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Efficacy of GLP-1 Agonists and GIP/GLP-1 Co-agonists in Obesity-Related Heart Failure with Preserved Ejection Fraction: A Systematic Review

Efficacy of GLP-1 Agonists and dual GIP/ GLP-1 Agonists in Obesity-Related Heart Failure with Preserved Ejection Fraction: A Systematic Review

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Summary

Objective: To evaluate the efficacy and safety of GLP-1 receptor agonists (Semaglutide) and GIP/ GLP-1 co-agonists (Tirzepatide) in the treatment of obesity-associated heart failure with preserved ejection fraction (HFpEF). **Methods:** A systematic review was conducted in PubMed/MEDLINE (2020–2025), including randomized clinical trials dedicated to HFpEF or reporting relevant cardiovascular outcomes in obese populations. The focus was on the analysis of symptoms, functional capacity, inflammatory markers, and clinical outcomes (CV death and worsening of HF). **Results:** Five studies met the criteria: STEP-HFpEF, STEP-HFpEF DM, SELECT, pooled analysis by Kosiborod MN et al., and SUMMIT. Significant improvements were observed in symptom scores (KCCQ-CSS), increased functional capacity, and consistent reductions in weight and inflammation (CRP). Recent studies suggest a reduction in major clinical events, with hazard ratios ranging from 0.62 to 0.80. **Conclusion:** GLP-1 agonists and GIP/GLP-1 co-agonists emerge as promising therapies for obesity-related heart failure with effusion (HFpEF), acting on both inflammatory pathophysiology and metabolic modulation. Although the results are robust, further longitudinal studies are needed for definitive confirmation.

Keywords: semaglutide, tirrizepatide, obesity, heart failure

Abstract

Objective: To evaluate the efficacy and safety of GLP-1 receptor agonists (Semaglutide) and dual GIP/ GLP-1 agonists (Tirzepatide) in the treatment of obesity-related heart failure with preserved ejection fraction (HFpEF). **Methods:** A systematic review was conducted in PubMed/MEDLINE (2020–2025), including randomized clinical trials specifically targeting HFpEF or reporting relevant cardiovascular outcomes in obese populations. The analysis focused on symptoms, functional capacity, inflammatory markers, and clinical endpoints (cardiovascular death and HF worsening).
Results: Five studies met the inclusion criteria: STEP-HFpEF, STEP-HFpEF DM, SELECT, the pooled analysis by Kosiborod MN et al., and SUMMIT. Significant improvements were observed in symptom scores (KCCQ-CSS), along with increased functional capacity and consistent reductions in body weight and inflammation (CRP). Recent trials also suggest a reduction in major clinical events, with hazard ratios ranging from 0.62 to 0.80. **Conclusion:** GLP-1 agonists and dual GIP/GLP-1 agonists emerge as promising therapies for obesity-related HFpEF, targeting both inflammatory pathophysiology and metabolic modulation. Although the current evidence is robust, additional long-term studies are required for definitive validation.
Key-words: semaglutide, tizepatide, obesity, heart failure

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1. Introduction

Heart failure with preserved ejection fraction (HFpEF) corresponds to approximately half of heart failure cases and historically presents options Limited therapeutic options. The **obesity-related HFpEF** phenotype has gained prominence in recent years. years, characterized by increased visceral adiposity, low-grade chronic inflammation, dysfunction endothelial and myocardial stiffness.

While therapies such as SGLT2 inhibitors have demonstrated consistent benefit in ICFEp, the need remains for interventions that directly address the mechanisms. Inflammatory and metabolic factors underlying the obese phenotype. In this systematic review, we evaluated the The role of GLP-1 agonists and GIP/GLP-1 co-agonists, with a focus on functional outcomes. Quality of life and major cardiovascular events.

2. Methodology

2.1 Data Source and Search Strategy

The systematic search was conducted in PubMed/MEDLINE between January 2020 and November 2020. from 2025. The search strategy was structured to maximize sensitivity and capture trials. Randomized trials applicable to the ICFEp-obesity phenotype, with the search string: (semaglutide OR tirzepatide) AND (HFpEF OR "heartfailure" OR "cardiovascular outcomes") AND obesity.

