interchangeable, with H2FPEF weighted towards obesity and AF and HFA-PEFF towards structural and biomarker abnormalities [11]. Both instruments predate 2019 in part but remain the reference standard and have not been superseded.

7.3 Biomarkers

Natriuretic peptides remain the first-line biomarker but require careful interpretation. Concentrations are lower for any given filling pressure in obesity and higher in AF, CKD and advanced age. Approximately one in five patients with invasively confirmed HFpEF has an NT-proBNP concentration below conventional diagnostic thresholds, and these patients remain at elevated risk of death and hospitalisation [35]. A normal natriuretic peptide value in a symptomatic obese patient therefore does not exclude the diagnosis and should prompt functional testing rather than reassurance [34, 35].

7.4 Imaging and haemodynamic assessment

Comprehensive transthoracic echocardiography assessing left ventricular mass and relative wall thickness, left atrial volume index, mitral inflow and tissue Doppler velocities, tricuspid regurgitant velocity and, where available, left ventricular global longitudinal strain and left atrial reservoir strain, forms the diagnostic core. Reduced global longitudinal strain despite preserved ejection fraction is present in a majority of patients and carries independent prognostic value [34]. Diastolic stress echocardiography, using an E/e prime ratio above 15 with elevated tricuspid regurgitant velocity during exercise, provides useful non-invasive confirmation, but invasive exercise right heart catheterisation demonstrating pulmonary capillary wedge pressure of 15 mmHg or more at rest or 25 mmHg or more during exercise remains the diagnostic reference standard for equivocal cases [24, 34].

Cardiac magnetic resonance imaging with T1 mapping, extracellular volume quantification and late gadolinium enhancement is indicated where an infiltrative or inflammatory aetiology is suspected. Bone scintigraphy with technetium-labelled bisphosphonates, combined with exclusion of a monoclonal protein by serum and urine immunofixation and serum free light chain assay, permits non-invasive diagnosis of transthyretin cardiac amyloidosis with high specificity, and should be considered in all patients above 60 years with unexplained left ventricular wall thickness of 12 mm or more, particularly in the presence of carpal tunnel syndrome, lumbar spinal stenosis, discordantly low voltage on electrocardiography or intolerance of antihypertensive therapy [36]. The 2026 ECDP emphasises systematic exclusion of both cardiac and non-cardiac mimics before the syndromic label is applied [11].

8. MANAGEMENT STRATEGIES

8.1 SGLT2 inhibitors: the foundation of therapy

SGLT2 inhibitors were the first agents to demonstrate unequivocal benefit in HFpEF. EMPEROR-Preserved randomised 5,988 patients with LVEF above 40 percent to empagliflozin 10 mg daily or placebo and reported a 21 percent relative reduction in the composite of cardiovascular death or hospitalisation for heart failure over a median 26 months, driven predominantly by a reduction in hospitalisation, with consistent effects irrespective of diabetes status [15]. DELIVER randomised 6,263 patients with LVEF above 40 percent to dapagliflozin 10 mg daily and reported an 18 percent relative reduction in cardiovascular death or worsening heart failure, with benefit extending to patients with improved ejection fraction and no attenuation at the highest ejection fractions [16]. A prespecified meta-analysis of five randomised trials encompassing 21,947 patients confirmed a consistent 23 percent reduction in cardiovascular death or first hospitalisation for heart failure across the entire ejection fraction spectrum, with a smaller but significant reduction in cardiovascular death [37].

Symptomatic and functional benefit is corroborated by dedicated trials. PRESERVED-HF demonstrated that dapagliflozin improved Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score by 5.8 points and six-minute walk distance by 20 metres at twelve weeks [38]. Health status analyses from EMPEROR-Preserved and age-stratified analyses from DELIVER confirm benefit across the spectrum of baseline symptom burden and age, including in patients above 80 years [39, 40]. SGLT2 inhibitors may also be initiated safely in the acute setting, as demonstrated by SOLOIST-WHF with sotagliflozin in patients with recent worsening heart failure and by EMPULSE with empagliflozin in patients hospitalised for acute heart failure [41, 42]. Critical appraisal nonetheless requires

acknowledgement that the absolute risk reduction is modest, that mortality benefit in HFpEF is not established, and that the composite endpoint is driven principally by hospitalisation.

