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Research Paper

Pharmacological management of heart failure with preserved ejection fraction: a narrative review of diagnosis, drug classes, and trial evidence

Abdul Mukit*
*Assistant Professor, Nemcare Group of Institutions, Guwahati, Assam, India.

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ABSTRACT

Introduction: Heart failure with preserved ejection fraction (HFpEF) has recently become the (increased) diagnosis of choice for about 50% of heart failure cases and has been the diagnosis that has been the most refractory to all the treatments that have proven successful for heart failure with reduced ejection fraction (HFrEF) for more than 20 years. No single test can confirm a diagnosis in the case of HFpEF and diagnosis is often deferred or missed. In conclusion, this narrative review summarizes (i) validated diagnostic and risk stratification criteria for HFpEF, and (ii) comparative pharmacology and randomized trial data of the various classes of drugs currently recommended in the management of HFpEF.

Methods: PubMed/MEDLINE, Cochrane Library and ClinicalTrials.gov were queried for phase 3 randomized outcome trials in HFpEF, along with current HFpEF guidance from the ESC and AHA/ACC/HFSA guidelines 1997-2025. There are nine phase 3 outcome trials, each with over 40,000 patients, being compared candesartan, irbesartan, perindopril, spironolactone, sacubitril/valsartan, empagliflozin, dapagliflozin, finerenone and tirzepatide. Reduced composite of cardiovascular death or hospitalization for heart failure (HR 0.79–0.82) was observed with SGLT2 inhibitors; previous neurohormonal interventions were only weakly or not observed; finerenone had a similar, significant result (RR 0.84). Along with the H_2FPEF score and the HFA-PEFF algorithm, a comparative pharmacology table, a safety/monitoring table, and a phenotype-guided treatment algorithm are presented.

Conclusions: HFpEF is now from a geographically undefined 'syndrome' to one with a number of evidence-based drug classes; the SGLT2 inhibitors form the bases of therapy with phenotypes of therapies added on according to phenotype, followed by the integration of incretin-based classes into HFpEF therapy, where useful, in the obesity phenotype. Early and more effective diagnosis and timely treatment with this proven combination of drugs offers a very significant opportunity to ease the impact of this increasingly common disease affecting human beings.

Corresponding Author:
Abdul Mukit
Assistant Professor, Nemcare Group of Institutions, Guwahati, Assam, India.
Email: abdulmukit13@gmail.com

1. INTRODUCTION

The term heart failure with preserved ejection fraction (HFpEF) refers to numerous signs and symptoms of heart failure with a LVEF usually at or above 50% (but some studies have designated an "mildly reduced" level as 41–49%). HFpEF used to be considered a diagnosis of exclusion, and was once thought to be less severe than heart failure with reduced ejection fraction (HFrEF); however, it is now known to be equally, if not more, frequent, deadly and pathophysiologically different. However, population-based surveillance reveals a relentless growing proportion and percentage of incident HFpEF due to population aging, and in parallel, due to the overall worldwide increase in obesity, hypertension, type 2 diabetes, and chronic kidney disease – comorbidities now known to actively contribute to the underlying myocardial and vascular pathobiology of HFpEF, not just to be correlated with it [1], [2].

For over 20 years, the role of disease-modifying pharmacologic therapy of HFpEF has not been clearly established. Indeed, the effectiveness of each of the neurotransmitter blocking therapies until recently shown to be effective in treating HFrEF ACE inhibitors, angiotensin receptor blockers, and steroidal mineralocorticoid receptor blockers were tested sequentially against HFpEF and were not significantly superior in the pre-specified analyses of their respective primary outcomes: candesartan (CHARM-Preserved); irbesartan (I-PRESERVE); perindopril (PEP-CHF); spironolactone (TOPCAT); and, recently, sacubitril/valsartan (PARAGON-HF) [3], [4], [5], [6], [7]. This period of indifferent-to-exceptional performance further cemented a pathophysiological re-thinking previously proposed by Paulus and Tschöpe, which blamed the syndrome on the effect of the biochemistry (systemic microvascular inflammation and myocardial/vascular stiffening) as opposed to the progressive ventricular remodeling that the neurohormonal-blockade model had excelled at explaining for HFrEF [8].

The situation has dramatically shifted in the last 10 years with the introduction of sodium glucose cotransporter-2 (SGLT2) inhibitors in the HFpEF outcome trial, non-steroidal mineralocorticoid receptor antagonist (ns-MRA) finerenone and, most recently, incretin-based agents for patients with a history of obesity. All of these classes of drugs has had a statistically significant impact on a composite endpoint of cardiac death and hospitalizations or hospitalization for worsening heart failure, which has transformed the landscape of available therapy for HFpEF within approximately five years from a medical field with no proven therapy to one in which multiple therapies meet several guideline-recommended goals. A second and even more significant barrier in this area has been the diagnosis of the condition. The diagnosis of HFpEF is often missed because there is no single confirmatory laboratory or imaging test, and consciousness of breathlessness and exertional intolerance can be confused with those associated with being overweight, deconditioning and chronic lung disease. Although the rapidly evolving clinical criteria of the era enable relatively clear identification of patients eligible for evidence-based therapy, many do not obtain a formal diagnosis, and thus do not benefit from such therapy, because the lack of a diagnosis is specifically targeted by the structured bedside and imaging-based diagnostic algorithms developed during the past decade [9], [10].

