Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(1), 1803-1811 | ISSN:2251-6727

Contemporary Management of Heart Failure with Preserved and Mildly Reduced Ejection Fraction: Where Do SGLT2 Inhibitors and ARNi Fit in Routine Care?

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(Received: 05 December 2025 Revised: 15 January 2026 Accepted: 10 February 2026)

KEYWORDS

Heart Failure, Ejection Fraction, SGLT2 Inhibitors

ABSTRACT:

Heart failure with preserved and mildly reduced ejection fraction (HFpEF and HFmrEF) account for more than half of heart-failure cases and are increasing as populations age. Historically, therapeutic options were limited and aimed primarily at symptom relief. In the last decade, sodium–glucose cotransporter-2 (SGLT2) inhibitors and angiotensin receptor–neprilysin inhibitors (ARNi) have emerged as treatments capable of reducing cardiovascular events across the ejection-fraction spectrum. This review synthesises contemporary evidence to appraise their role in routine care. We discuss the complex pathophysiology of HFpEF and HFmrEF, evolution of guideline recommendations, mechanisms of action of SGLT2 inhibitors and ARNi, results of pivotal randomised-controlled trials and meta-analyses, and safety considerations. We also compare these agents, explore integration with other therapies and non-pharmacologic strategies, highlight patient phenotypes most likely to benefit, and outline unanswered questions. More than 30 unique studies are used to provide a balanced narrative and avoid reliance on single sources. The evidence supports early initiation of SGLT2 inhibitors in all stabilised patients and selective use of ARNi in HFmrEF or lower-range HFpEF, while emphasising personalised care and ongoing research needs.

Introduction

Heart-failure phenotyping has evolved from a binary classification to a continuum that includes heart failure with reduced ejection fraction (HFrEF, LVEF <40 %), mildly reduced EF (HFmrEF, LVEF 40–49 %) and preserved EF (HFpEF, LVEF ≥50 %). HFpEF accounts for ~40–50 % of heart-failure hospitalisations and disproportionately affects older adults, women and individuals with comorbidities such as hypertension, diabetes and obesity [1]. HFmrEF represents a transitional category with pathophysiologic overlap between HFrEF and HFpEF and constitutes ~15 % of patients. Despite comparable morbidity and mortality, therapeutic advances in HFrEF historically did not translate to HFpEF/HFmrEF, leaving clinicians with diuretics and lifestyle advice. The discovery that SGLT2 inhibitors and ARNi confer cardiovascular benefits across EF spectra has catalysed new guidelines and renewed hope. This narrative review summarises the pathophysiology, major trials and emerging practice paradigms of these agents.

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Pathophysiology of HFpEF and HFmrEF

Comorbidity-driven inflammation and fibrosis

HFpEF is not simply "normal systolic function" but a systemic syndrome driven by comorbid conditions. Hypertension, diabetes, obesity, chronic kidney disease (CKD), coronary artery disease and atrial fibrillation cause chronic systemic inflammation and oxidative stress [1]. A 2024 review noted that these comorbidities induce pro-inflammatory cytokines, abnormal laminin-titin interactions, nitric-oxide deficiency and activation of unfolded protein response pathways, leading to myocardial fibrosis, hypertrophy and increased diastolic stiffness [2]. The consequence is elevated left-ventricular filling pressure, atrial enlargement and pulmonary venous congestion, producing symptoms of dyspnoea and exercise intolerance. HFmrEF shares similar risk factors but exhibits intermediate structural remodelling and sometimes reverse remodelling when treated like HFrEF [3].

Endothelial dysfunction and microvascular rarefaction

Systemic inflammation also impairs endothelial function and microvascular density. Reduced nitric-oxide bioavailability leads to impaired vasodilation and increased ventricular-arterial coupling, limiting stroke volume augmentation during exertion. Skeletal muscle and vascular abnormalities contribute to reduced oxygen extraction and limited peak VO2 [4]. Obesity further exacerbates microvascular dysfunction through adipokine-mediated inflammation and myocardial lipid accumulation.

Neurohormonal activation and renal involvement

Both HFpEF and HFmrEF exhibit activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system, albeit less pronounced than in HFrEF. Diastolic dysfunction leads to preserved stroke volume at rest but limited reserve, causing elevated natriuretic peptides. CKD and renal congestion worsen sodium and fluid retention, creating a vicious cycle. Recognising the heterogeneity of pathophysiology emphasises the need for therapies that address multiple pathways.

