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Dr. Phelopater Sedrak is an internal medicine resident at the University of Toronto, where he also completed his medical school education. His academic interests are in novel therapies for heart failure and the promotion of health equity in inpatient practices. Dr. Sedrak is actively involved in teaching and mentoring medical students across various stages of their training. He also has an interest in advancing the point of care ultrasound curriculum. He has received multiple awards for clinical excellence in patient care at the undergraduate medical level.

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The Role of GLP-1R and GIPR Agonism in Heart Failure

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Take Home Messages

- GLP-1RA and GLP-1R/GIPR dual agonism is safe and beneficial for patients with HF across the LVEF spectrum, but especially in obesity-related HFpEF.
- Semaglutide has shown favourable outcomes in both the STEP-HFpEF and STEP-HFpEF DM trials, while tirzepatide has demonstrated favourable outcomes in the SUMMIT trial.
- The proposed mechanism for GLP-RA in HF is through the promotion of favourable reverse cardiac remodelling and the reduction of inflammation.

Introduction

Heart failure (HF) is a clinical syndrome characterized by signs and symptoms of structural and functional cardiac abnormalities. It is corroborated by elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and objective evidence of pulmonary or systemic congestion. More than 100,000 Canadians are diagnosed with HF annually. For years, HF has been classified based on left ventricular ejection fraction (LVEF). HF with reduced ejection fraction (HFrEF) refers to symptomatic HF with an LVEF <40%. However, if the LVEF is >50%, this is known as HF with preserved ejection fraction (HFpEF). In HFpEF, obesity is commonly implicated in the disease pathophysiology, and is present in up to 80% of people with this condition.[1-3] Obesity contributes to concentric heart remodelling through mechanisms such as insulin resistance, diabetes, hyperlipidemia, visceral adipose tissue expansion, and myocardial steatosis.[1] Additionally, obesity leads to a pro-inflammatory state which affects the vasculature and visceral organs.[2] Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, have shown promise in weight reduction across multiple Phase 3 clinical trials. Agents combining GLP-1RA and glucose-dependent insulinotropic peptide receptor (GIPR) agonism, such as tirzepatide, have also contributed to clinically significant weight loss. As such, their impact in addressing obesity-related HFpEF is under investigation.[1] This paper reviews the data on GLP-1RAs and tirzepatide in patients with HF across the LVEF spectrum, with a particular focus on those with HFpEF.

Evidence from Earlier Trials: Are GLP-1RAs safe in Heart Failure?

Concerns were raised about the use of GLP-1RAs in the context of HF. The Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial was the first to raise safety concerns associated with the use of liraglutide in patients with type 2 diabetes mellitus (T2DM) and HF. FIGHT, a Phase 2 trial, randomized 300 participants to receive either liraglutide or placebo. There were no significant differences between the groups in the primary end point, which included the number of deaths, re-hospitalization for HF, or the composite of death or re-hospitalization for HF. Although the effect was not statistically significant, the authors commented that the rates of HF re-hospitalization were higher in the liraglutide group.[4] The Liraglutide on Left Ventricular Function (LIVE) study was a randomized, placebo-controlled trial that investigated the effects of liraglutide in participants with HF and an LVEF <45%. The

primary outcome they measured was the change in LVEF, with secondary outcomes including changes in plasma NT-proBNP levels. Liraglutide was associated with an increase in heart rate by 6 beats per minute compared to placebo.[5] As a result, a publication in 2020 included the following: "The uncertainty regarding the effect of GLP-1RAs in patients with HFrEF suggested in the smaller LIVE and FIGHT trials, coupled with the pharmacodynamic profile of GLP-1RAs including some plausibly pernicious secondary effects, raise concerns about their use in patients with HFrEF. These concerns make it incumbent to have dedicated randomized trials powered to properly assess clinical outcomes with the use of GLP-1RAs in patients with T2DM who have American College of Cardiology/American Heart Association stage C HF to firmly establish the risk/benefit ratio in these patients".[6]