1.1 Objectives

The purposes of this review are the following: (i) summarize validated and structured diagnostic and risk-stratification tools for HFpEF; (ii) place the current pharmacologic evidence in context of previous,

largely neutral trials to make clear why recent trials have succeeded; (iii) describe the pharmacology of the drug classes recommended for management across three domains: mechanism of action, principal trial evidence, and adverse-effect profile; (iv) present the accumulated trial evidence on HFpEF in tabulated and graphical format; and (v) propose an integrated, phenotype-guided treatment algorithm consistent with current international HFpEF management guidelines.

2. RELATED WORK

The current literature available on pharmacological treatment of HFpEF can be grouped into five main areas, all of which will be relevant to the synthesis reported in this review.

The Epidemiological and pathophysiological characterization. The prevalence of incident HFpEF has increased steadily and it is a highly prevalent syndrome among all cases of HF; outcomes (mortality and rehospitalization) are catching up to those of HFrEF despite a preserved pump function [1], [2]. The decision to look for other classes of drug with natriuretic, anti-fibrotic, and metabolic activity as well as pure neurohormonal blockade was directly spurred by an influential paradigm by Paulus and Tschöpe, who linked coronary microvascular endothelial dysfunction with systemic, low-grade inflammation driven by obesity, hypertension, diabetes and ageing [8]. Phenomapping with unsupervised statistical clustering of clinical and biomarker data and echocardiographic parameters showed that there was no single disease entity of HFpEF but rather a set of overlapping phenotypes, such as obese, hypertensive and cardiorenal phenotype, with variation in natural history and, in a plausible hypothesis, different optimal pharmacotherapy [11].

At the moment there are 5 broad categories of literature available on pharmacological treatment of HFpEF, all of which will have relevance to the synthesis reported in this review.

The Epidemiological and pathophysiological characterization. Despite their preserved pump function, the prevalence of incident HFpEF has risen over time, and is a very common syndrome in all HF cases, with outcomes (mortality and rehospitalization) now comparable to those of HFrEF. [1], [2] The idea to search for more classes of drugs with natriuretic, anti-fibrotic and metabolic properties as well as pure neurohormonal blockade was directly inspired by the influential paradigm of Paulus and Tschöpe, which provided the link between coronary microvascular endothelial dysfunction and the systemic, low-grade inflammation caused by obesity, hypertension, diabetes and ageing [8]. Phenomapping by statistical (unsupervised) clustering of clinical and biomarker data, and echocardiographic parameters, revealed no single disease entity of HFpEF but rather a group of overlapping phenotypes—such as the obese, hypertensive and cardiorenal phenotype with different natural history and, in a plausible hypothesis, different optimal pharmacotherapy [11].

Development of positive evidence base. The flip side of this story is also documented in a second, post-1960s, strand of literature. EMPEROR-Preserved and DELIVER proved that SGLT2 inhibition lower cardiovascular death and heart failure hospitalization irrespective of diabetes status and over the entire spectrum of preserved and mildly reduced ejection fractions [12], [13]. A pooled, individual-participant meta-analysis further revealed that the SGLT2-inhibitor effect was consistent across the whole spectrum of ejection fractions, thus suggesting that SGLT2 inhibition is therapy for heart failure as a syndrome rather than for distinct subgroups [14]. These positive studies were extended to non-steroidal MRAs by the findings with FINEARTS-HF and a subsequent meta-analysis found a similar, though slight, benefit that was statistically clear with the use of finerenone [15], [16]. The latest was the companion trial, STEP-HFpEF, in type 2 diabetes, and SUMMIT, which was the first study to explore pharmacology of the obesity phenotype.

Instructional literature for diagnosis and guidance. Alongside a separate literature has developed on structured diagnosis. Invase hemodynamic validation studies led to the use of invasive confirmation as a reference standard for equivocal cases, which was later reduced to the bedside scoring system, the H_2FPEF validated vs. invasive hemodynamic outcome [17], [18], [19]. A similar European initiative led to the development of the HFA-PEFF algorithm, which is a step-by-step approach based on pre-test clinical assessment, echocardiographic/natriuretic-peptide scoring and, if necessary, functional or invasive testing [20]. Recent trial evidence has been used to develop these tools as models for reaching clinical

recommendations that are part of current ESC and joint AHA/ACC/HFSA guidelines [21], [22]. The beginnings of review-level syntheses have merged these diagnostic and therapeutic strands, and the present review continues this process, but reviews them using a comparative pharmacology approach and an explicit, phenotype-directed treatment algorithm [23].

