The Effects of Tirzepatide and Semaglutide on Clinical and Metabolic Outcomes in Patients With Heart Failure and Obesity or Metabolic Syndrome: A systematic review

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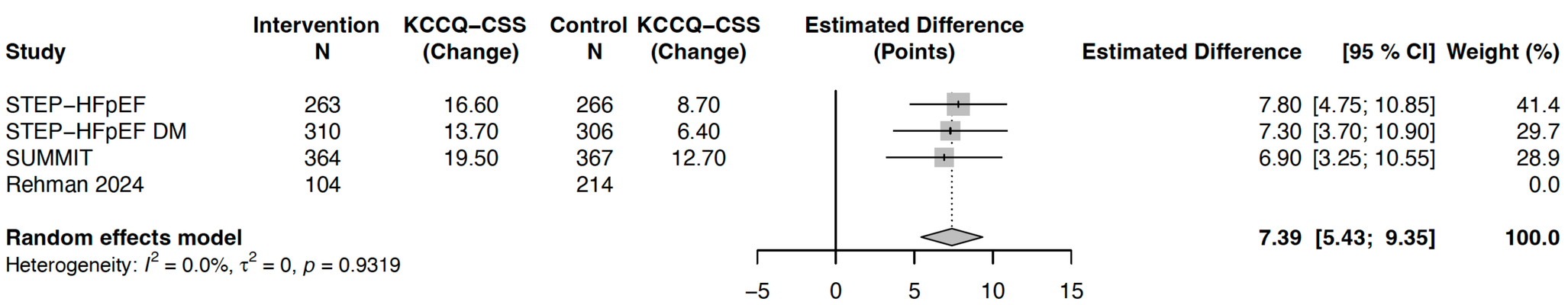
Introduction

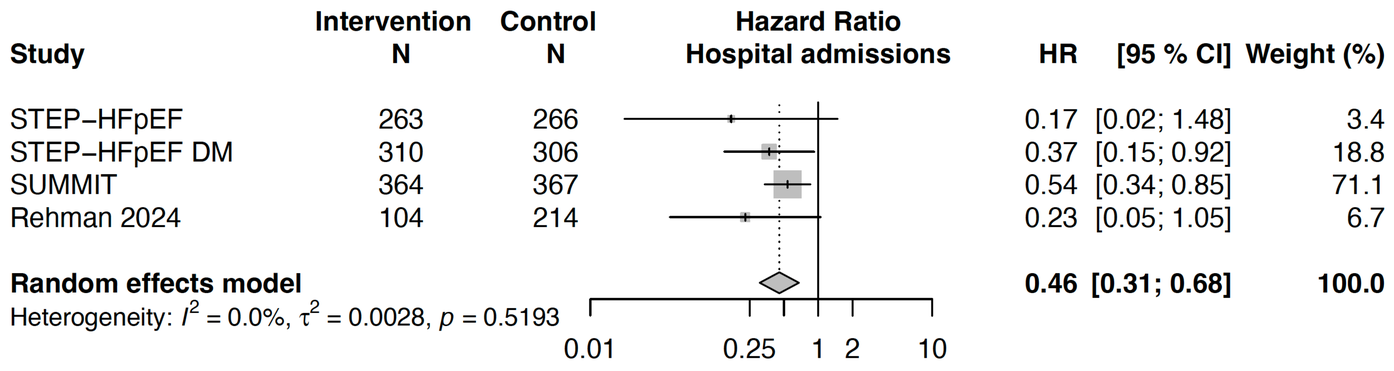
Heart failure with preserved ejection fraction (HFpEF) accounts for more than half of all heart failure cases and is strongly associated with obesity and metabolic syndrome. Patients with HFpEF and obesity experience a higher symptom burden, worse functional capacity, and diminished quality of life, while therapeutic options remain limited. Incretin-based drugs, including semaglutide (a GLP-1 receptor agonist) and tirzepatide (a dual GIP/GLP-1 receptor agonist), have demonstrated cardiovascular and metabolic benefits in other high-risk populations, but their role in HFpEF with obesity is still emerging. This systematic review aimed to evaluate the efficacy and safety of semaglutide and tirzepatide in improving symptoms, exercise capacity, weight, inflammatory markers, and cardiovascular outcomes in this population.

Methods

A systematic search of PubMed, Embase, Scopus, and CENTRAL up to May 2025 identified 626 records. After removal of 183 duplicates, 443 studies were screened and 67 were assessed in full text. Six studies were finally included: five randomized controlled trials, and one retrospective cohort Eligible studies involved adults with HFpEF and obesity or metabolic syndrome receiving semaglutide or tirzepatide, reporting clinical, functional, metabolic, or cardiovascular outcomes. Data extraction was performed independently by two reviewers, and quality assessment was conducted using the Cochrane RoB 2 tool for RCTs and ROBINS-I for the retrospective study.



Meta analysis findings



Results

Change in KCCQ-CSS (points): Across three trials (N=1876), the intervention significantly improved change from baseline in KCCQ-CSS compared with placebo, with a mean difference of +7.39 points (95% CI: 5.43–9.35; p<0.0001). There was no evidence of heterogeneity (I^2=0%, p=0.93).

Change in 6-minute walk distance (metres): Four trials (N=2194) demonstrated a significant improvement in 6-minute walking distance with the intervention, with a pooled mean difference of +16.66 metres (95% CI: 12.02–21.31; p<0.0001). No heterogeneity was detected (I^2=0%, p=0.82).

Hospital admissions: in four trials (N=2194), treatment significantly reduced the risk of hospital admissions compared with placebo (HR 0.46; 95% CI: 0.31–0.68; p=0.0001). Heterogeneity was not evident (I^2=0%, p=0.52).

Change in body weight (%): Four trials (N=2194) showed a significant reduction in body weight with treatment compared with placebo (−6.5%; 95% CI: −9.7 to −3.3; p<0.0001).

Discussion

- Incretin-based therapies (semaglutide and tirzepatide) consistently improved outcomes in HFpEF with obesity. Meta-analysis showed clinically meaningful gains in KCCQ-CSS (+7.4 points) and 6MWD (+16.7 m), alongside a >50% reduction in hospital admissions. Weight loss was significant (−6.5%), though variable across trials.
- Large-scale trials (SELECT, SUMMIT) further support reductions in cardiovascular events, highlighting potential disease-modifying effects. Safety was acceptable with mainly gastrointestinal side effects.
- The available evidence suggests that incretin-based therapies may represent a paradigm shift in the management of HFpEF with obesity, addressing both symptoms and outcomes in a group of patients who historically had few effective options.

Acknowledgements

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