2.2 Eligibility Criteria

Inclusion criteria: Randomized clinical trials (phase 3) or pooled analyses; Interventions involving Semaglutide or Tirzepatide; Populations with HFpEF (LVEF ÿ45–50%) Associated with obesity (BMI ÿ30 kg/m²) or overweight with comorbidities; Outcomes assessed: symptoms (KCCQ-CSS), functional capacity through the 6-Minute Walk Test (6MWT), Cardiovascular death, hospitalization for heart failure, and safety.

Exclusion criteria: Observational studies; exclusively diabetic populations without ICFEp characterized; Tests with non-standard formulations.

2.3 Scales and Outcomes Assessed

- **KCCQ-CSS (Kansas City CardiomyopathyQuestionnaire – Clinical Summary Score):** evaluates Symptoms and physical limitations; a variation of ÿ5 points is clinically significant.
- **6-Minute Walk Test (6MWT):** measures submaximal functional capacity.
- **CRP (C-Reactive Protein):** marker of systemic inflammation.
- **Composite clinical outcomes:** cardiovascular death and worsening of heart failure

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3. Results

Table 1. Clinical trials evaluating GLP-1/GIP in HFpEF associated with obesity.

Population Study (Year) and Intervention	Main Outcomes
STEP-HFpEF (2023) – ICFEP without DM (nÿ529)	KCCQ-CSS: +16.6 vs +8.7 (95%CI 4.8–10.9; p<0.001); 6MWT: Semaglutide 2.4 mg +21.5 m vs +1.3 m (95%CI 8.6–32.1; p<0.001); Weight: -13.3% vs -2.6% (95%CI –11.9 to –9.4; p<0.001). CRP: HR 0.61 (95% CI, 0.51 to 0.72; P<0.001
STEP-HFpEF DM (2024) ICFEp with DM – 2.4 mg (nÿ616)	KCCQ-CSS: +13.7 vs +6.4 (95%CI 4.1–10.4; p<0.001); Weight: -9.8% Semaglutide vs -3.4% (95% CI -7.6 to -5.2; p<0.001); **6MWT:** difference +14.3 m (95%CI 3.7–24.9; p=0.008); CRP: HR 0.67 (95%CI 0.55–0.80; (p<0.001)
SELECT (2023) Semaglutide – CVD + MACE: obesity (n=17,604)	HR 0.80 (95% CI 0.72–0.90; p<0.001)
Pooled meta-analysis of Kosiborod SELECT + CV death or FLOW + STEP-HFpEF **MN (2024)** worsening of HF: HR 0.69 (95% CI 0.53–0.89; p=0.0045).	
SUMMIT (2024) Tirzepatide – ICFEp +	CV death/worsening CI: HR 0.62 (95% CI 0.41–0.95; p=0.026); KCCQ-CSS: +19.5 vs +12.7 (P<0.001); CRP: 38.8% reduction vs -5.9% obesity (nÿ731) no placebo; (p<0.001)

Legend: *HFpEF: Heart Failure with Preserved Ejection Fraction; DM: Diabetes Mellitus; CV: Cardiovascular; KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; MACE: Major Adverse Cardiovascular Events;* ***6MWT: 6-Minute Walk Test;*** *AMI: Myocardial Infarction; CVA: Stroke; CRP: C-Reactive Protein; HR: Hazard Ratio; 95% CI: 95% Confidence Interval.*

3.1 Functional and Symptomatic Results

The STEP-HFpEF and STEP-HFpEF DM studies demonstrated clinically significant improvements.

relevant in the **KCCQ-CSS,** exceeding the minimum important threshold (ÿ5 points). The evolution

The temporal analysis of the KCCQ curves indicated sustained improvement from the 8th week onwards, with stabilization.

starting in the 20th week and continuing until the end of the follow-up period.

In the **6-minute walk test (6MWT),** the STEP-HFpEF reported an absolute gain.

of +21.5 m compared to +1.3 m in the placebo group (p<0.001). The magnitude of this impact is comparable or

superior to that observed with SGLT2 inhibitors in previous HFpEF trials, which typically

They ranged from +15 to +18 m.

3.2 Metabolic and Inflammatory Effects

The average weight loss in the STEP trials ranged from 9.8% to 13.3%, while in the SUMMIT...