A meta-analysis of seven cardiovascular outcomes trials on GLP-1RAs presented a pooled analysis of this class of drugs on cardiovascular (CV), kidney, and safety outcomes.[7] Across all trials, the prevalence of a history of HF in trial participants ranged from 9% to 24%, with an average prevalence of 17%. On average, 79% of study participants had established cardiovascular disease. This study has demonstrated the positive impact of GLP-1RAs, showing a 12% reduction in all-cause mortality (hazard ratio [HR] 0.88, p=0.001), a 9% reduction in hospital admissions for HF (HR 0.91, p=0.028), and a 17% improvement in composite kidney outcomes (HR 0.83, p<0.001).[7] This meta-analysis included a larger number of participants than the earlier FIGHT and LIVE trials, and commented that GLP-1RAs have an acceptable safety profile. Thus, in the broad population of HF patients included in this study, there was no signal for harm and a signal for potential benefit. However, further validation of this association requires dedicated trials to investigate these agents in HF patients.

Semaglutide Heart Failure Clinical Trials

The STEP-HFpEF trial included 529 participants with an LVEF >45% and a body mass index (BMI) of at least 30. They were followed for a duration of 52 weeks. The study compared 2.4 mg of semaglutide with a placebo and found a statistically significant difference in the 2 primary end points: the change in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and the percentage change in body weight. Additionally, there was a 21.5 meter improvement in the 6-minute walk distance (6MWD) and a reduction in C-reactive protein (CRP) levels.[8] The STEP-HFpEF DM trial had a similar design and measured outcomes. It included 616 participants, all of whom had T2DM. Semaglutide showed similar improvements in the KCCQ-CSS scores and 6MWD, along with reductions in body weight and CRP levels.[9] However, the rate of treatment discontinuation was higher in the semaglutide group in both trials, owing mainly to gastrointestinal events. Overall, the trials demonstrated that semaglutide significantly improved HF-related symptoms, physical limitations, and exercise function while promoting weight reduction.[10]

Tirzepatide Heart Failure Clinical Trial

The recently published SUMMIT trial investigated tirzepatide in patients with HFpEF and a BMI >30. This international, double-blind study randomized 731 participants to receive up to 15 mg of tirzepatide or a placebo. The primary outcome was a hierarchical composite of death from any cause including adjudicated death from CV causes or a worsening HF event resulting in hospitalization, the use of intravenous drugs in an urgent care setting, or the intensification of oral diuretic therapy. In addition, changes in the KCCQ-CSS score, the 6MWD, body weight, and CRP levels were taken into account. At 52 weeks of follow-up, the trial demonstrated that tirzepatide significantly reduced the risk of CV death or worsening HF compared to placebo. Specifically, worsening HF events occurred in 8.0% of tirzepatide-treated patients versus 14.2% in the placebo group. In addition, similar to semaglutide, tirzepatide resulted in a greater improvement in KCCQ-CSS scores, 6MWD, body weight reduction, and CRP levels compared to the placebo.[11] **Table 1** presents a summary of the trial design for these dedicated HF trials.

Contemporary Studies of GLP-1RA/GIPR Agonists Across the Spectrum of Heart Failure

In 2017, the EXSCEL trial investigated the effects of once-weekly exenatide in 14,752 patients with T2DM. While the primary outcome was the three-component major adverse cardiovascular event (3P-MACE), the study also evaluated worsening HF, hospitalization for HF

Trial	Inclusion Criteria	Participants	Outcomes
STEP-HFpEF (semaglutide)	LVEF >45% BMI >30	529	Δ in KCCQ-CCS; Δ in body weight; 6MWD; CRP level
STEP-HFpEF DM (semaglutide)	LVEF >45% BMI >30 HbA1c 6.5%–10%	616	Δ in KCCQ-CCS; Δ in body weight; 6MWD; CRP level
SUMMIT (tirzepatide)	LVEF >50% BMI >30	731	Death from CV causes; worsening HF event; Δ in KCCQ-CCS; Δ in body weight; 6MWD; CRP level

