Cardiovascular Implications of Semaglutide in Obesity Management: Redefining Cardiovascular Health Strategies

Aditya John Binu[1] and Nitin Kapoor[2,3]

1. Department of Cardiology, Christian Medical College, Vellore, Tamil Nadu, India; 2. Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India; 3. Non-Communicable Disease Unit, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

Semaglutide is a glucagon-like peptide 1 receptor agonist that has been noted to have a significant role in the reduction of body weight and glycaemic control. An increasing body of evidence from recent trials (SUSTAIN-6, SELECT and STEP HF) has shown significant cardiovascular benefits of semaglutide in both patients with and without diabetes and in people who are obese or overweight. Additional studies in a more diverse patient population and safety assessment are warranted prior to adding semaglutide to the increasing pool of guideline-directed medical therapy for the treatment and prevention of cardiac diseases.

Keywords

Cardiovascular risk, diabetes mellitus, glucagon-like polypeptide, glucagon-like peptide-1 (GLP-1) receptor agonists, incretins, obesity, semaglutide

Disclosures: Aditya John Binu and Nitin Kapoor have no financial or non-financial relationships or activities to declare in relation to this article.

Acknowledgements: We would like to acknowledge the Mentorship Program of Christian Medical College, Vellore, Tamil Nadu, India, for bringing the authors together to draft this manuscript.

Review Process: Double-blind peer review.

Compliance with ethics: This article is an opinion piece and does not report on new clinical data, or any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Received: 19 February 2024

Accepted: 22 April 2024

Published online: 22 May 2024

Citation: *Heart International.* 2024;18(1):Online ahead of journal publication

Corresponding author: Dr. Nitin Kapoor, Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore-632004, Tamil Nadu, India. E: nitin.endocrine@gmail.com, nitin.kapoor@cmcvellore.ac.in

Support: No funding was received in the publication of this article.

Glucagon-like peptide 1 (GLP-1) receptor agonists piqued our interest when Marso et al. demonstrated that liraglutide significantly reduced cardiovascular events (CVEs) in persons with type 2 diabetes mellitus (T2DM) who were at a high cardiovascular (CV) risk compared with placebo in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ClinicalTrials.gov identifier: NCT01179048) trial.[1] Semaglutide is a GLP-1 analogue with 94% amino acid homology to native GLP-1 with a half-life of 160 h, which can safely be administered as a once-weekly subcutaneous (SC) regimen.[2] Phase II clinical trials on semaglutide commenced in June 2008.[2] Semaglutide has been shown to provide significant reductions in glycated haemoglobin (HbA1c) and body weight in patients with T2DM.[2] The STEP 1 (Semaglutide Treatment Effect in People with Obesity Program 1; ClinicalTrials.gov identifier: NCT03548935) trial found that a regimen of 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reductions in body weight in patients who were obese or overweight and did not have diabetes (body mass index [BMI] ≥30 kg/m^2 and ≥27 in persons with one or more weight-related coexisting conditions) after 68 weeks of treatment.[3]

Evidence for cardiovascular benefits

Numerous clinical trials have been conducted to shed light on the CV benefits of semaglutide. In the SUSTAIN-6 (Semaglutide in Subjects with Type 2 Diabetes 6; ClinicalTrials.gov identifier: NCT01720446) trial published in September 2016, a total of 3,297 patients with T2DM were randomized to receive either once-weekly semaglutide (0.5 or 1.0 mg) or placebo for 104 weeks.[4] This trial showed that the rate of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke was significantly lower among patients receiving semaglutide than placebo in patients with T2DM at a high CV risk (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.58–0.95; p<0.001 for non-inferiority). The PIONEER-6 (Peptide Innovation for Early Diabetes Treatment; ClinicalTrials.gov identifier: NCT02692716) trial published in June 2019 was a randomized, placebo-controlled, phase III trial to assess CV outcomes with oral semaglutide in patients at a high CV risk (age ≥50 years with established CV disease or chronic kidney disease or age ≥60 years with CV risk factors only).[5] The primary outcome in a time-to-event analysis was the first occurrence of major adverse cardiovascular events (MACEs), such as death from CV events, non-fatal MI or non-fatal stroke. The CV risk profile of oral semaglutide was determined to be non-inferior to that of placebo (HR, 0.79; 95% CI, 0.57–1.11; p<0.001 for non-inferiority). Gastrointestinal (GI) adverse events (AEs) leading to discontinuation of oral semaglutide were noted in this trial.