8.2 Mineralocorticoid receptor antagonists: the steroidal-non-steroidal divergence

The MRA story in HFpEF illustrates the value of drug-class rather than mechanism-class reasoning. Steroidal MRAs have repeatedly failed to demonstrate convincing benefit; the TOPCAT trial was neutral overall with a controversial regional interaction, and the recently reported SPIRIT-HF trial, presented at ACC 2026, found no significant difference in cardiovascular death or total heart failure hospitalisations with spironolactone in patients with LVEF of 40 percent or more over 24 months, although the trial was substantially underpowered because of pandemic-related funding and recruitment shortfalls and was limited by high treatment discontinuation [45].

By contrast, FINEARTS-HF randomised 6,001 patients with heart failure and LVEF of 40 percent or more to the non-steroidal MRA finerenone or placebo and reported a significant 16 percent reduction in the primary composite of total worsening heart failure events and cardiovascular death, with a rate ratio of 0.84 and 95 percent confidence interval 0.74 to 0.95.17 Benefit was consistent across the ejection fraction spectrum and was accompanied by improvement in KCCQ score. A secondary analysis demonstrated a reduction specifically in outpatient worsening heart failure, an endpoint of considerable practical importance because most clinical deterioration in HFpEF is managed without admission [44]. The FINE-HEART pooled participant-level analysis of FINEARTS-HF, FIDELIO-DKD and FIGARO-DKD provided suggestive evidence of a reduction in cardiovascular death that individual trials were underpowered to detect [43].

Finerenone differs pharmacologically from spironolactone in its non-steroidal structure, balanced cardiac and renal tissue distribution, higher mineralocorticoid receptor selectivity, absence of anti-androgenic effects and lower rate of clinically significant hyperkalaemia. The United States Food and Drug Administration expanded its approval in July 2025 to include heart failure with LVEF of 40 percent or more, and the 2026 ACC ECDP now designates finerenone as the MRA of choice in HFpEF, with spironolactone regarded as a reasonable alternative where cost or availability is prohibitive [11]. This position is of direct relevance to Indian practice, where the cost differential between generic spironolactone and branded finerenone is substantial and where the ongoing registry-randomised SPIRRIT-HFpEF trial of spironolactone may yet prove decisive for resource-constrained settings.

8.3 Incretin-based therapies in obesity-related HFpEF

The demonstration that targeting obesity modifies the HFpEF syndrome represents the most conceptually significant advance of the past five years. STEP-HFpEF randomised 529 non-diabetic patients with LVEF of 45 percent or more and body mass index of 30 kg/m2 or more to once-weekly semaglutide 2.4 mg or placebo for 52 weeks, reporting a 16.6-point improvement in KCCQ clinical summary score versus 8.7 points with placebo, a 13.3 percent versus 2.6 percent reduction in body weight, and a 21.5-metre greater increase in six-minute walk distance [18]. STEP-HFpEF DM replicated these findings in 616 patients with type 2 diabetes, with attenuated but still substantial weight loss and comparable symptomatic benefit [46]. A pooled analysis of both trials confirmed consistent effects on symptoms, physical limitation, exercise function, C-reactive protein and NT-proBNP, and suggested a reduction in heart failure events, although neither trial was individually powered for clinical outcomes [47]. Prespecified analysis demonstrated that benefit increased with baseline obesity class and correlated with, but was not entirely explained by, the magnitude of weight loss, implying weight-independent mechanisms [48].