Table 1. The inclusion criteria and measured outcomes in the dedicated HF trials for semaglutide and tirzepatide.[8-11]

Abbreviations: 6MWD: 6-minute walk distance; **BMI:** body mass index, **CRP:** C-reactive protein, **DM:** diabetes mellites, **CV:** cardiovascular, **HF:** heart failure, **HFpEF:** heart failure with preserved ejection fraction, **KCCQ-CCS:** *Kansas City Cardiomyopathy Questionnaire* clinical summary score, **LVEF:** left ventricular ejection fraction.

(HHF), and death from CV causes.[12] Similarly, the SELECT trial assessed a composite HF endpoint, which included death from CV causes, hospitalization, or an urgent medical visit for HF, in 17,604 participants with obesity but without T2DM.[13] In a prespecified analysis of the SELECT trial, over 4,000 patients with atherosclerotic cardiovascular disease (ASCVD) were found to have a history of HF at enrolment. The benefits observed with semaglutide did not differ in patients with HFpEF compared with HFrEF.[14] These efficacy findings were in contrast to earlier studies suggesting that the use of GLP-1RAs in HF may be ineffective or even harmful.[4-6] In July, 2024, the FLOW trial reported on HF outcomes in 3,533 participants with T2DM and chronic kidney disease comparing semaglutide to a placebo.[15] A meta-analysis that combined results from these three trials, in addition to STEP-HFpEF, STEP-HFpEF DM, and SUMMIT, showed the benefit of GLP-1RAs and tirzepatide in reducing worsening HF events across the LVEF spectrum, with acceptable safety outcomes.[16-17] A summary of the timeline of the trials is presented in **Table 2**.

The Proposed Mechanisms of GLP-1RAs and GLP-1RA/GIPR Agonists in Heart Failure

The echocardiographic sub-study of the STEP-HFpEF clinical trial program found that semaglutide led to a reduction in left atrial (LA) volume and right ventricular dimensions, both of which are critical markers of adverse remodelling in HFpEF.[18] Additionally, semaglutide improved E-wave velocity, E/A ratio, and E/e' ratio, indicating enhanced diastolic relaxation and reduced left ventricular (LV) filling pressures. The observed correlation between greater weight loss and reductions in LA volume suggests that the primary driver behind the cardiac benefits of semaglutide in HFpEF may be its ability to reverse obesity-related cardiac structural abnormalities. These benefits were accompanied by reductions in CRP levels and NT-proBNP, suggesting an anti-inflammatory and congestion-relieving effect. The impact of semaglutide on promoting significant weight loss therefore contributes to its cardiac benefits by reducing ventricular strain, systemic inflammation, and myocardial stiffness.[18]

The SUMMIT trial and its secondary analyses have provided compelling evidence that tirzepatide improves cardiac structure and function by reducing LV mass, para-cardiac adipose tissue, and circulatory overload.[19-20] Cardiac magnetic resonance imaging demonstrated a significant reduction in LV mass with tirzepatide, which correlated with weight loss and improvements in waist circumference and blood pressure.[19] This suggests that the effect of tirzepatide on cardiac remodelling may be mediated through a combination of direct myocardial unloading and systemic metabolic improvements. Furthermore, tirzepatide decreased paracardiac adipose tissue, which is a known contributor to myocardial inflammation and fibrosis in obesity-related HFpEF. Beyond structural changes, tirzepatide also addressed hemodynamic

Study	Year	Outcome
FIGHT	2016	Liraglutide was associated with a higher rate of HF rehospitalization.
LIVE	2016	Liraglutide was associated with a 6 bpm increase in heart rate.
EXSCEL	2017	A meta-analysis of these 6 trials demonstrated the safety and benefit of GLP-1RAs and tirzepatide in participants with HF across the LVEF spectrum, but especially in patients with obesity-related HFpEF.
STEP-HFpEF	2023	
SELECT	2023	
STEP-HFpEF DM	2024	
FLOW	2024	
SUMMIT	2025	

