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Contemporary Management of Heart Failure with Preserved Ejection Fraction: What is Current and What Lies Ahead?

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Introduction

In Canada, the incidence of heart failure (HF) among adults ≥40 years has increased from 521 per 100,000 to 601 per 100,000 from 2013 to 2023,[1] and is expected to rise further in the coming decades.[2] HF is the second leading cause of death in Canada, with an age standardized all-cause mortality rate of 5,761 per 100,000 compared to people without HF at 913 per 100,000.[3] HF with preserved ejection fraction (HFpEF), defined as the clinical syndrome of HF with left-ventricular ejection fraction (LVEF) ≥50%, comprises approximately half of all HF diagnoses. Contemporary data published this year suggests one- and five-year mortality rates for HFpEF are similar to those seen in heart failure with reduced ejection fraction (HFrEF).[2]

The Canadian Cardiovascular Society (CCS) endorses the universal definition of HF, which classifies HFpEF as having an LVEF cutoff of 50% and emphasizes markers of increased left ventricular (LV) filling pressures as a reflection of the underlying pathophysiology.[4] HFpEF is associated with both functional and structural cardiac abnormalities, including diastolic dysfunction, ventricular and atrial remodelling, LV hypertrophy, and fibrosis.[5] In addition, systemic inflammation, endothelial dysfunction, altered myocardial energetics, and abnormalities in skeletal muscle are increasingly recognized as important contributors to HFpEF pathophysiology and serve as therapeutic targets.[5]

Comorbid conditions including type 2 diabetes mellitus (T2DM), obesity, atrial fibrillation, chronic kidney disease, pulmonary hypertension, obstructive sleep apnea, and iron deficiency have been associated with the development and progression of HFpEF.[6] Furthermore, there is growing interest in identifying distinct HFpEF phenotypes to better characterize patient populations beyond their comorbid conditions, with the aim of personalizing prognosis and treatment options. In a recent study, three distinct HFpEF phenotypes were identified, including a younger group with primarily New York Heart Association (NYHA) II symptoms, a higher prevalence of smoking, and a lower prevalence of diabetes and chronic kidney disease; another consisting of older age individuals (mean age 77 years), predominantly women with atrial fibrillation and chronic kidney disease; and a third group of intermediate age (mean age 66 years) with a very high prevalence of obesity and diabetes, greater functional impairment, and elevated inflammatory markers.[7] Notably, the patients in this latter phenotype, with a very high prevalence of obesity and diabetes, were most likely to be hospitalized for HF along with having an overall mortality risk comparable to those patients classified in the older, atrial fibrillation, chronic kidney disease phenotype, despite their younger age.[7]

Guideline Directed Medical Therapy

Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i)

SGLT2i inhibit the active reabsorption of glucose in the proximal tubule of the kidney, thereby reducing blood sugar levels. Several mechanisms of action have been proposed to explain their cardioprotective effects. At the cellular level, SGLT2i improve cardiac energetics through a hypoxic-like transcription paradigm and reduce inflammation and oxidative stress by decreasing epicardial adipose tissue and altering adipokine signalling.[8] At the structural level, they improve diastolic function by reducing myofilament stiffness and promoting extracellular matrix remodelling. In addition, they support cardiac workload and function through natriuresis and osmotic diuresis.[8]

The DELIVER (Dapaglaflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trials evaluated the effect of two SGLT2i in outpatients with HF and an LVEF of ≥40%, with or without type 2 diabetes mellitus (T2DM) on clinical outcomes **(Table 1)**.[9,10] Both trials showed a significant reduction in HF hospitalization (HFH) or cardiovascular (CV) death compared to a placebo, driven predominantly by reduction in HFH. In both trials, the effect of SGLT2i was independent of diabetes status. Additionally, the PRESERVED-HF (Dapagliflozin in Preserved Ejection Fraction Heart Failure) trial showed that dapagliflozin improved patient reported symptoms, physical limitations, and exercise function, when compared to a placebo.[11]

SGLT2i should strongly be considered for the treatment of HFpEF, barring cases of absolute contraindications, which should be documented by clinicians, given their positive impact in reducing morbidity and mortality.