Changes over time in guidelines as an indicator of the quality of the evidence base. By contrast, the most recent ESC document and the AHA/ACC/HFSA document give HFpEF pharmacotherapy a high-certainty class I recommendation for virtually all patients with HFpEF, whereas the previous guidance documents gave the least recent recommendations of a conditional, low-certainty nature for the use of HFpEF pharmacotherapy; the conditional, low-certainty nature of the recommendations for the previous guidance documents is also suggested by the trial record described above, which was largely neutral. This course is an independent indicator of the extent to which the underlying evidence base has developed in this area, and one of the reasons for a narrative synthesis like this one to be timely.

Combined, the literature sheds light on the difficulties of the past 20 years in developing a drug for HFpEF and the success of recent drug classes, and what is still missing in narrative form is the ability to connect the diagnostic tools, the comparative pharmacology of all the currently relevant drug classes, and the quantitative trial evidence in one phenotype-guided treatment framework; this is the void this review addresses.

3. METHODOLOGY

This is a narrative review without data collection of the patients and without formal meta-analytical pooling of trial results by the present authors. Searches of PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were performed using the combinations of the following terms: heart failure with preserved ejection fraction, HFpEF, SGLT2 inhibitor, mineralocorticoid receptor antagonist, finerenone, angiotensin receptor–neprilysin inhibitor, GLP-1 receptor agonist, tirzepatide, H2FPEF, HFA-PEFF, and randomized controlled trial, limited to English-language papers published from January 1997 through mid-2025.

The priority was given to the phase 3, event-driven, randomized, placebo- or active-controlled outcome trials with a pre-specified composite primary endpoint, current European Society of Cardiology (ESC) and joint American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guideline documents and widely cited mechanistic and phenomapping studies. Trials were included if they enrolled a majority HFpEF or mildly-reduced-ejection-fraction population and reported the pre-specified primary cardiovascular or heart-failure-related outcome; trials were excluded unless they are specifically referenced if they only included a population of HFrEF for background information on the general mechanism of a drug class.

The following information was obtained directly from the primary publication for each included outcome trial: year of publication, sample size, eligibility criterion for LVEF, definition of the primary composite outcome, point estimate (hazard ratio or rate ratio) and 95% confidence interval, and binary determination of conventional statistical significance of the primary composite outcome. No confidence intervals, rate ratios or diagnostic score components were calculated, pooled or simulated by the present authors and all reported are directly extracted from the cited primary publications. For drugs supported by more than one qualifying outcome trial, individual trials are presented in Table 3 and Figure 1, instead of summarizing them together to avoid implying a ranking of effects across trials with different eligibility criteria and background therapy.

4. RESULTS AND DISCUSSION

4.1 Diagnosis and Risk Stratification

Diagnostic algorithms for HFpEF are used and involve consideration of clinical probability, natriuretic peptide levels and echocardiographic or invasive hemodynamic findings. The H_2FPEF score is one of the most well-validated bedside scores to estimate the likelihood that a patient with an unexplained

exertional dyspnea and preserved EF will have an abnormal invasive exercise hemodynamic study and therefore meet criteria for a diagnosis of HFpEF, as summarized in Table 1; higher scores increase the likelihood that the patient has an abnormal invasive exercise hemodynamic study and therefore meets criteria for a diagnosis of HFpEF, and very low scores should raise the question concerning alternative explanations for symptoms [9], [10].

Table 1. H_2FPEF Score: A Validated Bedside Tool for Estimating HFpEF Probability

Component	Criterion	Points
Heavy	Body mass index >30 kg/m^2	2
Hypertensive	On ≥2 antihypertensive medications	1
Fibrillation	Paroxysmal or permanent atrial fibrillation	3
Pulmonary hypertension	Doppler echocardiographic pulmonary artery systolic pressure >35 mmHg	1
Elder	Age >60 years	1
Filling pressure	Doppler echocardiographic E/e′ ratio >9	1
Total possible score	—	0–9

Interpretation: A score from 0 to 1 suggests that HFpEF is unlikely, and as long as no further invasive testing is indicated, natriuretic peptide measurement or diastolic-stress echocardiography or invasive hemodynamic exercise testing is warranted for a score of 6 to 9, which has a >90% post-test probability of HFpEF and establishes the diagnosis of HFpEF without further testing [10]. The same pre-test-to-confirmatory approach has been explicitly codified into a structured algorithm called the HFA-PEFF algorithm that includes a pre-test assessment of symptoms, risk factors and electrocardiographic findings, followed by a step of structured echocardiographic and natriuretic-peptide scoring: for indeterminate cases, an additional step of functional testing or invasive hemodynamic confirmation [20]. In both schemes, elevated natriuretic peptides along with preserved or normal LVEF point towards the diagnosis and served as an enrollement criterion in all of the important outcome trials summarized in Section 4.3. Both of these have been added to the current ESC and AHA/ACC/HFSA guidelines as the initial step in the pathway for management, before any pharmacological decision has been made [21], [22].