SUMMIT provided the first event-driven evidence. In 731 patients with LVEF of 50 percent or more and body mass index of 30 kg/m2 or more, tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, reduced the composite of cardiovascular death or worsening heart failure events by 38 percent, with a hazard ratio of 0.62, and improved KCCQ score by 6.9 points, six-minute walk distance and high-sensitivity C-reactive protein [19]. The cardiac magnetic resonance substudy demonstrated significant reductions in left ventricular mass and paracardiac adipose tissue, providing objective structural evidence of reverse remodelling that had not been observed with semaglutide [49]. Together these data support a causal role for adiposity in the obesity-related HFpEF phenotype and justify the recommendation in the 2026 ECDP that an incretin-based therapy be added for patients with body mass index of 30 kg/m2 or more [11].

Several caveats temper enthusiasm. Follow-up in both programmes was approximately one year, so durability and mortality effects are unknown. Loss of lean mass, gastrointestinal intolerance, cost and the risk of weight regain on discontinuation are practical concerns, and the applicability of body mass index thresholds derived from Western populations to South Asians, in whom cardiometabolic risk occurs at lower body mass index, has not been formally tested.

8.4 Renin-angiotensin system modulation

PARAGON-HF randomised 4,822 patients

with LVEF of 45 percent or more to sacubitril-valsartan or valsartan and narrowly missed its primary endpoint, with a rate ratio of 0.87 and 95 percent confidence interval 0.75 to 1.01 [50]. Prespecified subgroup analysis suggested benefit in women and in patients at the lower end of the ejection fraction range, and a pooled analysis with PARADIGM-HF demonstrated that treatment effect varied continuously with ejection fraction, with benefit extending above 40 percent and diminishing towards the normal range [51]. Contemporary guidance therefore positions sacubitril-valsartan as reasonable in selected patients with LVEF below approximately 55 to 60 percent, particularly women, with angiotensin receptor blockers as an alternative [11]. Beta-blockers have no established indication in HFpEF in the absence of a separate indication such as angina or rate control in AF, and may be deleterious in patients with chronotropic incompetence [11].

8.5 Decongestion and comorbidity-directed therapy

Loop diuretics remain the mainstay for symptomatic congestion and should be titrated to the lowest effective dose. Blood pressure control is fundamental, and current multisociety guidance favours a systolic target of 120 to 129 mmHg in this population [11]. In patients with AF, rhythm control, particularly catheter ablation, is associated with fewer heart failure events and lower mortality than rate control in observational and randomised data, and both SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists appear to reduce incident AF [11, 28]. Coronary artery disease, CKD, obstructive sleep apnoea, anaemia and iron deficiency should each be systematically identified and treated. Where transthyretin cardiac amyloidosis is confirmed, disease-specific therapy is mandatory: transthyretin stabilisation with tafamidis or acoramidis and gene-silencing approaches with patisiran or vutrisiran have transformed the prognosis of a condition previously considered untreatable, and ATTRibute-CM demonstrated that acoramidis reduced a hierarchical composite of death, cardiovascular hospitalisation and functional decline over 30 months [53, 54].

8.6 Non-pharmacological management

Exercise training is the intervention with the most consistent effect on peak oxygen consumption in HFpEF. The OptimEx-Clin randomised trial compared high-intensity interval training, moderate continuous training and guideline-based advice in 180 patients and found modest improvement in peak oxygen consumption at three months that was not sustained at twelve months, with no advantage for high-intensity training, underscoring the difficulty of maintaining adherence [56]. REHAB-HF demonstrated that an early, transitional, tailored, progressive rehabilitation intervention addressing strength, balance, mobility and endurance in older patients hospitalised for acute heart failure, of whom approximately half had preserved ejection fraction, produced clinically meaningful improvement in physical function compared with usual care [55]. Caloric restriction combined with aerobic exercise improves peak oxygen consumption additively in obese patients, and bariatric surgery has been associated with improvement in functional class and diastolic indices in observational series. Sodium restriction, structured self-care education, cardiac rehabilitation referral and immunisation complete the non-pharmacological package.