Steroidal and Nonsteroidal Mineralocorticoid Receptor Antagonist (MRA)

MRAs block the binding of aldosterone to the mineralocorticoid receptor, which prevents the downstream effects of sodium retention, potassium excretion, and water retention, contributing to lower blood pressure. MRAs also help reduce cardiac fibrosis by inhibiting the upregulation of pro-fibrotic and inflammatory cytokines, which leads to improved diastolic function.[12] In addition, MRAs exert vascular effects by reducing arterial stiffness, thereby reducing afterload.[12] Steroidal MRAs, including spironolactone and eplerenone, bind non-selectively to various steroid receptors, which can contribute to hyperkalemia and hormonal disturbances –most notably anti-androgenic effects in men, particularly with spironolactone.[13] In contrast, nonsteroidal MRAs, such as finerenone, exhibit greater selectivity for mineralocorticoid receptors, offer greater potency, and have a slightly lower risk of hyperkalemia.[13]

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial demonstrated a significant reduction in HFH in patients with LVEF ≥45% who were in the spironolactone group compared to placebo.[14] Although the overall TOPCAT trial did not show a significant reduction in the primary outcome, a post-hoc analysis of TOPCAT found a significant reduction in the composite primary outcome of CV death, aborted cardiac arrest, or HFH among participants from North America and South America that was attributed to regional differences in patient characteristics.[15] The lack of definitive evidence from TOPCAT led to heterogeneity in the use of MRAs in HFpEF patients. Recently, the FINEARTS-HF (finerenone in Heart Failure with Preserved Ejection Fraction) trial enrolled patients with HF and LVEF ≥40% to receive finerenone versus standard of care including 13-14% of patients on SGLT2i. The trial demonstrated a significant reduction in the composite primary outcome of total worsening HF events (including first and recurrent unplanned hospitalizations or urgent HF visits) and CV death compared to placebo.[16]

Prior to the FINEARTS-HF trial, the CCS issued a weak recommendation, based on moderate-quality of evidence, for the use of MRAs in HFpEF with an updated guideline anticipated later this year.[17] Given the additive findings from FINEARTS-HF, clinicians should strive to use MRAs for managing HFpEF patients with acceptable renal function to reduce the risk of HFH.

Angiotensin Receptor Blocker (ARB) and Angiotensin Receptor Blocker Neprilysin Inhibitor (ARNI)

Angiotensin II blockade with ARBs reduces aldosterone secretion leading to decreased sodium and water retention which contributes to reduce blood pressure. In addition, ARBs mitigate the pro-fibrotic and hypertrophic effects of angiotensin II on the myocardium, thereby improving diastolic function.[18] In the CHARM-Preserved (Candesartan in Patients with Chronic HF and Preserved Left-Ventricular Ejection Fraction) trial, patients with LVEF ≥40% who were randomized to receive candesartan showed a non-significant trend in reduction of CV death and HFH, driven mostly by reduction in HFH when compared to placebo.[19] However, the I-PRESERVE (Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction) trial did not show a reduction in the primary composite outcome of all-cause mortality or CV hospitalization in patients with LVEF ≥45%.[20]

ARNIs incorporate neprilysin inhibition with angiotensin II inhibition. By preventing the degradation of natriuretic peptides, bradykinin, and substance P, ARNIs promote vasodilation, natriuresis, diuresis, and exert antifibrotic and