4.2 Comparative Pharmacology of HFpEF Drug Classes

Table 2 outlines the mechanism of action, main trial results, and pharmacokinetic properties of the randomized outcome-trial agents for each drug class, along with the previous drugs with largely neutral trial findings that provided the field with knowledge of what does not work.

Table 2. Comparative Pharmacology of Drug Classes Used or Studied in HFpEF Management

Drug Class	Representative Agent(s)	Mechanism of Action	Principal Trial Evidence	Renal/Hepatic Considerations
Loop diuretics	Furosemide, torsemide	Inhibits Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb, producing natriuresis and decongestion	Symptomatic therapy; no dedicated HFpEF outcome trial	Dose requirement rises as eGFR falls; electrolyte monitoring required
Angiotensin receptor blockers	Candesartan, irbesartan	Angiotensin II type-1 receptor blockade, reducing afterload and myocardial fibrotic signaling	CHARM-Preserved (2003); I-PRESERVE (2008) — both neutral	Dose adjustment with renal impairment; monitor potassium

ACE inhibitors	Perindopril	Inhibits conversion of angiotensin I to angiotensin II, reducing afterload and remodeling	PEP-CHF (2006) — neutral on primary endpoint	Cough; monitor renal function and potassium
Steroidal MRA	Spironolactone	Competitive aldosterone antagonism at the mineralocorticoid receptor, reducing sodium retention and myocardial fibrosis	TOPCAT (2014) — borderline	Avoid if eGFR <30 or K^+ >5.0 mmol/L; monitor potassium and creatinine
ARNI	Sacubitril/valsartan	Neprilysin inhibition (↑ natriuretic peptides) combined with angiotensin II receptor blockade	PARAGON-HF (2019) — borderline	Dose titration guided by blood pressure and renal function; 36-hour ACEi washout required
SGLT2 inhibitors	Empagliflozin, dapagliflozin	Proximal tubular SGLT2 inhibition; natriuresis, reduced plasma volume, altered myocardial substrate utilization	EMPEROR-Preserved (2021); DELIVER (2022) — both significant	Effective and generally well tolerated down to eGFR ~20–25; monitor for volume depletion
Non-steroidal MRA	Finerenone	Selective, non-steroidal mineralocorticoid receptor antagonism with balanced cardiac/renal tissue distribution	FINEARTS-HF (2024) — significant	Monitor serum potassium at baseline and after initiation; avoid if K^+ >5.0 mmol/L
GLP-1 receptor agonists	Semaglutide	Glucose-dependent insulinotropic and central satiety effects; weight loss; anti-inflammatory effects on the adipose-cardiac axis	STEP-HFpEF (2023); STEP-HFpEF DM (2024) — symptom/functional endpoints	Gradual titration; caution with severe gastrointestinal intolerance
Dual GIP/GLP-1 receptor agonist	Tirzepatide	Combined glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonism; pronounced weight loss and anti-inflammatory effect	SUMMIT (2025) — significant on composite clinical-worsening endpoint	Gradual titration; caution with severe gastrointestinal intolerance

4.3 Randomized Trial Evidence: Primary Outcomes

Modest, statistically marginally beneficial or no neurohormonal strategies (modest, statistically marginally beneficial, or null). Randomized patients with heart failure and LVEF >40% to candesartan or placebo; the primary composite endpoint of cardiovascular death or heart failure hospitalization was not significantly decreased, but the results from a secondary analysis suggested a decrease in heart failure hospitalization alone [3]. I-PRESERVE randomized 4128 patients with HFpEF (LVEF ≥45%) to irbesartan or placebo treatment and the primary composite outcome of death or cardiovascular hospitalization did not differ significantly between the groups [4]. PEP-CHF randomized older adults with a clinical diagnosis of diastolic heart failure to perindopril and placebo, but did not meet its pre-specified primary endpoint due to the lower than expected event rate and symptomatic and functional secondary measures favored perindopril [5]. TOPCAT recruited 3,445 HFpEF (LVEF ≥45%) patients in a randomized trial to spironolactone or placebo. The primary composite outcome of cardiovascular death, aborted cardiac arrest, and heart failure hospitalization was reduced, but not significantly (HR 0.89, 95% CI 0.77–1.04); the hospitalization for heart failure itself was significantly reduced (HR 0.83, 95% CI 0.69–0.99). A regionally heterogeneous treatment effect was then noted, with a significantly larger treatment effect in the Americas but not in Russia and Georgia, where there was a high percentage of patients that may not have had true HFpEF and subsequent analyses suggested [6]. The 4,822 patients with HFpEF (LVEF ≥45%) and elevated natriuretic peptides were randomized to sacubitril/valsartan or valsartan alone in PARAGON-HF. However, the composite end point of total heart failure admissions and cardiovascular mortality came close to being statistically significant (rate ratio 0.87, 95% CI 0.75–1.01, p = 0.06), with pre-specified subgroup analyses showing a more beneficial impact in women and in individuals with LVEF at the lower end of the patient population eligibility window [7].