Table 2. Early concerns and the cumulative evidence on GLP-1R and GIPR agonism in participants with HF.[4-5,12-17]

Abbreviations: bpm: beats per minute, **GLP-1RA:** glucagon-like peptide-1 receptor agonists, **GIPR:** glucose-dependent insulinotropic peptide receptor, **HF:** heart failure, **HFpEF:** heart failure with preserved ejection fraction, **LVEF:** left ventricular ejection fraction.

abnormalities characteristic of HFpEF. The secondary analysis of the SUMMIT trial showed that tirzepatide reduced circulatory volume expansion, lowered systolic blood pressure, and decreased systemic inflammation, as evidenced by reductions in CRP and troponin T levels.[20] Additionally, the improvement in the estimated glomerular filtration rate and the reduction in urine albumin-to-creatinine ratio suggest that tirzepatide confers renal protective effects, which may further contribute to favourable hemodynamic modulation.[20]

These findings highlight the potential of both agents as disease-modifying therapies in obesity-related HFpEF, targeting both myocardial remodelling and systemic congestion, as shown in **Figure 1**. Collectively, these effects correlate with improvements in symptoms, tolerance of exertion, and quality of life.

New and Ongoing Trials

The SOUL trial was a randomized, double-blind, parallel-group, placebo-controlled cardiovascular outcomes superiority trial involving patients with T2DM and established ASCVD.[21] In this trial, 23% of the patients had prevalent HF. The participants were randomized to receive either once-daily oral semaglutide up to 14 mg or a placebo, in addition to standard care. A notable aspect of this study was that 49% of the participants received a sodium-glucose cotransporter-2 inhibitor (SGLT2-i) at some point during the trial. On March 29, 2025, the study reported on the time to the first occurrence of MACE and a composite kidney outcome.[22] There was a statistically significant reduction in 3P-MACE among participants treated with oral semaglutide versus a placebo. However, the differences in the secondary outcomes, which included major kidney disease events and three-point composite for heart failure events (death from CV causes, an urgent visit for HF, or HHF) were not significant.[22] This suggests that patients with HF already receiving an SGLT2-i would benefit from GLP-1RA therapy, with additional efficacy in terms of 3P-MACE.