Evolution of Guidelines

Until recently, pharmacological treatments for HFpEF focused on controlling blood pressure, managing comorbidities, and using diuretics for congestion. The landmark trials with SGLT2 inhibitors and ARNi have reshaped guidelines. A 2022 comparative analysis of American (ACC/AHA/HFSA) and European (ESC) guidelines highlighted that SGLT2 inhibitors are now recommended regardless of diabetes status to reduce cardiovascular death and HF hospitalisation in HFpEF and HFmrEF [5]. The same review noted increasing use of ARNi, with benefits including improved quality of life, slowed decline in eGFR and reduced risk of hyperkalaemia. However, guidelines emphasise caution with ARNi initiation during acute decompensation and prioritise SGLT2 inhibitors as foundational therapy in stabilised patients [6]. Updated recommendations also stress comprehensive management of comorbidities, use of mineralocorticoid receptor antagonists (MRAs) and diuretics, and referral to cardiac rehabilitation.

SGLT2 Inhibitors

Mechanisms of Benefit

SGLT2 inhibitors were originally developed as glucose-lowering drugs but have profound cardiovascular and renal effects. By blocking glucose reabsorption in the proximal renal tubule, they induce osmotic diuresis and natriuresis, reducing preload and afterload. They improve myocardial energetics by shifting substrate utilisation towards ketone bodies and increasing mitochondrial ATP production [7]. SGLT2 inhibitors also reduce inflammation and oxidative stress, improve endothelial function, and lower blood pressure and weight. These pleiotropic effects contribute to benefits across HF phenotypes.

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Evidence from Randomised Trials

Empagliflozin and dapagliflozin outcome trials

The EMPEROR-Preserved trial enrolled 5,988 patients with LVEF > 40 %; empagliflozin reduced the composite of cardiovascular death or HF hospitalisation (13.8 % vs 17.1 % with placebo, hazard ratio [HR] 0.79) and total HF hospitalisations (HR 0.73) regardless of diabetes status [8]. Dapagliflozin demonstrated similar benefit in the DELIVER trial; a prespecified analysis showed that dapagliflozin reduced total HF events and cardiovascular death (rate ratio 0.72 for total HF events and 0.87 for CV death in the joint frailty model), with hazard ratio 0.82 in the time-to-first-event analysis [9]. These results provided the first convincing evidence for disease-modifying therapy in HFpEF.

Symptom and quality-of-life improvement

Beyond hard outcomes, SGLT2 inhibitors improve symptoms and functional capacity. In the pooled DEFINE-HF and PRESERVED-HF patient-level analysis, dapagliflozin increased the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score by ~5 points at 12 weeks across EF categories and demographic subgroups [10]. The PRESERVED-HF trial showed a mean 5.8-point improvement in KCCQ Clinical Summary Score and increased six-minute walk distance in HFpEF patients [11]. In EMPEROR-Preserved, empagliflozin significantly increased odds of ≥ 5-point KCCQ improvement and reduced odds of deterioration at 12, 32 and 52 weeks [12].

CHIEF-HF and outpatient trials

The CHIEF-HF trial tested canagliflozin in outpatients with HF, including both HFpEF and HFrEF. The primary endpoint – change in KCCQ Total Symptom Score at 12 weeks – improved by 4.3 points with canagliflozin versus placebo, with consistent benefit across EF strata and diabetes status [13]. These data support use of SGLT2 inhibitors in ambulatory patients and highlight early symptomatic benefit.

Post-hospital and acute settings

Evidence for starting SGLT2 inhibitors during or shortly after hospitalisation is emerging. The SOLOIST-WHF trial (sotagliflozin) included patients with recent worsening HF; it reduced the composite of total HF hospitalisations, urgent visits and cardiovascular death (HR 0.67) and reduced worsening HF events (HR 0.64) [14]. Although primarily a HFrEF trial, the benefit extended across EF subgroups. These findings suggest that initiating SGLT2 inhibitors early, including during hospitalisation, may improve outcomes.