SGLT2 inhibitors – consistent benefit with sound statistical significance. The EMPEROR-Preserved study was a randomized trial that compared empagliflozin with placebo in 5,988 patients with heart failure and LVEF ≥40%. The primary combination endpoint (cardiovascular death or hospitalization for heart failure) was significantly reduced (HR 0.79, 95% CI 0.69–0.90), largely owing to reduced hospitalization for heart failure and was present in both those with and without diabetes [12]. This study was a randomized trial of 6,263 patients with LVEF >40% who received dapagliflozin or placebo. This primary composite re: worsening heart failure or cardiovascular death was significantly lower (HR 0.82, 95% CI 0.73–0.92) and was observed with similar effects regardless of the range of eligible left ventricular ejection fraction which included patients with "heart failure with improved ejection fraction" [13]. This advantage was replicated across the entire spectrum of ejection fraction by a subsequent pooled, individual-participant meta-analysis of these and companion trials of HFrEF [14].

New, statistically significant pillar of non-steroidal MRAs. In FINEARTS-HF, 6,001 patients with heart failure and left ventricular ejection fraction (LVEF) ≥40% were randomized to finerenone or placebo, in addition to standard therapy. The primary outcome, a composite of cardiovascular death and worsening heart failure events (total) was significantly reduced (rate ratio 0.84, 95% CI 0.74–0.95; time-to-first-event HR 0.84, 95% CI 0.76–0.94), making finerenone the first mineralocorticoid receptor antagonist to have clear statistical significance with respect to a primary composite endpoint in this population [15]. A pooled analysis of patients from prior studies with finerenone and other steroidal-MRA trials further confirmed the magnitude and consistency of the mineralocorticoid receptor antagonist effects throughout the whole range of ejection fraction, and the greatest and most statistically robust benefit was seen with the use of the non-steroidal agent [16].

Obesity-phenotype and incretin-phenotype therapy. In STEP-HFpEF, participants with HFpEF and obesity were randomized to semaglutide or placebo; semaglutide led to significantly better results on the dual primary outcomes of symptom burden (based on Kansas City Cardiomyopathy Questionnaire clinical summary score) and body weight, and on the secondary endpoint of 6-minute walk distance [17]. These functional and symptomatic benefits were reproduced in a companion trial with participants who had HFpEF, obesity and type 2 diabetes (STEP-HFpEF DM) [18]. Most recently, SUMMIT randomized patients with HFpEF and obesity to tirzepatide (dual GIP/GLP-1 receptor agonist) or placebo; this trial showed a significant improvement in the composite outcome of cardiovascular death or worsening heart failure

events, along with significant improvements in symptom burden, functional capacity, and body weight, bringing incretin-based pharmacotherapy from symptom management to clinical outcome benefit in this phenotype [19].

Calculating effect sizes. The hazard or rate ratios and 95% confidence intervals for the five landmark event-driven cardiovascular outcome trials are displayed (as shown in Figure 1), and have been retrieved directly from the primary literature.

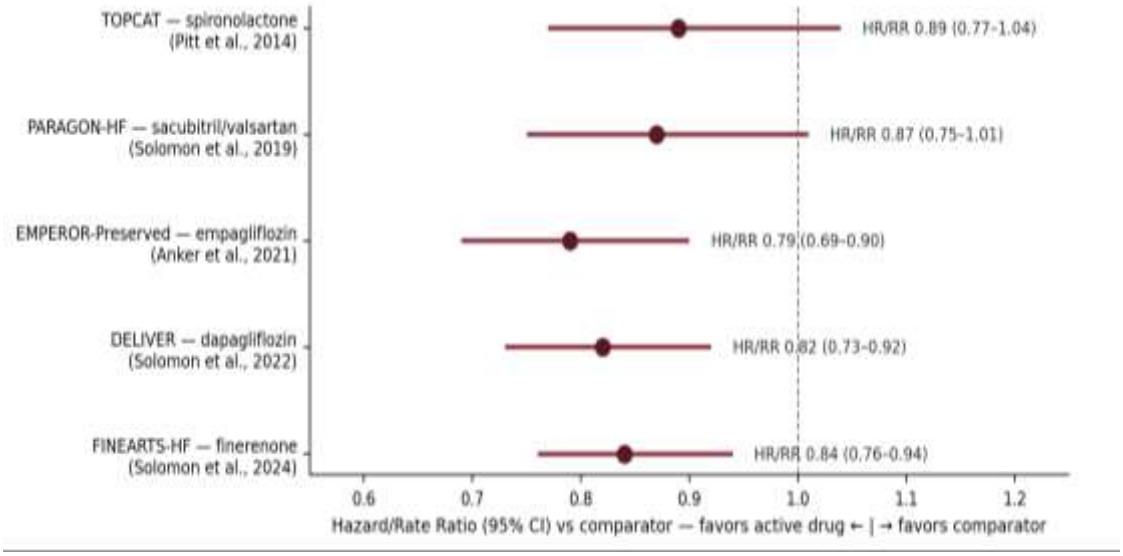

Figure 1. Effect of Pharmacotherapy on Primary Composite Outcomes in Landmark Randomized Trials of Heart Failure with Preserved Ejection Fraction