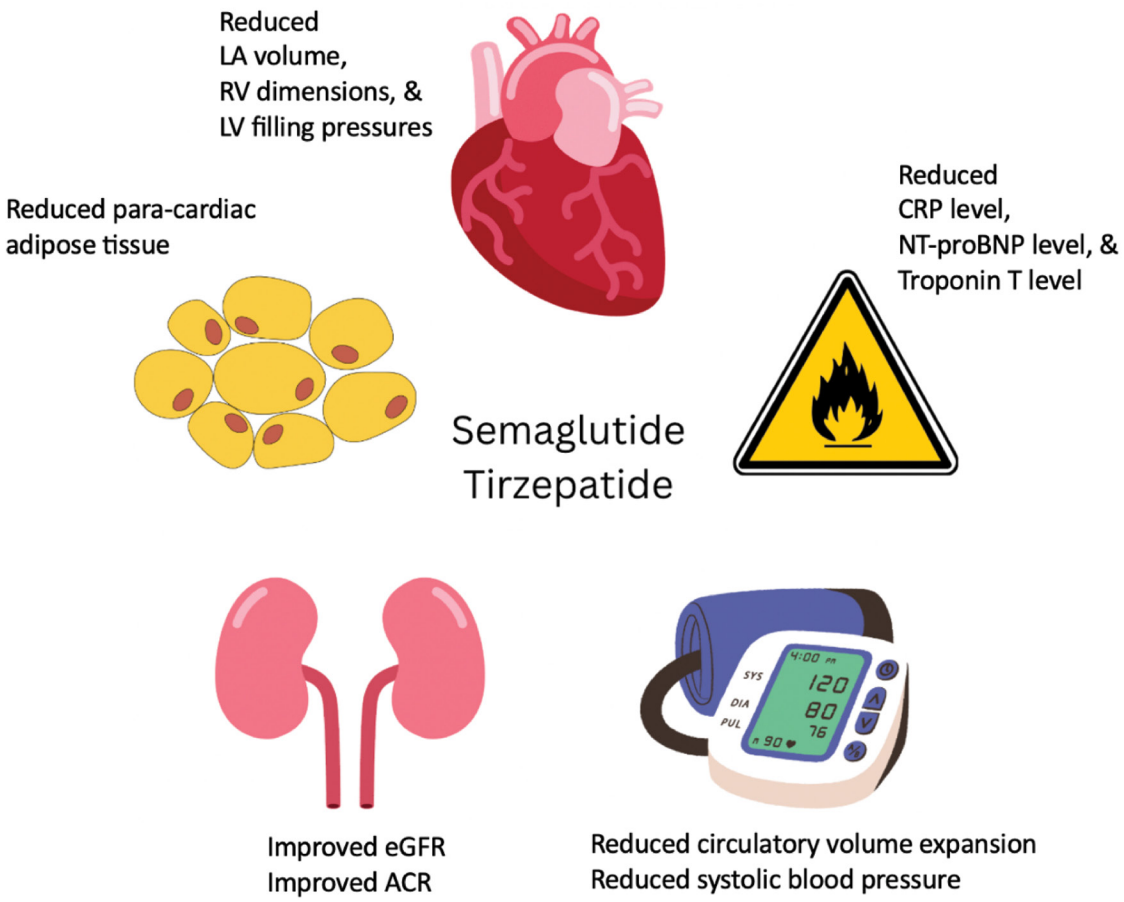

Figure 1. The proposed mechanisms by which semaglutide and tirzepatide contribute to improved HF outcomes; *courtesy of Phelopater Sedrak, MD and Kim Connelly, MBBS, PhD.*

Abbreviations: ACR: albumin-creatinine ratio, **CRP:** C-reactive protein, **eGFR:** estimated glomerular filtration rate, **LA:** left atrial, **LV:** left ventricular, **NT-proBNP:** N-terminal pro-B-type natriuretic peptide, **RV:** right ventricular.

Regarding ongoing trials, SURMOUNT-MMO is a Phase 3 randomized, placebo-controlled study designed to evaluate the impact of tirzepatide on reducing morbidity and mortality in adults with obesity. The study started on October 11, 2022, and is expected to conclude in October, 2027. The primary objective is to assess whether tirzepatide can effectively reduce the incidence of MACE in people with ASCVD or those at high-risk for primary prevention who are living with obesity but do not have diabetes. The SURPASS-CVOT is a Phase 3 randomized, active controlled study designed to evaluate the CV safety and efficacy of tirzepatide compared to dulaglutide in adults with T2DM and established ASCVD. The primary endpoint is the time to the first occurrence of MACE. The primary analysis aims to demonstrate that tirzepatide is not inferior to dulaglutide by establishing an upper confidence limit of less than 1.05 for the HR, which would also confirm its superiority to a putative placebo. The trial is fully recruited and ongoing.

Conclusion

Medical management of HF has seen significant advances in recent decades, including most recently with the introduction of SGLT-2i agents. The recent data unequivocally removes any concerns of harm regarding the safety of GLP-1RA monotherapy or GLP-1RA and GIPR agonism. Furthermore, these agents have shown clear improvements in quality of life, functional status, and a reduction in HF admissions across the LVEF spectrum. This effect is observed in patients already receiving standard therapies for HF and demonstrates the additive effect of these agents. Current Canadian guidelines focus on the use of these agents in patients with HF and known T2DM, have/are overweight or obesity, and have ASCVD or multiple risk factors for ASCVD.[23] The proposed mechanisms include promoting favourable cardiac remodelling, and reducing inflammation and congestion. Ongoing trials continue to measure HF outcomes in various populations, which will allow for the integration of these agents into standard care.

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