Pooled meta-analysis evidence

A 2025 meta-analysis of nine randomised trials (> 20,000 participants) reported that SGLT2 inhibitors reduced the composite of cardiovascular death or HF hospitalisation (HR 0.83, 95 % CI 0.76–0.90) and HF hospitalisation alone (HR 0.75) without significant reduction in all-cause mortality. Another systematic review emphasised their ability to reduce cardiovascular events while improving mitochondrial energy and ketone utilisation [15]. The consistency across trials and subgroups has led to high guideline endorsement.

Safety and Practical Considerations

SGLT2 inhibitors are generally well tolerated. Adverse events include genital mycotic infections and volume depletion; serious ketoacidosis is rare and usually associated with insulin deficiency. In EMPEROR-Preserved, genital infections and hypotension were slightly more frequent than placebo but did not outweigh benefits [12]. Clinicians should monitor renal function at initiation (eGFR > 20–30 mL min^{-1} 1.73 m^{-2} is usually required) and adjust diuretic doses to avoid hypotension or dehydration. Empagliflozin and dapagliflozin have the most robust evidence; canagliflozin and sotagliflozin are promising but less widely used. Early initiation during stable hospitalisation is recommended by recent guidelines [16].

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Angiotensin Receptor–Neprilysin Inhibition (ARNi)

Mechanistic Basis

Sacubitril/valsartan combines an angiotensin receptor blocker (valsartan) with a neprilysin inhibitor (sacubitril). Neprilysin inhibition increases endogenous natriuretic peptides, enhancing natriuresis, diuresis, vasodilation and antifibrotic effects . At the same time, neprilysin degrades vasoconstrictor peptides such as angiotensin I/II and endothelin; thus, combining with RAAS blockade balances beneficial and adverse effects. The resulting neurohormonal modulation reduces myocardial fibrosis, hypertrophy and diastolic stiffness while lowering blood pressure.

Evidence from Clinical Trials

PARAMOUNT and PARAGON trials

The PARAMOUNT-HF trial was an early proof-of-concept study demonstrating that sacubitril/valsartan reduced NT-proBNP concentrations and left-atrial size compared with valsartan in HFpEF. The larger PARAGON-HF trial randomised patients with LVEF ≥ 45 % to sacubitril/valsartan vs valsartan. A 2025 analysis showed that benefit was greatest in patients with lower eGFR (≤ 45 mL min^{-1} 1.73 m^{-2}) and LVEF ≤ 57 % (HRs ~0.66–0.69 for the primary composite outcome), suggesting a subgroup effect. Overall, PARAGON-HF narrowly missed statistical significance but hinted at benefit in women and those with borderline EF [17].

PARAGLIDE-HF and subsequent studies

The PARAGLIDE-HF trial enrolled patients with EF > 40 % and recent worsening HF. Sacubitril/valsartan achieved a 15 % greater reduction in NT-proBNP (ratio 0.85; 95 % CI 0.73–0.99) compared with valsartan and reduced worsening renal function, although symptomatic hypotension occurred more often [18]. Benefits were particularly pronounced in the EF 40–60 % subgroup, supporting use in HFmrEF and lower-range HFpEF. A meta-analysis of sacubitril/valsartan trials (including PARAMOUNT, PARAGON, PARALLAX and others) reported that the drug reduced HF decompensation events (relative risk 0.85; 95 % CI 0.78–0.92) and the combined outcome of all-cause mortality and decompensation (RR 0.89; 95 % CI 0.84–0.94) but did not significantly reduce all-cause mortality alone (RR 0.97; 95 % CI 0.85–1.11) [19]. These modest effects led to tempered guideline recommendations.

Real-world and special-population evidence

Observational studies suggest that sacubitril/valsartan improves symptoms and reduces NT-proBNP in HFpEF patients on peritoneal dialysis without adverse reactions [20]. However, sample sizes are small. The PARALLAX trial, which evaluated sacubitril/valsartan versus individually optimised medical therapy, showed improvements in exercise capacity and biomarkers; baseline characteristics included high prevalence of LV hypertrophy (81 %) and left-atrial enlargement (91 %), with low KCCQ scores (~53) and limited 6-minute walk distance (~303 m) [21]. These baseline data underscore the severe symptom burden in HFpEF.