Trial Name Intervention and Comparator	Number of Participants per Arm	Primary Outcome	Number of Events	Effect Measure
DELIVER Dapagliflozin vs Placebo	3,131 vs 3,132	CV death or worsening HF (HFH or urgent visit for HF)	512 vs 610	HR 0.82 (95% CI, 0.73–0.92)
EMPEROR-Preserved Empagliflozin vs Placebo	2,997 vs 2,991	CV death or HFH	415 vs 511	HR 0.79 (95% CI, 0.69–0.90)
PRESERVED-HF Dapagliflozin vs Placebo	152 vs 152	KCCQ-CSS	N/A	Mean change +5.8 points (95% CI, 2.3–9.2)
TOPCAT Overall Spironolactone vs Placebo	1,722 vs 1,723	CV death, aborted cardiac arrest, or HFH	320 vs 351	HR 0.89 (95% CI, 0.77–1.04)
TOPCAT Americas Spironolactone vs Placebo	886 vs 881	CV death, aborted cardiac arrest, or HFH	242 vs 280	HR 0.82 (95% CI, 0.69–0.98)
FINEARTS-HF Finerenone vs Placebo	3,003 vs 2,998	CV death or worsening HF (HFH or urgent visit for HF)	1,083 vs 1,283	HR 0.84 (95% CI, 0.74–0.95)
CHARM-Preserved Candesartan vs Placebo	1,514 vs 1,509	CV death or HFH	333 vs 366	HR 0.89 (95% CI, 0.77–1.03)
I-PRESERVE Irbesartan vs Placebo	2,067 vs 2,061	All-cause mortality or CV hospitalization	742 vs 763	HR 0.95 (95% CI, 0.86–1.05)
PARAGON-HF Sacubitril/Valsartan vs Valsartan	2,407 vs 2,389	HFH or CV death	894 vs 1,009	Rate Ratio 0.87 (95% CI, 0.75–1.01)
PARAGLIDE-HF Sacubitril/Valsartan vs Valsartan	233 vs 233	NT-proBNP reduction	N/A	Ratio of Change 0.85 (95% CI, 0.73–0.99)
Pooled PARAGLIDE-HF and PARAGON-HF Sacubitril/Valsartan vs Valsartan	541 vs 547	Total worsening HF events and CV death	281 vs 358	Rate Ratio 0.78 (95% CI, 0.61–0.98)
STEP-HFpEF Semaglutide vs Placebo	263 vs 266	Change in KCCQ-CSS	N/A	Estimated Difference 7.8 points (95% CI, 4.8–10.9)

Trial Name Intervention and Comparator	Number of Participants per Arm	Primary Outcome	Number of Events	Effect Measure
STEP-HFpEF DM Semaglutide vs Placebo	310 vs 306	Change in KCCQ-CSS	N/A	Estimated Difference 7.3 points (95% CI, 4.1 – 10)
SUMMIT Tirzepatide vs Placebo	364 vs 367	CV death or worsening HF event	36 vs 56	HR 0.62 (95% CI, 0.41–0.95)
SODIUM-HF Restricted sodium intake vs Standard of Care	397 vs 409	CV hospitalization, CV ED visit, or all-cause mortality	60 vs 70	HR 0.89 (95% CI, 0.63–1.26)
FRESH-UP Fluid restriction vs Liberal	250 vs 254	Change in KCCQ-OSS	N/A	Mean Difference 2.17 (95% CI, -0.06–4.39)

Table 1. Summary of Contemporary Trials in Patients with Heart Failure with Preserved Ejection Fraction; *courtesy of Abdullah Malik, MD, Natasha Aleksova, MD, MSc*

Abbreviations: CV: cardiovascular; **HFH:** heart failure hospitalization; **HR:** hazard ratio; **CI:** confidence interval; **KCCQ:** Kansas City Cardiomyopathy Questionnaire; **CCS:** Clinical Summary Score; **OSS:** Overall Summary Score; **NT-proBNP:** N-terminal pro brain natriuretic peptide; **ED:** emergency department.

antihypertrophic effects, leading to overall decreased myocardial stress.[18] In the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial, sacubitril-valsartan did not show a statistically significant reduction in the primary composite outcome of HFH and CV death compared to valsartan in patients with LVEF ≥45%.[21] In an exploratory subgroup analysis, a statistical significant reduction in the primary outcome was seen in patients with LVEF of ≤57%. The PARAGLIDE-HF (Prospective Comparison of ARNI with ARB Given Following Stabilization in Decompensated HFpEF) trial enrolled patients with LVEF >40% within
30 days of a worsening HF event and randomized them to either sacubitril-valsartan or to valsartan alone.[22] In the ARNI group, the primary outcome of time-averaged proportional change in NT-proBNP from baseline through week 4 and 8 was decreased compared to the valsartan group. Furthermore, a pre-specified patient-level pooled analysis of these two trials demonstrated that ARNIs significantly reduced total worsening HF events and CV death compared to valsartan.[23]

In considering this class of therapeutics for heart failure, the 2017 CCS guidelines make a weak recommendation in favor of the ARB candesartan, citing evidence from the abovementioned CHARM-Preserved.[17] These guideline recommendations do not incorporate more recent evidence supporting the use of ARNIs for HFpEF however will likely do so in the future. Given their mechanism of action, ARNIs are more likely to potentiate stronger cardiorenal benefits than ARB. When considering the use of ARNIs, clinicians should adopt a more personalized approach that includes a discussion with the patient about the side effects of ARNIs, which include hypotension and angioedema, as well as cost considerations.