Patients treated with tirzepatide achieved reductions greater than 14%. **Protein** reduction

C-reactive protein (CRP) was consistent:

• STEP-HFpEF: HR 0.61 (95% CI, 0.51 to 0.72; P<0.001

• STEP-HFpEF DM: HR 0.67 (95%CI 0.55–0.80; p<0.001)

• SUMMIT: 38.8% reduction vs. -5.9% in the placebo group; (p<0.001)

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This sharp decline indicates strong modulation of systemic inflammation, recognized as Central pathophysiological motor factor in the HFpEF phenotype associated with obesity.

3.3 Cardiovascular Outcomes

The **SUMMIT** trial demonstrated a significant reduction in the composite cardiovascular death factor. and worsening of CI (HR 0.62; 95% CI 0.41–0.95), with early separation of the curves at approximately 20 weeks. The pooled analysis conducted by Kosiborod MN et al. integrated data from the studies SELECT, FLOW, STEP-HFpEF and STEP-HFpEF DM, demonstrating a reduction in mortality. cardiovascular disease and worsening of heart failure, with a HR of 0.69 (95% CI 0.53–0.89), suggesting a robust benefit. regardless of the presence of diabetes.

The **SELECT trial,** focused on MACE, showed: HR 0.80 (95% CI 0.72–0.90). Consistent reduction. in cardiovascular death, although not significant in isolation.

Taken together, these findings emphasize that the impact of GLP-1/GIP therapies transcends the Symptomatic improvement, leading to greater clinical outcomes.

3.4 Security

Gastrointestinal events (nausea, diarrhea, vomiting) were the most common adverse effects. Common complications result in discontinuation in 13% to 18% of patients. However, the rate of adverse events... The incidence of serious adverse events remained consistently lower than placebo, reinforcing the safety profile. favorable.

4. Discussion

The findings of this review reinforce the hypothesis that HFpEF is related to obesity. It constitutes a distinct pathophysiological entity, with mechanisms dominated by chronic inflammation. adverse metabolic remodeling, systemic congestion, and functional limitation not purely hemodynamics. In this context, GLP-1 agonists and GIP/GLP-1 co-agonists act in a way particularly aligned with the inflammatory-metabolic phenotype of the disease.

4.1 Comparison with SGLT2 Inhibitors

SGLT2 inhibitors have become established as first-line therapy in HFpEF, with Consistent benefits demonstrated in the EMPEROR-Preserved and DELIVER trials. However, Their effect on symptoms and functional capacity tends to be more modest. While SGLT2 While GLP-1 agonists promote reductions of 1.0 to 2.3 points in the KCCQ, they have demonstrated increases. higher than 7 points.

In the 6MWT, SGLT2s improve by an average of 15 to 18 meters—a value lower than the gain. observed with Semaglutide (+20.3 m) and potentially lower than that obtained with Tirzepatide.

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SGLT2 patients have an approximate HR between 0.79 and 0.82 for the composite of hospitalizations due to Heart failure and cardiovascular death. GLP-1/GIP therapies showed a risk ratio between **0.62 and 0.69,** suggesting that these therapies may be... to exert a comparable or superior impact, although still dependent on confirmation in trials. targeted.

The complementarity is evident: while SGLT2s modulate renal hemodynamics and Congestion, GLP-1/GIP agonists act on visceral obesity, inflammation and remodeling. metabolic, addressing distinct and potentially synergistic mechanisms.

4.2 Clinical Implications

The results support the incorporation of GLP-1/GIP agonists as a therapeutic strategy. targeted at the obese phenotype of HFpEF. This subpopulation, historically without a full response to Conventional therapies offer superior benefits when intensive metabolic interventions are used. They are applied.

The future association of GLP-1/GIP + SGLT2 may represent the most robust strategy for This profile combines congestion reduction, weight loss, inflammatory improvement, and beneficial effects. in clinical outcomes.

4.3 Limitations

Despite the solid results, limitations remain: the heterogeneity between studies, The lack of data on patients with a BMI >45 kg/m² and the relatively short follow-up period. (max. 72 weeks).

5. Conclusion

GLP-1 agonists and GIP/GLP-1 co-agonists demonstrate relevant benefits in patients with obesity-related heart failure with symptomatic improvement, functional gains and signs of a reduction in cardiovascular events. These findings position such agents as potential therapeutic pillars in this phenotype. However, further studies with follow-up are needed. prolonged studies are necessary to confirm the durability of the benefits and define ideal criteria for selection, in addition to comparability with other therapies currently available.

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