The improvement in CV outcomes with GLP-1 receptor agonists was attributed to their effects on numerous metabolic pathways associated with glucose metabolism, homeostasis and inflammation, hypothesizing that they improve CV outcomes among non-diabetic subjects as well. The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity; ClinicalTrials.gov identifier: NCT03574597) trial was a landmark trial published in November 2023, which was a multicentre, double-blind, randomized, placebo-controlled trial to study the

superiority of semaglutide compared with placebo in reducing the risk of MACE among overweight or obese patients with preexisting CV diseases who did not have diabetes.[6] In this study, 17,604 patients aged ≥45 years who had preexisting CV diseases and a BMI of ≥27 kg/m^2 but no history of diabetes were randomized in a 1:1 ratio to receive once-weekly SC semaglutide at a dose of 2.4 mg or placebo. The primary outcome assessed was a composite of CV death, non-fatal MI or non-fatal stroke in a time-to-first-event analysis. The primary composite CV outcome was noted to be significantly lower in the semaglutide group (6.5% versus 8.0%; HR, 0.80; 95% CI, 0.72–0.90; p<0.001) at a mean follow-up duration of 39.8 months. AEs leading to discontinuation of semaglutide were significantly higher in the semaglutide group (16.6% versus 8.2%; p<0.001); these included GI- and gall bladder-related disorders. The effects of semaglutide were observed to occur early after the treatment initiation. An important limitation of the SELECT trial was that it included only patients with preexisting CV diseases. The effects of semaglutide on the primary prevention of CVEs in persons with overweight or obesity but without previous atherosclerotic disease were not assessed. Another drawback was the limited diversity among patients.

The effects of semaglutide in patients who were obese with features of heart failure with preserved ejection fraction (HFpEF) were studied in the STEP-HFpEF (Semaglutide Treatment Effect in People With Obesity and HFpEF; ClinicalTrials.gov identifier: NCT04788511) trial.[7] In this trial, 529 patients with HFpEF and a BMI of ≥30 kg/m^2 were randomized to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The two primary outcomes studied were the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) from baseline and the change in body weight. The mean change in the KCCQ-CSS was significantly higher in the semaglutide group (16.6 versus 8.7 points [estimated difference, 7.8 points; 95% CI, 4.8–10.9; p<0.001]). The mean percentage change in body weight was also noted to be higher with semaglutide (–13.3% versus –2.6% [estimated difference, –10.7%; 95% CI, –11.9 to –9.4; p<0.001). The mean change in the 6-minute walk distance was 21.5 m with semaglutide and 1.2 m with placebo (estimated difference, 20.3 m; 95% CI, 8.6–32.1; p<0.001). On analyzing the hierarchical composite endpoint, semaglutide produced more wins than placebo (win ratio, 1.72; 95% CI, 1.37–2.15; p<0.001). In patients who were obese with HFpEF, semaglutide led to higher reductions in symptoms and physical limitations, higher magnitude of improvement in exercise function and increased weight loss compared with placebo. A significant limitation of the STEP-HFpEF trial was that it was not adequately powered to evaluate clinical events, such as hospitalizations for heart failure and urgent visits. The STEP-HFpEF DM (Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus; ClinicalTrials.gov identifier: NCT04916470) trial randomized 616 patients who had HFpEF, a BMI of ≥30 and T2DM to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks.[8] The primary endpoints were the change from baseline in the KCCQ-CSS and the change in body weight. The mean change in the KCCQ-CSS was again significantly higher in the semaglutide group (13.7 versus 6.4 points [estimated difference, 7.3 points; 95% CI, 4.1–10.4; p<0.001]), while the mean percentage change in body weight was again noted to be higher with semaglutide (–9.8% versus –3.4% [estimated difference, –6.4%; 95% CI, –7.6 to –5.2; p<0.001]).

