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Investigation of clinical outcomes on the oral or injectable use of semaglutide and cardiovascular risks: a systematic review

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Abstract

Introduction: In the context of GLP-1 analogs and cardiovascular risks, both subcutaneous and oral formulations of semaglutide have undergone extensive phase 3 clinical trials. **Objective:** It was to analyze, through a systematic review, the main clinical findings of the oral or injectable use of semaglutide and its relationship with cardiovascular risks. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from November 2024 to January 2025 in the Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 132 articles were found. A total of 35 articles were fully evaluated and 25 articles were included. According to the GRADE instrument, most of the studies presented homogeneity in their results, with X^2 = 87.5%> 50%. It was concluded that subcutaneous injection is more likely to result in endocrine-related adverse events. Oral administration is more likely to induce gastrointestinal adverse events. Furthermore, it significantly accelerates the onset of adverse reactions. As one of the newer agents in the class, the safety of semaglutide in both subcutaneous and oral formulations has been examined in phase 3 and CVOT programs. However, no major safety concerns have emerged to date, although definitive conclusions for pancreatic cancer, thyroid cancer, and complications of polycystic kidney disease cannot be drawn at this time. Compared with the beneficial effects of these drugs on glucose metabolism, blood pressure, body weight, and cardiovascular (and potentially even renal) outcomes, these agents have an overall beneficial risk/benefit profile for treating patients with T2DM. GLP-1RAs are safe, well tolerated, and improve cardiovascular outcomes, largely independent of their antihyperglycemic properties, but they remain underutilized by cardiologists and require therapy management in patients with T2DM and established atherosclerotic cardiovascular disease or high risk for established atherosclerotic cardiovascular disease.

Keywords: Semaglutide. GLP-1 analogues. Oral. Injectable. Cardiovascular risk sclerosus. Nutrology. Immunity. Gut microbiota. Treatments.

Introduction

In the context of GLP-1 analogs and cardiovascular risks, semaglutide, when compared to liraglutide (administered once daily), has a longer half-life, allowing once-weekly dosing. Although this is a significant improvement over once- or twice-daily subcutaneous administration, the injection route may be a barrier for some potential users **[1]**. An absorption enhancer has been discovered (sodium N-8-(2-hydroxybenzoyl) aminocaprylate or SNAC), which, when co-administered with semaglutide, has been shown to provide therapeutic levels of the latter **[2]**.

SNAC helps protect semaglutide from proteolytic degradation in the stomach and facilitates its absorption across the gastric mucosa by transient effects on

transcellular pathways. At equivalent exposure levels, similar glycaemic and weight responses were observed with oral and subcutaneous semaglutide **[3]**. In this regard, both subcutaneous and oral formulations of semaglutide have undergone extensive phase 3 clinical trials. For the once-weekly subcutaneous formulation, the SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) program included 13 separate phase 3a and 3b randomized clinical trials **[4–11]**. SUSTAIN 1–10 were global international trials, while three additional trials were specific to China and Japan. In four studies, semaglutide was compared with placebo in different patient populations. SUSTAIN-6 is the cardiovascular outcome trial (CVOT) of subcutaneous semaglutide **[11]**.

In addition, the PIONEER (Peptide InnOvatioN for the Early diabEtes tReatment) program comprised 10 individual trials comparing once-daily oral semaglutide with placebo (six studies) or an active comparator in different populations. Similar to the SUSTAIN program, PIONEER 6 was the CVOT. PIONEER 9 and 10 are specific to the Japanese population **[6,7]**. The SOUL (A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes) study is a larger CVOT with oral semaglutide that is ongoing (NCT03914326). Combining all individual studies, the SUSTAIN program contained almost 12,000 participants, with over 9,500 individuals in the PIONEER program. With a treatment duration of at least 26 weeks, this represents many years of patient follow-up, allowing for an adequate review of semaglutide safety **[10]**.

Therefore, the present study aimed to analyze through a systematic review the main clinical findings of oral or injectable semaglutide use and its relationship with cardiovascular risks.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 11/17/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 11/17/2024.

Search Strategy and Search Sources

The search strategies for this systematic review were based on the keywords (DeCS /MeSH Terms): *Semaglutide. GLP-1 analogs. Oral. Injectable. Cardiovascular risk*. The search was conducted from November 2024 to January 2025 in the Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 15 years were selected. In addition, a combination of keywords with the Boolean terms "OR", "AND" and the operator "NOT" were used to target the scientific articles of interest.

Study Quality and Risk of Bias

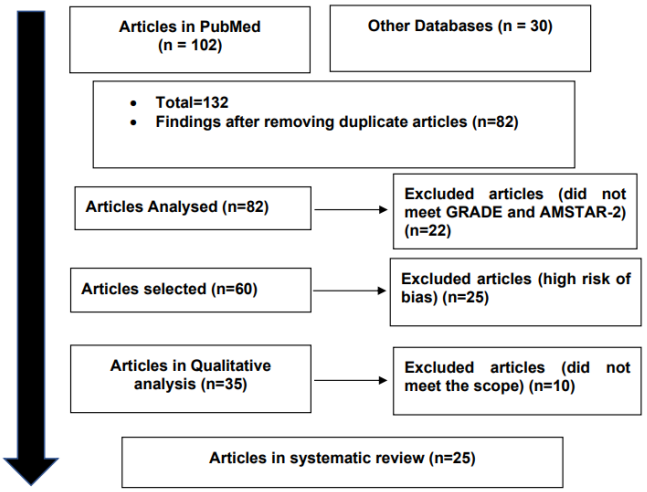
Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

A total of 132 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 82 articles. A total of 35 articles were evaluated in full and 25 articles were included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=87.5%>50%.