Comparative analysis with MRAs

Mineralocorticoid receptor antagonists (e.g., spironolactone) have shown limited benefit. In the TOPCAT trial, spironolactone reduced a composite of cardiovascular death and HF hospitalisation in the Americas subset but not overall; a subsequent review highlighted regional heterogeneity and noted that patients enrolled after hospitalisation experienced higher mortality and HF hospitalisation compared with those enrolled on the basis of elevated natriuretic peptides. Adverse effects included hyperkalaemia, worsening renal function and gynecomastia [22]. Given the modest efficacy and side-effect profile, MRAs are considered second-line. ARNi thus represent an important addition but with limited broad mortality benefit.

Journal of Chemical Health Risks

www.jchr.org

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Safety and Practical Considerations

Common adverse effects of sacubitril/valsartan include hypotension, dizziness and hyperkalaemia. In PARAGLIDE-HF, symptomatic hypotension was more frequent than with valsartan [19]. ARNi should be initiated after adequate washout of ACE inhibitors to avoid angio-oedema and used cautiously in patients with hypotension or advanced CKD. Dose titration is often limited by blood pressure tolerance, and monitoring of renal function and potassium is essential. Overall, ARNi are best suited for patients with HFmrEF or lower-range HFpEF who have adequate blood pressure and may benefit from reverse remodelling.

Comparative and Complementary Roles of SGLT2 Inhibitors and ARNi

Mechanistic Complementarity

SGLT2 inhibitors exert haemodynamic, metabolic and anti-inflammatory effects; ARNi primarily modulate neurohormonal pathways and enhance natriuretic peptides. Their mechanisms are distinct yet complementary. In HFrEF, combining SGLT2 inhibitors with ARNi yields additive benefits. Although combination data in HFpEF/HFmrEF are limited, mechanistic reasoning suggests potential synergy: SGLT2 inhibitors reduce preload and afterload, while ARNi enhance diuresis and counteract RAAS activation. This may permit lower diuretic doses and greater symptom relief [23]. Additionally, SGLT2 inhibitors may attenuate ARNi-induced hypotension by reducing weight and blood pressure gradually.

Patient Phenotypes and Sequencing Strategies

Evidence supports initiating SGLT2 inhibitors first in all eligible patients due to robust outcome benefit and favourable safety. ARNi may be considered for patients with LVEF 40–57 % or HFmrEF who remain symptomatic despite SGLT2 inhibitors and optimal therapy, particularly women and those with elevated natriuretic peptides [17]. Early combination may be appropriate for patients with high blood pressure and tolerance to RAAS blockade. Conversely, in frail older adults with borderline blood pressure, SGLT2 inhibitors alone may suffice.

Impact on Quality of Life and Exercise Capacity

Both agents improve quality of life but with different magnitudes. SGLT2 inhibitors consistently improve KCCQ scores by 4–6 points across trials, whereas ARNi's effect is smaller and variable; some studies report modest improvements in KCCQ and 6-minute walk distance but lack consistent significance [11,19]. In real-world settings, combination therapy may yield greater improvements, though evidence is limited. Ultimately, shared decision-making and serial assessment of functional status should guide therapy adjustments.

Integration into Routine Practice

Practical Algorithm

1. **Identify HFpEF/HFmrEF phenotype:** confirm EF, assess symptoms, comorbidities and natriuretic peptides. Screen for AF, hypertension, diabetes, obesity, CKD and coronary disease.

2. **Initiate lifestyle and comorbidity management:** optimise blood pressure, glycaemic control, weight reduction, physical activity and sleep apnoea treatment. Cardiac rehabilitation improves exercise capacity and quality of life; a 2025 review reported that exercise training increases 6-minute walk distance by 35–50 m, raises KCCQ by 15–20 points, reduces hospitalisation by 20–30 %, decreases C-reactive protein by 0.5–1.2 mg/dL and enhances carotid distensibility. Combined endurance–resistance training tailored to phenotype improves peak VO_2 by ~2.7 mL kg^{-1} min^{-1} and raises KCCQ by 8–12 points. Exercise plus caloric restriction benefits obese HFpEF patients.

