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VIEWPOINT

Tailoring medical therapy for heart failure with preserved ejection fraction

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Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for half of the hospitalization for heart failure (HF) worldwide, and the prevalence is expected to increase along with population aging and increasing burden of cardio-kidney-metabolic disorders.[1] Treatment options for chronic HFpEF have expanded in recent years.[2] Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are now guideline-recommended as a first-line treatment in patients with mildly reduced and preserved ejection fraction. In a meta-analysis of the EMPEROR-Preserved and DELIVER trials, SGLT2i reduced cardiovascular (CV) death or first hospitalization for HF by 20% with consistent reductions in both components (12% risk reduction in CV death and 26% risk reduction in first hospitalization for HF), among HF patients with left ventricular ejection fraction (LVEF) >40%.[3] In the PARAGON-HF trial, treatment with sacubitril/valsartan led to a marginal reduction of total hospitalizations for HF and CV death compared to valsartan in patients with HF and LVEF ≥45%, with a more pronounced benefit observed in those with an LVEF below normal.[4] Based on the results of this trial, sacubitril/valsartan received indications for use in patients with HF with mildly reduced ejection fraction (HFmrEF) and selected patients with HFpEF with an LVEF below normal in the United States. Lastly, in the FINEARTS-HF trial, the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone showed a 16% relative risk reduction of worsening HF events and death from CV causes compared to placebo among patients with HF and LVEF ≥40%.[5]

These advances in HFpEF pharmacotherapy, along with the substantial residual risk of this population, highlight the need for an accelerated optimization of foundational medical therapy.

Upfront integrated phenotype-based approach treatment of heart failure with preserved ejection fraction

Practical consideration for a comprehensive optimization of medical therapy

Clinical decision-making has become complex in the current era of HFpEF therapeutics. While multiple classes of drugs have been recently tested, there is a need to adopt an integrated optimization of foundational therapy to improve the care of chronic HFpEF (*Figure 1*). From a practical standpoint, a comprehensive treatment approach incorporating all evidence-based therapies should represent the cornerstone of HFpEF management. At the same time, patients with HFpEF may have different clinical presentations and phenotypes, degrees of congestion, haemodynamic status, and comorbidities. Therefore, adjusting or prioritizing drugs according to the HFpEF phenotype would permit a personalized implementation of evidence-based medications. Clinical inertia should not defer initiation of evidence-based treatment, and starting effective therapy can rapidly reduce risk in HFpEF.

Given the large benefits shown in major trials, the SGLT2i dapagliflozin and empagliflozin should be considered as first-line therapy regardless of the phenotype and the clinical settings for all HFpEF patients lacking contraindications. Based on the results of the SOLOIST-WHF trial, the dual SGLT1/2 inhibitor sotagliflozin has also indication for HF patients irrespective of LVEF in the United States.[6] The non-steroidal MRA finerenone might represent

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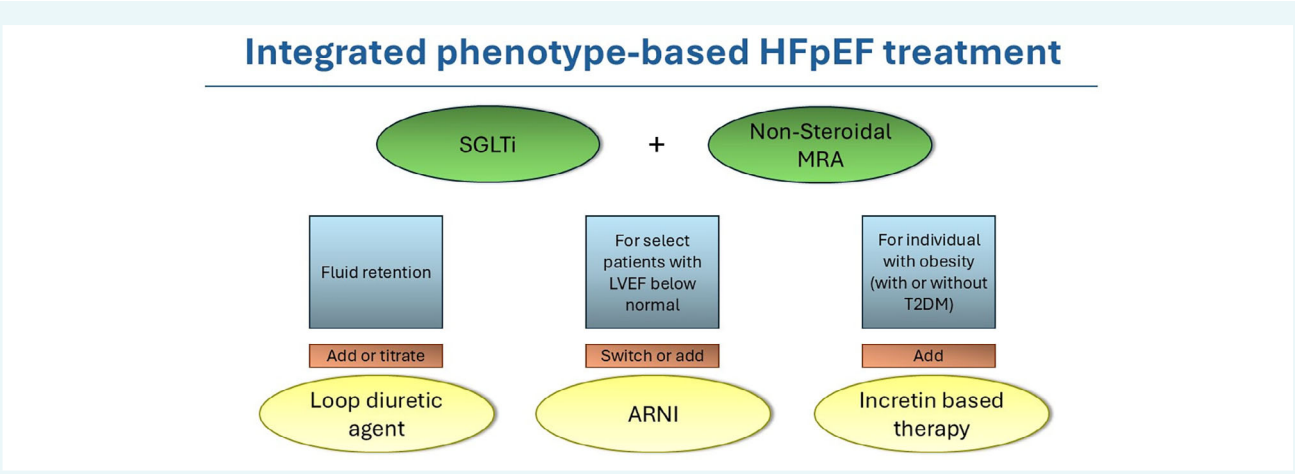

Figure 1 Contemporary heart failure with preserved ejection fraction (HFpEF) treatment approach. ARNI, angiotensin receptor–neprilysin inhibitor; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLTi, sodium–glucose cotransporter inhibitor; T2DM, type 2 diabetes mellitus.

the second foundational therapy for HFpEF. This drug should be administered simultaneously or in rapid sequence with SGLTi.[7] This appears even more critical among patients with a recent worsening HF event who showed greater absolute treatment benefit.[8] As many patients presenting with HFpEF may already be on a background steroidal MRA, the switch to finerenone might be considered once this drug is approved. In countries where there is an indication, angiotensin receptor–neprilysin inhibitors (ARNI) should be considered in all patients with HFmrEF as well as in HFpEF patients with below normal LVEF and among those recently hospitalized or in the worsening HF setting.[9] Recent analyses suggest that a combination therapy with ARNI, MRA and SGLTi may have positive CV effects on patients with LVEF up to 55–60%.[10]