Figure 1. Effect of pharmacotherapy on primary composite outcomes in landmark randomized trials of heart failure with preserved ejection fraction. Point estimates and 95% confidence intervals extracted directly from the primary trial publications.

Table 3. Landmark Randomized Trials in Heart Failure with Preserved Ejection Fraction

Trial (Drug)	Year	N	LVEF Eligibility	Primary Composite Outcome	HR/RR (95% CI)	Significant?
CHARM-Preserved (candesartan)	2003	3,023	>40%	CV death or HF hospitalization	0.89 (0.77–1.03)	No
I-PRESERVE (irbesartan)	2008	4,128	≥45%	All-cause death or CV hospitalization	0.95 (0.86–1.05)	No
PEP-CHF (perindopril)	2006	850	Clinical diastolic HF	All-cause death or unplanned HF hospitalization	0.92 (0.70–1.21)	No
TOPCAT (spironolactone)	2014	3,445	≥45%	CV death, aborted cardiac arrest, or HF hospitalization	0.89 (0.77–1.04)	No
PARAGON-HF (sacubitril/valsartan)	2019	4,822	≥45%	Total HF hospitalizations + CV death	0.87 (0.75–1.01)	No (borderline)
EMPEROR-Preserved (empagliflozin)	2021	5,988	>40%	CV death or HF hospitalization	0.79 (0.69–0.90)	Yes

DELIVER (dapagliflozin)	2022	6,263	>40%	Worsening HF or CV death	0.82 (0.73–0.92)	Yes
FINEARTS-HF (finerenone)	2024	6,001	≥40%	CV death + total worsening HF events	0.84 (0.74–0.95)	Yes
SUMMIT (tirzepatide)	2025	731	≥50% + obesity	Composite of CV death or worsening HF events	0.62 (0.41–0.95)	Yes

4.4 Adverse Effects and Safety Monitoring

Table 4. Safety Profile and Recommended Monitoring for HFpEF Pharmacotherapy

Drug Class	Key Trial-Reported Adverse Effects	Absolute Incidence Signal	Recommended Monitoring
Spironolactone	Hyperkalemia; doubling of serum creatinine	Hyperkalemia 18.7% (spironolactone) vs 9.1% (placebo), TOPCAT	Serum potassium and creatinine at baseline, 1 and 4 weeks after initiation, then periodically
Sacubitril/valsartan	Hypotension; renal function decline; angioedema (rare)	Hypotension 15.8% vs 10.8% (valsartan alone), PARAGON-HF	Blood pressure at each visit; avoid concurrent ACE inhibitor (36-hour washout required)
SGLT2 inhibitors	Genital mycotic infection; volume depletion; rare euglycemic ketoacidosis	Consistent with the SGLT2-inhibitor class safety profile established in diabetes and HFrEF trials	Volume status assessment; sick-day dose interruption counselling
Finerenone	Hyperkalemia	Numerically higher than placebo but lower discontinuation rate than steroidal MRAs in comparative program data	Serum potassium at baseline and after initiation; avoid if K^+ >5.0 mmol/L
GLP-1/GIP-based agents	Nausea, vomiting, diarrhea (dose-dependent, transient)	Gastrointestinal adverse events in 20–40% during dose titration	Slow up-titration; monitor weight and nutritional status

The two drugs that have demonstrated benefit at the trial level have done so with relatively more favorable safety profiles (SGLT2 inhibitors and finerenone compared to the previous steroidal mineralocorticoid receptor antagonist and ARNI strategies), which has directly influenced their roles as nearly foundational and foundational therapy in current guidance, respectively (Table 4).

4.5 Integrated, Phenotype-Guided Treatment Algorithm

A stepwise, phenotype-guided approach to pharmacotherapy for HFpEF is summarized in Figure 2, in keeping with ESC and AHA/ACC/HFSA recommendations: diagnostic confirmation using the tools outlined in Table 1 plus treatment of underlying comorbidities and congestion will serve as the baseline; essentially all patients are recommended to receive an SGLT2 inhibitor; in those with a persistent congestion phenotype, an SGLT2 inhibitor, followed by finerenone or sacubitril/valsartan as needed, is recommended; in those with a persistent obesity phenotype, a GLP-1 or dual GIP/GLP-1 receptor agonist may be added if symptoms remain in those with an SGLT2 inhibitor, sacubitril/valsartan is indicated by

elevated natriuretic peptides, or hypertension is present or LVEF is closer to the mildly reduced range [21], [22].