Adverse effects and other concerns

Semaglutide was approved by the U.S. Food and Drug Administration (FDA) in December 2017 for the treatment of T2DM in adults.[9] The FDA expanded the indication of semaglutide in January 2020 to include adults with T2DM and CV disease based primarily on the results of the SUSTAIN-6 clinical trial; this was followed by the FDA approval for semaglutide use in long-term weight management in obese or overweight adults in June 2021.[10]

The most common AEs reported with GLP-1 receptor agonists were GI disorders, such as nausea, diarrhoea, vomiting and abdominal pain.[10] Their use may also be associated with a risk of acute pancreatitis and thyroid cancer.[11] Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.[12] The FDA has also been evaluating the reports of suicidal thoughts or actions in patients treated with GLP-1 receptor agonists.[13] Although the preliminary evaluation is yet to unearth the significant evidence that their use may cause suicidal ideations or actions, the FDA is continuing its investigations into this matter.

Conclusion

Semaglutide is another significant addition to the armamentarium to counter the CV risk in susceptible patients in addition to glycaemic control and obesity management. In March 2024, semaglutide became the first weight loss medication to also be approved by the FDA to help prevent life-threatening CV events in adults with CV disease and either obesity or overweight.[14] Data from recent trials further reinforce the evidence that GLP-1 receptor agonists have a role in the reduction of MACE as well as symptomatic relief. Additional studies may be required to assess concerns regarding dosing and safety profile as well as a more diverse patient pool before it may be added to the guidelines for the management of CV diseases. ❑

1. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–22. DOI: 10.1056/NEJMoa1603827.
2. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open- label liraglutide in patients with type 2 diabetes. *Diabetes Care*. 2016;39:231–41. DOI: 10.2337/dc15-0165.
3. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384:989–1002. DOI: 10.1056/NEJMoa2032183.
4. Marso SP, Holst AG, Vilsbøll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2017;376:891–2. DOI: 10.1056/NEJMc1615712.
5. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841–51. DOI: 10.1056/NEJMoa1901118.
6. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221–32. DOI: 10.1056/EJMoa2307563.
7. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med*. 2023;389:1069–84. DOI: 10.1056/NEJMoa2306963.
8. Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *N Engl J Med*. 2024;390:1394–407. DOI: 10.1056/NEJMoa2313917.
9. US Food Drug Administration, Washington. OZEMPIC (Semaglutide) injection, for subcutaneous use. highlights of prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf (Date last accessed: 14 January 2024).
10. Shu Y, He X, Wu P, et al. Gastrointestinal adverse events associated with semaglutide: A pharmacovigilance study based on FDA adverse event reporting system. *Front Public Health*. 2022;10:996179. DOI: 10.3389/fpubh.2022.996179.
11. Smits MM, Van Raalte DH. Safety of semaglutide. *Front Endocrinol*. 2021;12:645563. DOI: 10.3389/fendo.2021.645563.
12. Chao AM, Tronieri JS, Amaro A, Wadden TA. Clinical insight on semaglutide for chronic weight management in adults: Patient selection and special considerations. *Drug Des Devel Ther*. 2022;16:4449–61. DOI: 10.2147/DDDT.S365416.
13. US Food and Drug Administration. Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity. 2024. Available at: www.fda.gov/drugs/drug-safety-and-availability/update-fdas-ongoing-evaluation-reports-suicidal-thoughts-or-actions-patients-taking-certain-type (Date last accessed: 14 January 2024).
14. US Food and Drug Administration. FDA approves first treatment to reduce risk of serious heart problems specifically in adults with obesity or overweight. 2024. Available at: www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-reduce-risk-serious-heart-problems-specifically-adults-obesity-or (Date last accessed: 18 April 2024).