In the SELECT trial,[11] which enrolled more than 2000 obese patients with HFpEF without type 2 diabetes (T2D), a pre-specified analysis showed benefits of the glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide in terms of CV death or hospitalization or urgent hospital visit for HF irrespective of investigator-reported HF subtype (HFpEF vs. HF with reduced ejection fraction, interaction $p = 0.79$). In the STEP-HFpEF and STEP-HFpEF DM trials, semaglutide was safe and effective in improving health-related quality of life, exercise function and weight loss than placebo among obesity-related HFpEF with and without T2D.[12] Similar results were observed in the SUMMIT trial with tirzepatide, an agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors.[13] According to available evidence, initiation of GLP1-RA may be considered to improve health status and manage body weight among obese HFpEF. Recent evidence further suggests that GLP1-RA may also have direct effects on reducing inflammation not weight loss-mediated.[14] The ongoing HERMES trial will provide additional insights regarding the potential therapeutic effects of inflammation suppression in HFpEF.

Diuretic therapy should be used judiciously for patients with overt congestion.[15] Modulation of diuretic therapy dosage may be required after implementation with SGLTi, non-steroidal MRA, ARNI or GLP1-RA. Finally, beta-blockers may be used in individuals with HFpEF who have specific indications, such as atrial fibrillation or active angina, but exercise tolerance may be reduced due to chronotropic incompetence.[1]

Clinical barriers facing combination therapy in heart failure with preserved ejection fraction

Although advances have been made in understanding the pathophysiology of HFpEF, the diagnosis and management is challenging in clinical practice. The multifactorial aetiologies and the heterogeneous clinical presentation results in uncertainties to provide adequate care. Also, the residual mortality and morbidity risk associated with HFpEF is often not perceived by clinicians. Improvements in care delivery require more education to overcome perception bias in diagnosis and prognosis. Enhancing screening in primary care and an early referral to secondary care in case of suspected HFpEF, as well as better access to clinicians with adequate knowledge of the disease process, diagnostic testing, and management strategies is required. Effective implementation of team-based care to tackle multiple comorbidities is pivotal to improve patients' care.[16]

Data from clinical trials showed consistent efficacy/safety by the use of SGLTi across different clinical settings and phenotypes. Similarly, the non-steroidal MRA finerenone showed consistent benefit across pre-specified subgroups including those defined according to baseline LVEF, kidney function, background HF medical therapy with SGLTi or renin–angiotensin system inhibitors. The safety/efficacy of non-steroidal MRA in patients previously taking steroidal MRA is less established. FINEARTS-HF indeed excluded those with recent treatment with an MRA within 12 months of screening. Further data are needed to address this important question as many HFpEF patients may already take a steroidal MRA.

There is a biological rationale for the combined use of non-steroidal MRA and SGLTi. Both drugs showed favourable physiological effect at a renal and myocardial level through different pathways targeting haemodynamic perturbations and inflammation.[10] SGLTi may further offset hyperkalaemic effects of concomitant use of an MRA, supporting their role together to mitigate these safety issues.

While improving health status and reducing body weight with biological evidence of myocardial benefit as shown by consistent N-terminal pro-B-type natriuretic peptide reduction, there is a lack of well-established data on traditional HF outcomes (including HF hospitalization and CV mortality) supporting the use of incretin-based therapies. As such, dedicated large HF outcome trials are needed. GLP1-RA may however provide complementary benefits on clinical outcomes along with SGLTi and non-steroidal MRA by targeting specific obesity-related HFpEF pathways.[17] Additionally, among T2D and albuminuria, combination treatment of SGLTi, GLP1-RA, and non-steroidal MRA has been projected to meaningfully extend survival free from HF and kidney events.[18]

Concerns may also derive from the risk of hypoglycaemic events in patients already on SGLTi. Nevertheless, except for concomitant other antidiabetic agents such as insulin, clinical data showed an excellent profile with a similar rate of safety events among patients with combined GLP-1RA and SGLTi treatment compared with monotherapy.[19] More data are instead needed to assess long-term safety in terms of risks of gastrointestinal disorders. Regimen complexity derived by the subcutaneous use of GLP1-RA may limit its broad adoption. This may create logistic challenges for patients with HF that, as opposite to patients with diabetes, are not used to self-administering injectable therapies. Although oral semaglutide is also available, and other molecules are under development, most of the outcome data from clinical trials have evaluated subcutaneous regimens.

The lack of net benefit of sacubitril/valsartan among HFpEF patients and the weak guideline recommendation represent the first barriers in the implementation of ARNI in HFpEF. Combination of steroidal MRA and ARNI appeared safe and effective in reducing HF and renal endpoints. SGLTi similarly showed consistent safety and efficacy according to background medical therapy, including ARNI, from clinical trials.[3]

Conclusion

The rising prevalence worldwide, the burden on the healthcare system and costs related to hospitalization represent critical challenges in the management of HFpEF. Novel therapeutic options advocate a transformative change in the care of chronic HFpEF patients encompassing recognition of multiple treatments, along with the management of comorbidities according to specific HFpEF phenotype. An upfront combination of foundational therapies, potentially enhancing tolerance and persistence of each other, should represent the bedrock of HFpEF treatment by targeting multiple pathophysiological drivers. A simultaneous or rapid sequence initiation of SGLTi and the non-steroidal MRA finerenone may be considered along with tailored therapies including incretin-based therapies and ARNI (*Figure 1*), based on clinical phenotype and settings, to optimally improve health status and clinical outcomes of patients with HFpEF.

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