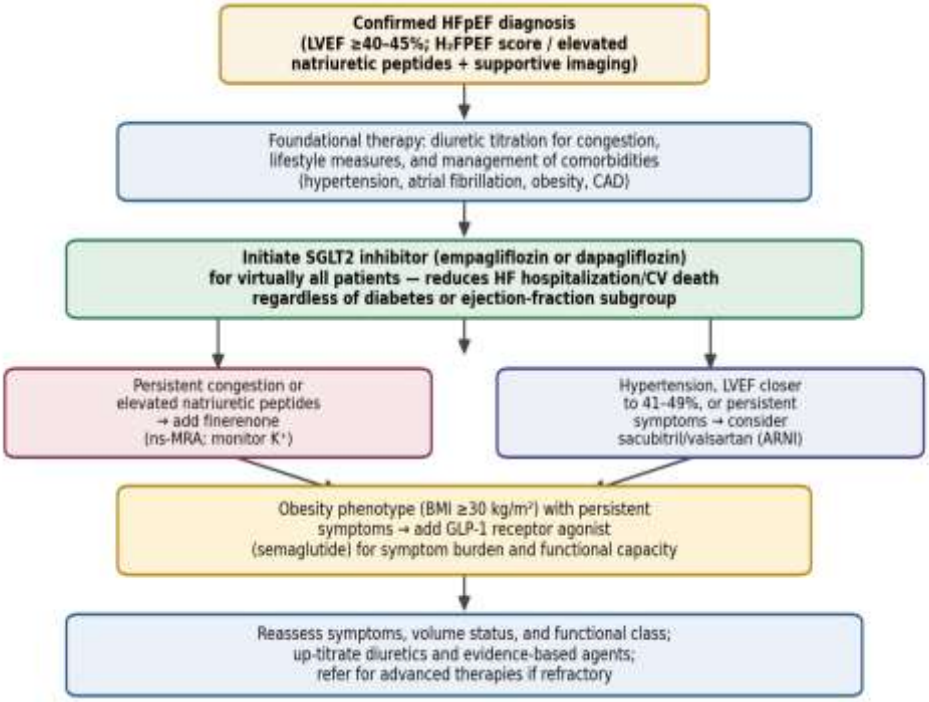

Figure 2. Stepwise Pharmacological Management Algorithm for Heart Failure with Preserved Ejection Fraction (HFpEF)

Figure 2. Integrated, phenotype-guided pharmacotherapy algorithm for heart failure with preserved ejection fraction, synthesized from current ESC and AHA/ACC/HFSA guidance and the trial evidence summarized in Table 3.

4.6 Discussion

The evidence from trials in this review shows a definite progression in the pharmacology of HFpEF, which is only apparent when the older (neutral) trials are reviewed in the context of the more recent positive trials. Drugs that worked in HFrEF, such as the renin–angiotensin–aldosterone system inhibitors (candesartan, irbesartan, perindopril, and spironolactone) or the neprilysin inhibitors (sacubitril/valsartan), had only modest, borderline, or null effect in HFpEF [3], [7]. This aligns with the "comorbidity-driven paradigm" presented by Paulus and Tschöpe, where myocardial/vascular stiffening, systemic inflammation due to obesity, hypertension and ageing, in addition to microvascular dysfunction, are key factors, instead of the progressive remodeling that tends to dominate in HFrEF [8]. This paradigm also suggests a purely neurohormonal blocking strategy is targeting only a small component of the underlying biology and has its logical explanation as to why the first generation of medications derived from HFrEF therapy failed to show efficacy in HFpEF.

In contrast, the benefit of SGLT2 inhibitors and finerenone, whose mechanisms also involve natriuresis, myocardial/vascular fibrosis, and independent of EF, were consistent and statistically significant and are now considered foundational and near foundational therapy, respectively [12], [13], [15]. The pooled, ejection-fraction-spectrum meta-analysis of both classes supports this: the effect of the SGLT2-inhibitors is essentially unchanged across the full spectrum of ejection fractions and mineralocorticoid-receptor antagonism is directionally consistent with the effect becoming statistically unambiguous with the non-steroidal agent, suggesting both drug classes influence a process (most likely natriuresis, anti-fibrotic signaling, vascular and renal tissue effects) that is independent of reduced systolic function [14], [16]. This changes the perspective of treating HFpEF pharmacologically from “the HFrEF

armamentarium, minus what doesn't work" to a new perspective as a syndrome with a new and evolving, partially overlapping pharmacology.

