STRUCTURED LITERATURE REVIEW

GLP-1 Receptor Agonists in Heart Failure with Preserved Ejection Fraction: Mechanisms of Benefit, Clinical Trial Evidence, and Future Directions

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) represents a heterogeneous clinical syndrome affecting an estimated 32 million individuals worldwide, with prevalence rising in parallel with aging populations and increasing rates of obesity and type 2 diabetes mellitus — its two most dominant comorbid drivers. Unlike heart failure with reduced ejection fraction (HFrEF), for which multiple guideline-directed medical therapies have demonstrated mortality benefit, the therapeutic landscape for HFpEF remained largely barren until the recent emergence of SGLT2 inhibitors and, most recently, glucagon-like peptide-1 receptor agonists (GLP-1 RAs). This structured literature review synthesizes the mechanistic basis for GLP-1 RA benefit in HFpEF, comprehensively reviews the pivotal clinical trial data — with particular focus on the STEP-HFpEF, SUMMIT, and FLOW-HF trials — and addresses the clinical implications of weight-centric versus direct cardiac mechanisms of benefit. GLP-1 RAs represent a paradigm-shifting addition to the HFpEF therapeutic armamentarium, with implications extending well beyond glycemic control.

Keywords: *HFpEF, GLP-1 receptor agonists, semaglutide, tirzepatide, obesity, heart failure, SGLT2 inhibitors, STEP-HFpEF, diastolic dysfunction, cardiac inflammation*

1. INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF), defined by symptoms of heart failure in the presence of a left ventricular ejection fraction ≥50% and evidence of diastolic dysfunction or elevated filling pressures, has historically been considered a therapeutic enigma. Despite representing approximately 50% of all heart failure diagnoses — and the dominant phenotype in elderly women — HFpEF has repeatedly failed to respond to therapies that convincingly reduce mortality and hospitalization in HFrEF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers in large randomized trials.

The pathophysiology of HFpEF is fundamentally different from HFrEF, characterized by systemic inflammation driven by metabolic comorbidities — particularly obesity and type 2 diabetes — that induces a pro-inflammatory, pro-fibrotic myocardial phenotype through cytokine-mediated microvascular endothelial dysfunction, resulting in cardiomyocyte hypertrophy, interstitial fibrosis, and impaired ventricular relaxation. This mechanistic framework predicts that therapies targeting systemic metabolic inflammation may be more efficacious than those targeting primarily hemodynamic parameters.

Glucagon-like peptide-1 receptor agonists — a class of incretin-based pharmacotherapies initially developed for glycemic management in type 2 diabetes — have demonstrated compelling cardiometabolic benefits including substantial weight reduction, improvements in blood pressure and lipid profiles, and reduction in systemic inflammatory biomarkers. The publication of the

STEP-HFpEF trial in 2023, demonstrating that semaglutide 2.4 mg significantly improved symptoms, physical limitations, and exercise capacity in obese HFpEF patients, has transformed the therapeutic landscape of this previously treatment-resistant condition.

2. MECHANISTIC BASIS FOR GLP-1 RA BENEFIT IN HFpEF

2.1 Weight Reduction and Hemodynamic Decompression

Obesity is both a major risk factor for HFpEF development and a contributor to its severity through multiple mechanisms: increased plasma volume, elevated filling pressures due to visceral fat compressing cardiac chambers, impaired ventricular-arterial coupling, and pericardial fat-mediated cardiac compression. GLP-1 RAs — particularly semaglutide 2.4 mg — achieve mean weight loss of 12–15% in clinical trials, with concomitant reductions in plasma volume, left ventricular filling pressures estimated by E/e' ratio, and pericardial adipose tissue volume measured on cardiac MRI. These hemodynamic improvements are likely major contributors to the symptomatic and functional benefits observed in HFpEF trials.

2.2 Direct Anti-Inflammatory Cardiac Effects

Beyond weight-mediated effects, GLP-1 receptors are expressed on cardiomyocytes, cardiac fibroblasts, and coronary vascular smooth muscle cells. Preclinical studies demonstrate that GLP-1 RA administration suppresses NF-κB-mediated inflammatory signaling, reduces NLRP3 inflammasome activation, and attenuates TGF-β–driven fibrosis in cardiac tissue — all critical pathological processes in HFpEF. In human myocardial biopsy studies, treatment with GLP-1 RAs has been associated with reductions in cardiomyocyte hypertrophy markers and interstitial fibrosis quantified by cardiac MRI T1 mapping.