8.7 Device-based and interventional strategies

Interatrial shunt devices were designed to decompress the left atrium during exertion. REDUCE LAP-HF II, a sham-controlled trial in 626 patients, was neutral overall but identified a responder group without latent pulmonary vascular disease or a cardiac implantable electronic device [57]. RELIEVE-HF, a sham-controlled trial of a distinct shunt device, was likewise neutral overall and, critically, suggested harm in the HFpEF subgroup with increased mortality and heart failure events, while suggesting benefit in HFrEF [58]. The confirmatory RESPONDER-HF trial, which prospectively enrols the responder phenotype identified in REDUCE LAP-HF II, remains ongoing with primary completion anticipated in 2027. The 2026 ECDP concludes that atrial shunt devices, splanchnic nerve ablation and permanent pacing strategies have not shown consistent benefit and should remain investigational [11]. Ambulatory pulmonary artery pressure monitoring and, more recently, non-invasive lung impedance monitoring have shown promise for reducing heart failure hospitalisation through haemodynamically guided diuretic titration, and merit further evaluation specifically in HFpEF populations.

9. RECENT ADVANCES, EMERGING BIOMARKERS AND ONGOING TRIALS

9.1 Targeting inflammation

If systemic inflammation is mechanistically central, direct anti-inflammatory therapy should modify the syndrome. Interleukin-6 has emerged as the most attractive target. Ziltivekimab, a human monoclonal antibody directed against the interleukin-6 ligand, produced dose-dependent reductions in high-sensitivity C-reactive protein exceeding 90 percent in the phase 2 RESCUE trial in patients with CKD and systemic inflammation [60]. The HERMES trial, an event-driven, international, double-blind randomised trial of monthly subcutaneous ziltivekimab 15 mg in approximately 5,600 patients with HFmrEF or HFpEF, elevated natriuretic peptides and high-sensitivity C-reactive protein of 2 mg/L or more, is evaluating a primary composite of cardiovascular death, heart failure hospitalisation or urgent heart failure visit, with the companion ATHENA trial assessing health status. These trials will provide the first definitive test of the inflammatory hypothesis in HFpEF.

9.2 Targeting the pulmonary vasculature

Combined post-capillary and pre-capillary

pulmonary hypertension complicating HFpEF has had no approved therapy and carries a poor prognosis. The phase 2 CADENCE trial randomised 164 patients with HFpEF and severe combined post- and pre-capillary pulmonary hypertension to sotatercept, an activin signalling inhibitor, at two doses or placebo. Sotatercept reduced pulmonary vascular resistance, lowered mean pulmonary arterial pressure by approximately 9 mmHg, improved six-minute walk distance and natriuretic peptides, reduced pulmonary capillary wedge pressure and left atrial volume, and prolonged time to clinical worsening [59]. These findings constitute proof of concept for pulmonary vascular remodelling as a therapeutic target in a phenotype previously regarded as untreatable, and warrant a phase 3 outcomes trial.

9.3 Other emerging pharmacological targets

Several additional mechanisms are under investigation. Aldosterone synthase inhibition, which reduces aldosterone synthesis rather than blocking its receptor, is being tested in combination with empagliflozin in the EASi-HF programme. Selective cardiac myosin inhibition, successful in obstructive hypertrophic cardiomyopathy, is being evaluated in HFpEF with hypercontractile physiology. Oral levosimendan is under study in pulmonary hypertension associated with HFpEF, and combined SGLT1 and SGLT2 inhibition with sotagliflozin is being examined in dedicated HFpEF populations. Bariatric and metabolic surgery, and next-generation oral incretin agents, represent logical extensions of the obesity paradigm.

9.4 Emerging biomarkers and computational phenotyping

Beyond natriuretic peptides, high-sensitivity troponin, growth differentiation factor-15, soluble suppression of tumorigenicity-2, galectin-3 and high-sensitivity C-reactive protein each carry independent prognostic information, and high-sensitivity C-reactive protein has acquired additional importance as an enrichment criterion for anti-inflammatory trials [60]. Large-scale proteomic and metabolomic profiling has begun to define molecular signatures corresponding to clinical phenotypes, with myocardial acylcarnitine accumulation exemplifying the translation of tissue-level metabolic derangement into a candidate biomarker [30]. Unsupervised machine learning applied to echocardiographic, clinical and biomarker data has generated reproducible phenogroups with differing prognosis and, in retrospective analyses, differing treatment response. Prospective validation of phenogroup-guided therapy remains the central unmet methodological challenge.