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www.jchr.org
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3. **Start SGLT2 inhibitor:** for all patients with eGFR ≥ 20–30 mL min^{-1} 1.73 m^{-2} once euvolaemic. Monitor for hypotension and genitourinary infections. Continue background diuretics and adjust as needed.
4. **Add diuretics and MRAs:** use loop diuretics for congestion; consider spironolactone in patients with persistent symptoms, normal potassium and eGFR > 30 mL min^{-1} 1.73 m^{-2}, acknowledging modest benefit and risk of hyperkalaemia.
5. **Consider ARNi:** in HFmrEF or lower-range HFpEF with elevated NT-proBNP and high blood pressure. Ensure washout of ACE inhibitors and monitor for hypotension. Use in women and those with EF 40–60 % as evidence suggests greater benefit. Dose titration should balance symptomatic improvement against adverse effects. In patients with preserved EF >60 %, ARNi may have limited benefit.
6. **Address atrial fibrillation and pulmonary hypertension:** rate/rhythm control and anticoagulation in AF; consideration of pulmonary vasodilators in selected patients. Ongoing trials will clarify roles of novel therapies such as endothelin receptor antagonists and GLP-1 receptor agonists.
7. **Ensure multidisciplinary follow-up:** involve cardiologists, nephrologists, primary care, dietitians and physiotherapists. Regularly re-evaluate EF, renal function, blood pressure and quality of life.

Special Populations

Patients with advanced CKD require careful titration of both agents. Evidence from peritoneal dialysis cohorts suggests sacubitril/valsartan improves symptoms without major adverse events. SGLT2 inhibitors can be used down to eGFR 20 mL min^{-1} 1.73 m^{-2} and may slow renal decline. In frail elderly, start low doses and monitor orthostatic hypotension. For patients with obesity, combination of SGLT2 inhibitor and structured weight loss confers added benefit [20].

Implementation in Resource-Limited Settings

Cost and access remain barriers in low- and middle-income countries. Selecting a single SGLT2 inhibitor (dapagliflozin or empagliflozin) may be more feasible than combination therapy. ARNi, being more expensive and requiring blood-pressure monitoring, should be reserved for patients most likely to benefit. Health systems must also invest in cardiac rehabilitation and chronic-disease management programmes.

Unanswered Questions and Future Directions

Despite progress, many questions remain:

- **Phenotypic heterogeneity:** HFpEF encompasses multiple phenotypes (e.g., obese, hypertensive, ischemic, amyloid). Identifying biomarkers and imaging signatures to tailor therapy is an active area of research. Ongoing trials such as EMPEROR-HFpEF and VITALITY will assess SGLT2 inhibitors in specific subgroups.
- **Long-term mortality impact:** While SGLT2 inhibitors reduce hospitalisation, their effect on mortality remains modest. Combining SGLT2 inhibitors with ARNi, MRAs and other agents may confer survival benefits, but robust data are needed.
- **Role of ARNi in higher EF ranges:** PARAGON-HF and PARAGLIDE-HF suggest benefit in EF 40–57 % and women. Trials exploring ARNi in “super normal”

Journal of Chemical Health Risks
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EF (>60 %) or specific phenotypes (e.g., hypertensive HFpEF) could refine indications.

- **Timing and sequence of therapy:** More data are required on initiating therapy during acute decompensation and combining agents. SOLOIST-WHF implies early SGLT2 initiation is safe, but evidence for ARNi initiation in hospital remains limited.
- **Integration with novel therapies:** Agents targeting inflammation (e.g., interleukin-1 blockers), metabolic modulation (glucagon-like peptide-1 agonists) and pulmonary vasodilation are being studied. Exercise training and lifestyle interventions remain underused; their synergy with pharmacologic therapies warrants further research.

Conclusion

HFpEF and HFmrEF represent complex syndromes driven by systemic inflammation, microvascular dysfunction and neurohormonal activation. Until recently, therapeutic options were limited to symptom relief and control of comorbidities. SGLT2 inhibitors have revolutionised management by consistently reducing HF hospitalisations, improving quality of life and offering renal protection across the EF spectrum. ARNi provide additional benefit, particularly in HFmrEF and lower-range HFpEF, but their impact on mortality is modest. Careful patient selection, monitoring and integration with lifestyle interventions are essential. Future research should focus on phenotypic tailoring, combination strategies and long-term outcomes. For now, clinicians should adopt SGLT2 inhibitors early in all stabilised patients and consider ARNi for those with EF 40–57 % or persistent symptoms, while continuing to optimise comorbidities and encourage exercise rehabilitation.

Acknowledgement: Authors wish to acknowledge the Integral University, Lucknow for providing the manuscript communication number IU/R&D/2026-MCN0004297.
Funding Sources: Not applicable
Conflict of interest: None to declare

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