Nonpharmacologic Management Considerations

Previous CCS guidelines provided a weak recommendation based on low-quality evidence for restricting dietary sodium intake to 2-3 grams per day.[17] Since then, the SODIUM-HF (Study of Dietary Intervention under 100 mmol in Heart Failure) trial evaluated patients with HF and a

median LVEF of 36% (IQR 27-49) comparing a low sodium diet <1500 mg per day versus standard of care. The trial found no significant differences in the primary composite outcome of CV hospitalization, CV related emergency department visits, or all-cause mortality between the two groups.[24] In subgroup analysis comparing patients with LVEF >40% to those with LVEF <40%, there was still no difference in the primary outcome. As such, suggested sodium intake should be individualized with consideration of dietary habits and concurrent use of diuretics.

The CCS also provides a weak recommendation with low-quality evidence for restricting daily fluid to approximately 2 litres per day for patients experiencing fluid retention or congestion not easily controlled with diuretics. Recently, the FRESH-UP (Fluid Restriction in Heart Failure versus Liberal Uptake) trial randomized patients with HF and a mean LVEF of 40.3% (SD 10.9) to either a restricted fluid intake of up to 1500 ml per day or a liberal intake.[25] The primary outcome, a change in the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS), was not significantly lower in the treatment group and secondary outcomes of death, HFH, and changes in loop diuretic use also showed no differences. In a subgroup analysis of patients with HFpEF, there was no difference in the KCCQ-OSS between the intervention and control groups. Given the limited evidence, tailored recommendations for fluid restriction with consideration of the specific HFpEF phenotype are prudent.

Considerations for Obesity in HFpEF

Obesity has become a growing area of interest in the HFpEF scientific community given its high prevalence in HFpEF and its involvement