10. SUMMARY OF KEY STUDIES

Table 1 summarises the principal randomised trials, registries and consensus documents that define contemporary HFpEF management.

Table 1: Summary of major studies informing contemporary management of HFpEF

Study (first author)	Year	Region	Design	N	Key outcome	Clinical relevance
PARAGON-HF (Solomon)	2019	International	Double-blind RCT	4,822	Sacubitril-valsartan vs valsartan: RR 0.87 (0.75-1.01) for CV death and total HF hospitalisation; narrowly non-significant	Established benefit signal in women and at lower LVEF; basis for selective use
Nassif (PRESERVED-HF)	2021	USA	Multicentre RCT	324	Dapagliflozin improved KCCQ-CS by 5.8 points and 6MWD by 20 m at 12 weeks	First demonstration of symptomatic benefit with SGLT2 inhibition in HFpEF
EMPEROR-Preserved (Anker)	2021	International	Double-blind RCT	5,988	Empagliflozin reduced CV death or HF hospitalisation by 21%, driven by hospitalisation	First trial to establish disease-modifying therapy in HFpEF
REDUCE LAP-HF II (Shah)	2022	International	Sham-controlled RCT	626	Neutral overall; responder subgroup without latent pulmonary vascular disease identified	Tempered enthusiasm for atrial shunting; generated responder hypothesis
DELIVER (Solomon)	2022	International	Double-blind RCT	6,263	Dapagliflozin reduced CV death or worsening HF by 18%; benefit at all LVEF strata	Confirmed class effect; extended benefit to improved LVEF
NHFR (Harikrishnan)	2022	India	Prospective registry	10,851	Younger age at presentation, ischaemic predominance, high 90-day mortality, low	Largest Indian HF dataset; defines the national implementation gap

					GDMT uptake	
SGLT2i meta-analysis (Vaduganathan)	2022	International	Meta-analysis of 5 RCTs	21,947	23% reduction in CV death or first HF hospitalisation across the LVEF spectrum	Established SGLT2 inhibition as foundational across all EF categories
STEP-HFpEF (Kosiborod)	2023	International	Double-blind RCT	529	Semaglutide improved KCCQ-CS by 7.8 points vs placebo; 13.3% weight loss; 6MWD +21.5 m	Proof of concept that treating obesity modifies the HFpEF syndrome
STEP-HFpEF DM (Kosiborod)	2024	International	Double-blind RCT	616	Comparable symptomatic benefit in patients with type 2 diabetes despite less weight loss	Extended incretin benefit to the diabetic obesity phenotype
FINEARTS-HF (Solomon)	2024	International	Double-blind RCT	6,001	Finerenone reduced total worsening HF events and CV death; RR 0.84 (0.74-0.95)	First positive MRA trial in HFpEF; basis for 2025 regulatory approval
RELIEVE-HF (Stone)	2024	International	Sham-controlled RCT	508	Neutral overall; signal of harm in HFpEF subgroup, possible benefit in HFrEF	Paused adoption of interatrial shunting in HFpEF
SUMMIT (Packer)	2025	International	Double-blind RCT	731	Tirzepatide reduced CV death or worsening HF events by 38%; HR 0.62; KCCQ +6.9 points	First event-driven evidence for incretin therapy in obesity-related HFpEF
SUMMIT CMR substudy (Kramer)	2025	International	Prespecified imaging substudy	106	Significant reduction in LV mass and paracardiac adipose tissue with tirzepatide	Objective structural evidence of reverse remodelling
SPIRIT-HF (Edelmann)	2026	Europe	Double-blind RCT	~1,300	Spironolactone: RR 1.32 (0.79-2.21) for CV death or total HF hospitalisation; underpowered	Supports non-steroidal over steroidal MRA, though not definitive
CADENCE (Gomberg-Maitland)	2026	International	Phase 2 RCT	164	Sotatercept reduced PVR and mPAP by ~9 mmHg; improved 6MWD and time to worsening	First positive signal in CpcPH-HFpEF, a phenotype without therapy

