

GLP-1 agonists and GLP-1/GIP dual agonist use in heart failure with preserved ejection fraction

Abstract

Pharmacotherapeutic options for heart failure with preserved ejection fraction (HFpEF) have been historically limited. While treatment options for those with reduced ejection fraction are numerous, the landscape for patients with HFpEF remains an area of interest for researchers. Though the introduction of glucagon-like peptide-1 agonists (GLP-1) and GLP-1/glucose-dependent insulinotropic polypeptide agonists (GIPs) is widely recognized for its treatment indications in type 2 diabetes mellitus and weight-loss, the underlying mechanism has led to advancements and further research into their potential benefits for patients with heart failure. Some GLP-1s have data highlighting their cardioprotective benefits, whereas others are still being evaluated in clinical studies. Over the past few years, the search for potential cardioprotective benefits as result of GLP-1/GIP therapy has made its way into the HFpEF subpopulation of heart failure. This review serves to present a summary of the emerging data for GLP-1/GIP agonists as it relates to heart failure with HFpEF.

Keywords: GLP-1 receptor agonists, GLP-1/GIP dual agonist, HFpEF, heart failure with preserved ejection fraction

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Introduction

Significant improvement in the availability of treatment options for patients with heart failure with preserved ejection fraction (HFpEF) has occurred in the last several years. Guideline-directed medical therapy consists of diuretics, sodium glucose co-transporter 2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor-neprilysin inhibitors (ARNIs).¹ Recently, there has been a shift of focus in clinical studies to obtain data on the cardioprotective benefits of glucagon-like peptide-1 agonists (GLP-1) and GLP-1/glucose-dependent insulinotropic polypeptide agonists (GIPs), particularly as it pertains to patients with HFpEF. Myocardial fibrosis and wall thinning in heart failure with reduced ejection fraction (HFrEF) are downstream effects of systolic dysfunction, whereas HFpEF is a result of progressive left ventricular wall thickening.^{2,3} GLP-1 agonists have been shown to have positive effects on symptoms and outcomes related to heart failure, which makes them a potential medication in the treatment landscape for HFpEF.³ This manuscript presents a mini review of the data related to GLP-1 and GLP-1/GIP agonists in the treatment of HFpEF.

Data sources and selection

A literature review was conducted in PubMed, MEDLINE, National Institutes of Health Clinical Trials Registry, and ClinicalTrials.gov from inception through February 2026, using the search terms GLP-1, GLP-1/GIP, HFpEF. Articles from reference lists were included to identify potential relevant literature. Data was limited to studies published in the English language which evaluated the efficacy and safety of GLP-1 agonists and HFpEF.

Mechanism of action

GLP-1 is an incretin hormone released from intestinal enteroendocrine L-cells and brainstem neurons. Although it is continuously secreted, levels increase rapidly following nutrient intake and decrease during interprandial or fasting states.^{4,5} In response to food ingestion, GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon release, and slows gastric emptying.⁴ Rapid enzymatic breakdown by dipeptidyl peptidase-4

(DPP4) limits its duration of action, prompting the development of GLP-1 agonists. These synthetic analogues are structurally modified and designed to resist degradation, which prolongs their duration of action and enables sustained receptor activity.⁶ This leads to weight reduction by means of appetite suppression and indirect effects such as blood pressure reduction, improved glycemic control, lipid modulation, myocardial effects, and endothelial modulation.^{4,7} Recently, dual incretin therapies have expanded this by combining GLP-1 agonists with GIPs, providing complementary and synergistic metabolic effects. GIP agonists enhance glucose-dependent insulin secretion and improves insulin sensitivity by activating GIP receptors on pancreatic β -cells and peripheral tissues, contributing to improved glycemic control and metabolic regulation. While GLP-1 receptor activation predominantly promotes appetite suppression and weight loss, GIP receptor engagement enhances insulin sensitivity and broader metabolic health, thus emphasizing the benefits of a dual mechanism regimen.⁴

Clinical studies

STEP-HFpEF was a randomized, double-blind, placebo controlled clinical study published in 2023 that evaluated the effect of 2.4 mg of semaglutide weekly on physical limitation and symptom reduction, improved exercise function, and weight loss in patients with heart failure with preserved ejection fraction and obesity. Patients aged 18 years or older were included if they had documented left ventricular ejection fraction (LVEF) of at least 45%, a body-mass index (BMI) of at least 30 kg/m², New York Heart Association (NYHA) functional class II, III, or IV symptoms, a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) of less than 90 points, and a 6-minute walk distance of at least 100 meters. Patients were excluded if they had a known history of diabetes. The primary outcome assessed dual endpoints of change in KCCQ-CSS score and body weight, demonstrating an estimated difference of 7.8 point increase in KCCQ-CSS score and a 10.7% reduction in body weight from baseline.⁸

SUMMIT was an international, double-blind, randomized, placebo-controlled clinical study published in 2024 and evaluated

the effect of tirzepatide on cardiovascular death and worsening heart-failure events, health status, and functional capacity. Patients aged 40 years or older were included if they had chronic heart failure (defined as NYHA class II to IV), a LVEF of at least 50%, a BMI of at least 30 kg/m², a 6-minute walk distance of between 100 and 425 meters, and a KCCQ-CSS of 80 points or lower. The dual primary endpoints of this study were: an adjudicated death either from cardiovascular causes or a worsening heart failure event, and a change in KCCQ-CSS at 52 weeks. The study found a 38% risk reduction (hazard ratio, 0.62; 95% confidence interval [CI], 0.41 to 0.95; P=0.026) in cardiovascular death and worsening heart-failure and a between-group difference in change in KCCQ-CSS score of 6.9 (95% CI, 3.3 to 10.6; P<0.001) at 52 weeks.⁹

DUP-TIRZSEMA was a non-randomized, non-interventional clinical study that compared the effects of tirzepatide vs semaglutide on a primary composite end point of all-cause mortality or heart failure hospitalization in patients with cardiometabolic HFpEF in clinical practice. Insurance claims data were used to identify patients who had received semaglutide and tirzepatide based on criteria from STEP-HFpEF and SUMMIT studies. Results were published in August 2025 and revealed that there was no clinically meaningful difference in the pooled 1-year risk of the primary endpoint: tirzepatide 3.3% (95% CI, 2.8% to 3.9%) and semaglutide 3.4% (95% CI, 2.9% to 4.1%), with a risk difference of -0.1% (95% CI, -0.9% to 0.7%; number needed to treat=1000). In addition, in analyses using expanded eligibility criteria assessing a sitagliptin cohort, the authors concluded that in patients with cardiometabolic HFpEF, the initiation of tirzepatide or semaglutide had more than a 40% lower risk of all-cause mortality or heart failure hospitalization, compared to sitagliptin, which historically has shown no added benefit in heart failure patients.¹⁰

Conclusion

The results of the STEP-HFpEF, SUMMIT, and DUP-TIRZSEMA studies show promising data for patients with HFpEF and obesity regarding treatment with GLP-1 and GLP-1/GIP agonists. Improvement in various outcomes (KCCQ-CSS score, body weight, heart failure hospitalizations, and all-cause mortality) following treatment with GLP-1 and GLP-1/GIP dual-agonists in patients with HFpEF demonstrates their potential utility in this medical condition. Future studies should continue to demonstrate positive results, should there be a place in guideline-directed medical therapy for the GLP-1 and GLP-1/GIP classes in patients with HFpEF and obesity.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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