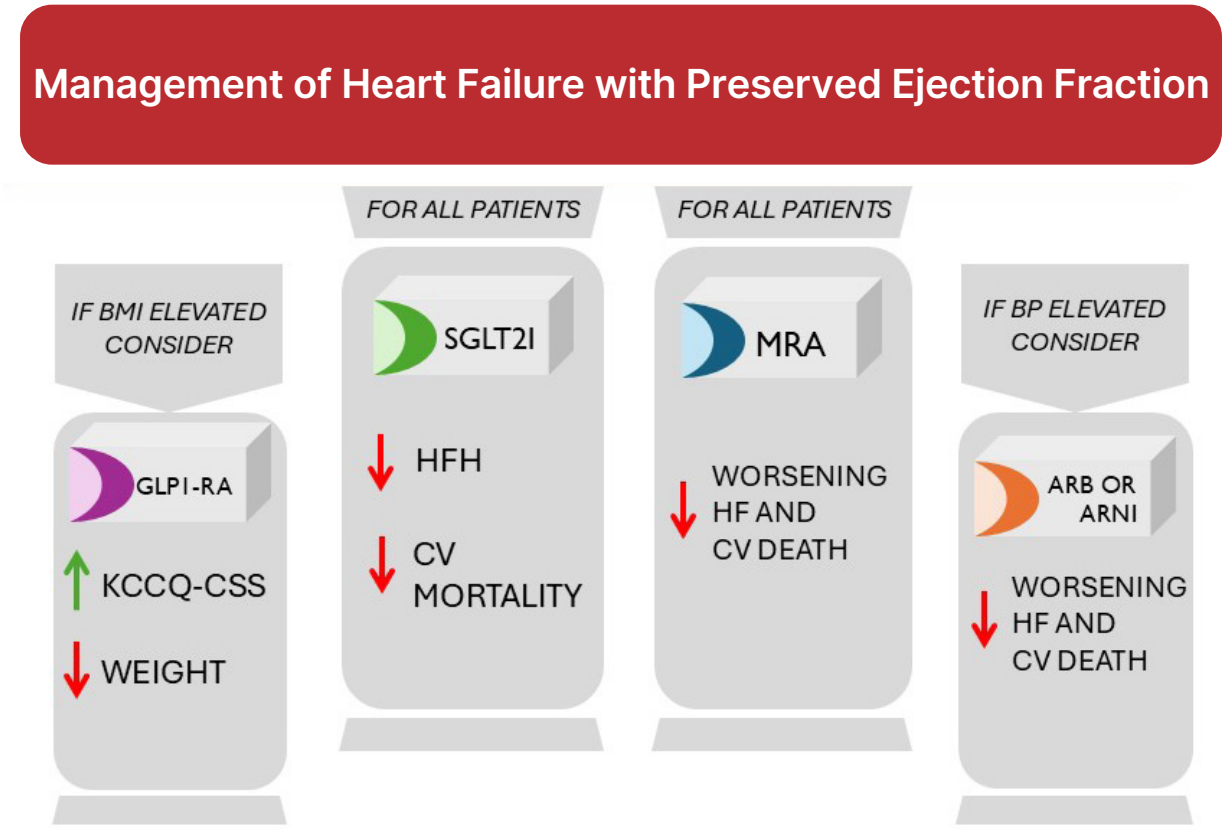

Figure 1. Summary of Pharmacologic Management Principles for Heart Failure with Preserved Ejection Fraction; *courtesy of Abdullah Malik, MD, Natasha Aleksova, MD, MSc*

Abbreviations: BMI: body mass index; **BP:** blood pressure; **GLP1-RA:** glucagon like peptide 1 receptor agonist; **SGLT2I:** Sodium Glucose Cotransporter 2 Inhibitor; **MRA:** mineralocorticoid receptor antagonist; **ARB:** angiotensin receptor blocker; **ARNI:** angiotensin receptor blocker neprilysin inhibitor; **KCCQ-CCS:** Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; **HFH:** heart failure hospitalization; **CV:** cardiovascular.

in promoting a pro-inflammatory state that contributes to altered cardio-metabolic and fibrosis pathways. In the STEP-HFpEF and STEP-HFpEF DM (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction) trials, obesity HFpEF patients with and without diabetes with LVEF ≥45% were randomly assigned to either the subcutaneous glucagon like 1 receptor agonist (GLP1-RA) semaglutide or placebo group for 52 weeks.[26, 27] At 52 weeks, the semaglutide group showed a significantly greater improvement in the KCCQ clinical summary score (KCCQ-CSS) compared to placebo along with a significant reduction in weight. In a secondary win ratio analysis of a hierarchical composite of all-cause mortality, number and timing of HF events, differences in the KCCQ-CSS, and differences in the 6-minute walk distance, semaglutide demonstrated a greater number of wins over placebo. Secondary outcomes also showed a significant improvement in 6 minute walk distance as well as a significant reduction in hsCRP. In the SUMMIT (A Study of Tirzepatide in Participants with Heart Failure with Preserved Ejection Fraction and Obesity) trial, obesity HFpEF patients regardless of diabetes status with LVEF ≥50% were randomly assigned to either tirzepatide, a combination glucose-dependent insulinotropic polypeptide receptor agonist (GIP-RA) and GLP1-RA or placebo.[28] The composite primary outcome of CV death or worsening HF events was significantly reduced in the tirzepatide group, primarily driven by a reduction in the number of worsening HF events.

Irrespective of diabetes, GLP1-RA analogues are promising therapeutic options for patients with HFpEF and obesity. Not only do they result in significant weight loss, improvement in metabolic parameters and decrease in inflammation, they offer improvements in quality of life, functional status and reduce the risk of HF events such as HFH.

Future Directions

Several ongoing trials for patients with HFpEF are targeting various pathophysiologic mechanisms related to disease origin and progression. Among these, more studies evaluating MRAs in HFpEF are on the horizon, including the SPIRRIT-HF trial investigating spironolactone and the REDEFINE-HF trial evaluating finerenone in hospitalized patients with acute decompensated heart failure and LVEF≥40%.[29] To determine if reducing inflammation can improve outcomes, ziltivekimab, a monoclonal antibody targeting the interleukin-6 ligand, is being compared to placebo in patients with LVEF >40%, focusing on a composite outcome of CV death, HFH, or urgent HF visits.[30]

Conclusion

Therapeutic options for the contemporary management of HFpEF continue to expand. SGLT2i and MRAs remain the cornerstone of treatment, while ARNIs and GLP1-RAs may be considered for specific populations of patients living with HFpEF. This highlights the need for an individualized approach to patient care **(Figure 1)**. Future research into the treatment and management of HFpEF is promising, with increasing recognition that targeting the pathophysiology associated with HFpEF may lead to improved patient outcomes.

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