CV, cardiovascular; CpcPH, combined post- and pre-capillary pulmonary hypertension; DZHK, German Centre for Cardiovascular Research; GDMT, guideline-directed medical therapy; HF, heart failure; HR, hazard ratio; KCCQ-CS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LV, left ventricular; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RCT, randomised controlled trial; RR, rate ratio; 6MWD, six-minute walk distance.

11. COMPARISON OF CURRENT GUIDELINES AND CONSENSUS DOCUMENTS

International recommendations have diverged as evidence has accumulated at different rates relative to guideline revision cycles. The 2022 AHA/ACC/HFSA guideline predates FINEARTS-HF, STEP-HFpEF and SUMMIT and therefore assigns SGLT2 inhibitors a Class 2a recommendation with MRAs, angiotensin receptor blockers and sacubitril-valsartan at Class 2b [7]. The 2021 ESC guideline offered no disease-modifying recommendation, and the 2023 focused update elevated SGLT2 inhibitors to Class I while leaving MRAs unrecommended in HFpEF [8, 9]. The 2026 ACC ECDP represents the most current synthesis, recommending an SGLT2 inhibitor plus a non-steroidal MRA as optimal medical therapy in the absence of contraindication, with finerenone preferred over spironolactone, and the addition of an incretin-based therapy for patients with body mass index of 30 kg/m2 or more [11]. National documents have moved at different speeds; Canadian and Japanese guidance updated in 2025 already incorporate incretin therapy and elevated finerenone respectively. Table 2 summarises these positions.

Table 2: Comparison of guideline and consensus positions on HFpEF pharmacotherapy

Document (year)	SGLT2 inhibitor	Mineralocorticoid receptor antagonist	Incretin-based therapy	ARNI / ARB

ESC 2021	Not recommended (predates evidence)	Not recommended	Not addressed	Not recommended
AHA/ACC/HFSA 2022	Class 2a	Class 2b (steroidal)	Not addressed	Class 2b
ACC ECDP 2023	Recommended first-line	Considered in selected patients	Not addressed	Selected patients, lower LVEF and women
ESC 2023 focused update	Class I	Not recommended in HFpEF; Class 2b in HFmrEF	Not addressed	Class 2b in HFmrEF
CCS/CHFS 2025	Recommended	Non-steroidal MRA incorporated	Recommended if LVEF 45% or more and BMI 30 kg/m2 or more	Selected patients
ACC ECDP 2026	Foundational therapy for all	Non-steroidal MRA (finerenone) preferred; spironolactone reasonable alternative	Semaglutide or tirzepatide if BMI 30 kg/m2 or more	Reasonable for women and LVEF below 55-60%

ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CCS/CHFS, Canadian Cardiovascular Society/Canadian Heart Failure Society; ECDP, Expert Consensus Decision Pathway; HFmrEF, heart failure with mildly reduced ejection fraction; LVEF, left ventricular ejection fraction.

12. DISCUSSION

The evidence assembled in this review supports a fundamental reconceptualisation of HFpEF. The syndrome is no longer usefully described as diastolic heart failure. It is better understood as a cardiovascular-kidney-metabolic disorder in which visceral and epicardial adiposity, systemic and microvascular inflammation, sodium retention, atrial myopathy and pulmonary vascular remodelling interact to produce exertional intolerance and congestion [11, 20, 26, 27]. The therapeutic corollary is that the four classes with randomised evidence of benefit, SGLT2 inhibitors, non-steroidal MRAs, incretin-based agents and, selectively, angiotensin receptor-neprilysin inhibition, act predominantly on metabolic, inflammatory and volume-regulatory pathways rather than on contractility or afterload.