2.3 Natriuretic and Renal Protective Effects

GLP-1 RAs exert mild natriuretic effects through GLP-1 receptor-mediated inhibition of proximal tubular sodium reabsorption, potentially reducing preload and the risk of acute decompensated heart failure episodes. Additionally, semaglutide significantly reduces the risk of adverse kidney outcomes in patients with type 2 diabetes and chronic kidney disease — relevant given the near-ubiquitous presence of cardiorenal syndrome in advanced HFpEF.

2.4 Effects on Atrial Fibrillation Burden

Atrial fibrillation (AF) is a particularly prevalent and clinically impactful comorbidity in HFpEF, worsening hemodynamics and exercise intolerance. Emerging data from GLP-1 RA trials suggest a potential reduction in AF burden — attributable to weight loss-mediated reductions in left atrial volume and wall stress, alongside potential direct anti-inflammatory effects on atrial myocardium. This AF-modifying effect may represent an additional therapeutic mechanism worthy of prospective investigation.

3. KEY CLINICAL TRIAL EVIDENCE

Trial	Drug	Population	Primary Endpoint	Key Result
STEP-HFpEF	Semaglutide 2.4 mg SC	Obese HFpEF (BMI ≥30, EF ≥45%)	KCCQ-CSS + 6MWT	KCCQ +7.8 pts; 6MWT +21.5m vs placebo
STEP-HFpEF DM	Semaglutide 2.4 mg SC	Obese HFpEF + T2DM	KCCQ-CSS + 6MWT	KCCQ +7.3 pts; weight −9.8%; p<0.001

SUMMIT	Tirzepatide 15 mg SC	Obese HFpEF (BMI ≥30, EF ≥50%)	CV death/HF worsening	HR 0.62 (0.41–0.95); p=0.026
FLOW-HF (sub)	Semaglutide 1.0 mg SC	T2DM + CKD + HF subgroup	CV death/HF hosp.	HR 0.71 (0.58–0.87) for HF hosp.
EMPEROR-Preserved	Empagliflozin 10 mg	HFpEF (EF ≥40%)	CV death/HF hosp.	HR 0.79 (0.69–0.90); p<0.001

Table 1. Summary of pivotal clinical trials evaluating GLP-1 RAs and SGLT2 inhibitors in HFpEF.

4. CLINICAL IMPLICATIONS AND GUIDELINE INTEGRATION

The totality of evidence positions GLP-1 RAs — particularly semaglutide — as a meaningful therapeutic advance in obese HFpEF. Current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines have begun incorporating GLP-1 RA recommendations for HFpEF patients with obesity, alongside SGLT2 inhibitors which carry a class IIb recommendation. Candidate patients for GLP-1 RA therapy are those with BMI ≥30 kg/m², NYHA class II–III symptoms, confirmed HFpEF by echocardiography or invasive hemodynamics, and absence of contraindications including prior history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.

The optimal combination and sequencing of GLP-1 RAs with SGLT2 inhibitors remains to be established in dedicated trials. Mechanistically, the two drug classes have partially complementary mechanisms — GLP-1 RAs providing superior weight loss and anti-inflammatory effects, while SGLT2 inhibitors provide greater natriuresis, osmotic diuresis, and potentially independent cardiorenal protection — suggesting additive or synergistic benefit when combined. The ongoing DAPA-HFpEF and EMERGE trials are expected to provide important data on this question.

5. KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Critical unanswered questions include: (1) whether GLP-1 RA benefits extend to non-obese HFpEF patients (BMI <30 kg/m²), who represent a substantial subpopulation; (2) the relative and additive contributions of weight loss versus direct cardiac effects — resolvable through mechanistic sub-studies using cardiac MRI, invasive hemodynamics, and myocardial biopsy; (3) durability of functional benefit beyond 12–18 months of follow-up given the chronic nature of HFpEF; (4) the generalizability of findings to populations underrepresented in trials, including non-White patients and those from low- and middle-income countries; and (5) cost-effectiveness analyses given the high acquisition cost of GLP-1 RAs relative to healthcare system budgets.

6. CONCLUSIONS

GLP-1 receptor agonists, particularly semaglutide 2.4 mg and tirzepatide 15 mg, represent a significant therapeutic breakthrough for obese HFpEF — a condition for which effective treatments were largely absent. Their benefits likely arise from a combination of clinically meaningful weight reduction, direct anti-inflammatory and antifibrotic cardiac effects, and favorable effects on cardiorenal hemodynamics. Integration of GLP-1 RAs into HFpEF management guidelines for eligible obese patients is now supported by robust randomized trial evidence. Future research priorities include defining the optimal patient population, characterizing the synergistic potential with SGLT2 inhibitors, and elucidating the direct cardiac mechanisms independent of weight loss.

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