Another implication is related to the phenotypic heterogeneity of HFpEF, which has been established by phenomapping [11]. The drugs used for HFpEF are more and more phenotype guided; for example, patients that are obese, have AF, hypertension, and congestive or hypertensive predominance should receive different therapy, as demonstrated in Figure 2. The move of incretin-based therapy (semaglutide, and now tirzepatide, from symptom and functional endpoints to a significant hard clinical composite outcome in SUMMIT marks the first formal evidence that the obesity phenotype is a more than just symptom-based disease target that can be addressed with a pharmacointervention. [17], [18], [19] This reflects the trend in precision phenotyping in cardiovascular pharmacology more generally, and highlights the importance of the H_2FPEF score and HFA-PEFF algorithm in guiding treatment decisions, not only as to whether a patient should be treated, but which agents to prioritize [9], [10], [20].

Another aspect that needs to be highlighted is the evolution of the definition of a "successful" HFpEF trial. The preliminary neurohormonal trials were driven primarily by a single composite endpoint, derived from HFrEF trials. FINEARTS-HF and, in part, PARAGON-HF, however, performed recurrent-event (total-events) analyses targeting recurrent hospitalizations, as opposed to only the first hospitalization typically encountered, which tend to be more numerous than deaths and therefore more likely to increase statistical power in a population with recurrent nonfatal worsening events. It's not just about the pharmacology, though, as this methodological change was a factor in the success of the later trials, and the reason that the earlier ones failed. It is therefore important that authors reporting the results of pharmacotherapy in HFpEF also report the structure of the outcome (as it is for other comparisons), because comparing outcomes across trials without considering this may result in an over- or underestimate of relative efficacy.

A practical implication of the safety and monitoring requirements in Table 4 is to combination therapy: Monitoring requirements for SGLT2 inhibitors, finerenone and sacubitril/valsartan are cumulative, as all three are often prescribed together within the algorithm in Figure 2, so that potassium is monitored for finerenone and, to a lesser extent, sacubitril/valsartan, and volume status and renal function are monitored for SGLT2 inhibitors and sacubitril/valsartan together. The safety of simultaneous initiation of all three classes, rather than the sequential initiation suggested by a single algorithm tested in none of the pivotal trials listed in Table 3, continues to build.

4.7 Limitations

This is a narrative and not a systematic review, and the present authors did not conduct formal risk-of-bias assessment or conduct a meta-analytic pooling. The hazard and rate ratios in Table 3 and Figure 1 are based on cross-trial comparisons, which have important limitations, such as different patient eligibility criteria (LVEF), different definitions of the primary outcome (single time-to-first-event versus recurrent-event analyses), different background therapy, and, in the case of SUMMIT, a smaller number of patients than in other trials listed, and should therefore be treated as trial-specific effect estimates and not as a direct comparison of efficacy. Although well validated, both H_2FPEF and the HFA-PEFF algorithm were developed and validated mainly in tertiary-referral populations, and the performance of the algorithms in unselected primary-care populations may vary [10], [20]. This pharmacological review did not address the issues of cost or access to these therapies and did not consider them to be used in the real world, especially in resource-limited areas.

5. CONCLUSION

In the last decade or so, heart failure with preserved ejection fraction has shifted, from having a long track record of trials, mostly neutral to having multiple drug classes with evidence-based mechanisms of action. The previous generation of neurohormonal blocking agents (candesartan, irbesartan, perindopril, spironolactone, and sacubitril/valsartan) set the standards of what can be accomplished by a renin–angiotensin–aldosterone–neprilysin-targeted strategy in this syndrome, whereas SGLT2 inhibitors, now

supported by the most consistent clinical trial evidence across the entire ejection-fraction spectrum, combined with finerenone, sacubitril/valsartan (when appropriate phenotypes), and incretin-based agents (when appropriate phenotypes), represent a logical, combination-based strategy for the pharmacological management of this syndrome. Diagnostic delay can be significantly shortened by structured diagnostic tools, like the H_2FPEF score and the HFA-PEFF algorithm, which ensure that patients who fulfill the criteria at the time are captured and provided with this proven approach to treatment instead of going undiagnosed. Earlier diagnosis plus this phenotypically guided pharmacotherapy offers a great opportunity for the prevention, diagnosis and management of this now one of the most common chronic cardiovascular syndromes affecting the adult world.

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Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Abdul Mukit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study and their voluntary consent was obtained prior to data collection.

Ethical Approval

Not Applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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BIOGRAPHIE OF AUTHOR

Abdul Mukit, is an Assistant Professor at the NEMCARE Group of Institutions, Guwahati, Assam, India. He is associated with the Department of Pharmacology at the NETES Institute of Pharmaceutical Science. His academic interests include pharmaceutical sciences, pharmacology, drug research, and related areas of healthcare and biomedical research. He is actively involved in teaching, academic activities, and research. He holds an M.Pharm degree and is committed to contributing to scientific research and the advancement of pharmaceutical education. Email: abdulmukit13@gmail.com