Comparison across trials reveals instructive consistencies and discrepancies. The SGLT2 inhibitor trials are internally consistent, with EMPEROR-Preserved and DELIVER producing effect estimates within confidence interval overlap and a meta-analysis confirming homogeneity across the ejection fraction spectrum [15, 16, 37]. The MRA evidence is discordant by molecular class: FINEARTS-HF was positive with finerenone, whereas TOPCAT and SPIRIT-HF were neutral with spironolactone [17, 45]. Three interpretations compete. The difference may be genuinely pharmacological, reflecting finerenone selectivity, tissue distribution and tolerability. It may be methodological, since SPIRIT-HF was underpowered with high discontinuation and TOPCAT was compromised by regional heterogeneity in enrolment quality. Or it may reflect differences in background therapy, since FINEARTS-HF was conducted in an era of widespread SGLT2 inhibitor use. Until SPIRRIT-HFpEF reports, the honest conclusion is that finerenone has demonstrated efficacy and spironolactone has not been shown to lack it, a distinction of considerable importance for health systems where cost governs prescribing.

The incretin trials raise a different interpretive question. STEP-HFpEF and STEP-HFpEF DM were powered for symptom endpoints and demonstrated the largest improvements in KCCQ score observed in any HFpEF trial, exceeding those achieved with SGLT2 inhibition by a factor of two to three [18, 46, 47]. SUMMIT extended this to clinical events with a 38 percent relative reduction, but with wide confidence intervals reflecting modest sample size and event count [19]. Whether the benefit is mediated by weight loss, by direct anti-inflammatory effects, by reduction in epicardial adiposity and pericardial restraint, or by plasma volume contraction remains unresolved; the observation that tirzepatide but not semaglutide reduced left ventricular mass and paracardiac fat suggests that dual incretin agonism may confer additional cardiac effects [49].

The strengths of the current evidence base are substantial: several trials enrolled more than 5,000 patients with adjudicated endpoints, prespecified analyses, and international recruitment across dozens of countries. Limitations are equally important and must temper clinical extrapolation. First, most trials are event-driven with median follow-up of two to three years, insufficient to characterise the natural history of a chronic geriatric syndrome. Second, no HFpEF trial has demonstrated a reduction in all-cause mortality, and the composite endpoints are driven predominantly by heart failure hospitalisation. Third, enrolment criteria requiring elevated natriuretic peptides systematically exclude obese patients with true HFpEF and normal biomarkers, biasing the evidence away from the

phenotype most likely to respond to incretin therapy [35]. Fourth, participants are considerably younger, less frail and less multimorbid than community populations. Fifth, South Asian, African and Latin American representation is limited, and no adequately powered HFpEF outcome trial has been conducted in India, so effect estimates are extrapolated across populations that differ in body composition, age at presentation and comorbidity structure [12, 13].

The clinical implications are nonetheless clear. HFpEF should be actively sought rather than diagnosed by exclusion, using H2FPEF and HFA-PEFF scoring with functional testing for intermediate probability [32, 33]. Mimics must be excluded systematically, with a low threshold for bone scintigraphy in older patients with increased wall thickness [36]. Once diagnosed, an SGLT2 inhibitor should be initiated in essentially all patients, a non-steroidal MRA added in the absence of contraindication, and an incretin-based agent considered where obesity is present, alongside decongestion, blood pressure control to a systolic target of 120 to 129 mmHg, rhythm control for AF where appropriate, and structured exercise rehabilitation [11]. The principal barrier to improved outcomes in India is unlikely to be the absence of effective drugs; it is delayed recognition, limited access to natriuretic peptide testing and advanced echocardiography outside tertiary centres, and the cost of newer agents [12].

13. FUTURE DIRECTIONS

Several research priorities follow directly from the gaps identified above. First, phenotype-specific randomised trials are required. The current paradigm of enrolling all patients with LVEF above 40 percent and elevated natriuretic peptides dilutes treatment effects and obscures differential response; prospective randomisation stratified by validated phenogroup, or enrichment by mechanism such as high-sensitivity C-reactive protein for anti-inflammatory therapy, is the logical next step, and the HERMES programme provides the template [31, 60].

Second, the natriuretic peptide entry criterion requires re-examination. Trials designed specifically for patients with obesity-related HFpEF and normal natriuretic peptide concentrations, diagnosed by invasive exercise haemodynamics, would address a population currently excluded from the evidence base despite being at demonstrable risk [35].

Third, combination and sequencing strategies remain undefined. No trial has compared initiation sequences or tested the incremental benefit of adding a third or fourth agent, and the additive versus redundant nature of SGLT2 inhibition, non-steroidal MRA and incretin therapy in the same patient is unknown. Factorial or sequential-nesting designs, and pragmatic registry-randomised trials of the SPIRRIT type, offer efficient routes to these answers.

Fourth, mortality remains unaddressed. Whether the absence of a mortality signal reflects insufficient follow-up, the high competing risk of non-cardiovascular death in a multimorbid elderly population, or genuine failure of current therapy to alter the fundamental disease trajectory is unresolved and will require longer trials with prespecified cause-of-death adjudication.

Fifth, translational priorities include validation of nitrosative stress, proteostasis, myocardial energetics and epicardial adipose biology as druggable targets, moving beyond the murine two-hit model to human tissue and induced pluripotent stem cell platforms [22, 23, 30]. Novel classes under evaluation, including aldosterone synthase inhibitors, activin signalling inhibitors, cardiac myosin inhibitors and interleukin-6 antagonists, will define whether mechanism-directed therapy can outperform the metabolic agents that currently dominate [59, 60].

Sixth, implementation science deserves parity of esteem with drug discovery. Indian registry data demonstrate that even long-established therapies reach only a minority of eligible patients.12 Cost-effectiveness analyses in low- and middle-income settings, evaluation of generic and biosimilar pathways, task-shifted diagnostic algorithms deployable at district hospital level, and pragmatic trials of nurse-led or pharmacist-led titration are needed if the therapeutic advances of the past five years are to translate into population-level benefit. Prospective community-based Indian cohorts characterising HFpEF prevalence, phenotype distribution and body mass index thresholds appropriate to South Asian body composition are a specific and urgent priority.

14. CONCLUSION

Heart failure with preserved ejection fraction has moved decisively from therapeutic nihilism to evidence-based, multidrug management within a single decade. Contemporary understanding frames the syndrome as a systemic cardiovascular-kidney-metabolic disorder rather than an isolated abnormality of diastole, and this reconceptualisation has yielded four classes of effective therapy. SGLT2 inhibitors are foundational for all patients, reducing cardiovascular death and worsening heart failure across the ejection fraction spectrum. The non-steroidal mineralocorticoid receptor antagonist finerenone provides additional event reduction and is now the preferred agent of its class. Incretin-based therapies produce the largest symptomatic and functional improvements yet observed in this population and, in the case of tirzepatide, reduce clinical events in obesity-related disease. Sacubitril-valsartan retains a defined role at the lower end of the ejection fraction range and in women, while device-based left atrial decompression remains investigational and, on current evidence, potentially harmful in HFpEF.

The residual challenges are those of precision, durability and delivery. No therapy has yet reduced mortality, phenotype-directed treatment remains an aspiration rather than a practice, and the populations enrolled in pivotal trials differ materially from those seen in Indian and other low- and middle-income clinical settings. For the practising clinician, the immediate imperative is early and confident diagnosis using validated scoring systems, systematic exclusion of treatable mimics, and prompt initiation of the therapies that are now proven. For the research community, the priority is to move from syndromic to mechanistic trial design. For health systems, the priority is access. HFpEF is no longer an untreatable condition; whether it becomes a well-treated one will depend as much on implementation as on further discovery.

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