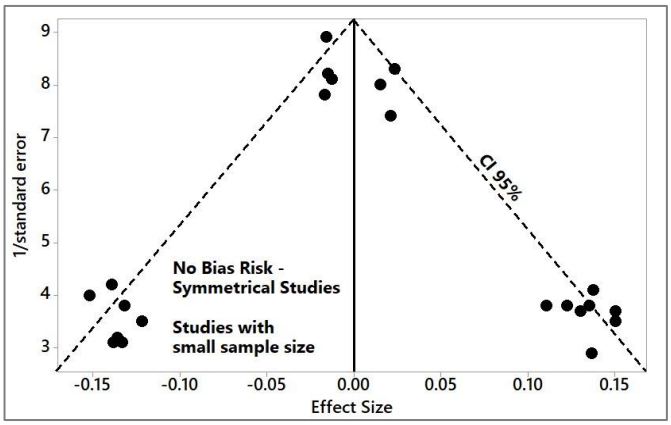
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=25 studies).



Source: Own authorship.

Major Clinical Findings

The glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide is the most recently approved agent in this class of medications and the only GLP-1RA currently available as a subcutaneous and oral formulation. Although GLP-1RAs effectively improve glycemic control and cause weight loss, potential safety concerns have emerged over the years **[11,12]**.

For semaglutide, such concerns have been addressed in the extensive phase 3 registrational trials, including cardiovascular outcomes trials for both subcutaneous (SUSTAIN: Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) and oral (PIONEER: Peptide InnOvatioN for the Early diabEtes tReatment) semaglutide and are being studied in additional trials and registries, including real-world data studies **[13]**. In this regard, clinical findings have shown that semaglutide mainly induces mild to moderate and transient gastrointestinal disturbances and increases the risk of biliary disease (cholelithiasis). No unexpected safety concerns have emerged to date, and the established safety profile for semaglutide is similar to that of other GLP-1RAs, where definitive conclusions for pancreatic and thyroid cancer cannot be drawn at this time due to the low incidence of these conditions **[10-14]**.

In addition, due to its potent glucose-lowering effect, patients at risk of existing polycystic kidney disease should be carefully monitored if treated with semaglutide, especially if also treated with insulin. Given the beneficial metabolic and cardiovascular actions of semaglutide and the low risk of serious adverse events, semaglutide has an overall favorable risk/benefit profile for patients with type 2 diabetes **[14]**.

The on-target effects of GLP-1RAs are those that lead to a reduction in glucose levels. Any other effect may be considered a pleiotropic, off-target effect or, in the case of undesirable actions, adverse effects. Many of the class (adverse) effects are shared between the different GLP-1RAs, however, differences do occur. For semaglutide, a different side effect profile can be expected for the oral versus the subcutaneous formulation. Apart from the obvious (the tablets will not induce injection site reactions), it can be suggested that higher levels induce more gastrointestinal disturbances. Furthermore, with the maximum oral dosage, plasma levels are lower compared to the maximum subcutaneous dose (20 mg oral produces plasma levels of ~25 nM, and 1 mg subcutaneous produces plasma levels of ~45 nM). Despite this, there is no data available comparing the pharmacokinetic profile of both formulations with each other **[12,13]**.

All GLP-1RAs increase heart rate, and this is no different for semaglutide. In SUSTAIN 6, a placebo-corrected increase in heart rate of 2.75 beats per minute (bpm) was observed for semaglutide 0.5 mg and 3.2 bpm for the 1.0 mg dosage **[15]**. This increase was not associated with adverse cardiac events. Furthermore, no increase in cardiovascular outcomes was observed in SUSTAIN 6 and PIONEER 6.

Large epidemiological studies have found that an increase of 5 bpm is associated with an increase of 17% in mortality **[16]**. It is unclear whether this association holds for drug-induced heart rate acceleration. The α-blocking agent doxazosin increases heart rate by ~25% **[17]** and is associated with an increased incidence of heart failure (compared to the diuretic agent chlorthalidone) **[18]**. In contrast, reducing heart rate by ~10 bpm using the inhibitor ivabradine did not affect mortality in patients with stable coronary artery disease. At this point, it is clear that the beneficial effects of GLP-1RA on cardiovascular risk factors and physiology outweigh a potential risk from the associated heart rate increase.

Increased heart rate is also important in patients with heart failure (HF). Although semaglutide CVOTs have not shown an increased incidence of HF

hospitalization compared with placebo [19], in previous smaller studies of liraglutide in patients with HF with reduced left ventricular ejection fraction, GLP-1RA was associated with an increased incidence of serious cardiac events (rhythm disturbances, worsening of HF) [20,21]. Because patients with New York Heart Association class IV HF were excluded from CVOTs, it is unclear whether safety risks could arise in patients treated with semaglutide. However, a recent meta-analysis of all current CVOTs showed that GLP1RAs were associated with a (non-significant) reduction in HF [22].

Several mechanistic clinical trials have provided conflicting evidence when trying to understand the GLP-1RA-induced increase in heart rate. Some studies have found systemic vasodilation (with likely consequent reflex tachycardia), while others have failed to show this [23-25]. Similarly, conflicting findings are available for activation of the (cardiac) sympathetic nervous system [24, 26-29]. A direct effect of GLP-1RA on sinoatrial cells may exist [24], after excluding other potential causes. This postulation was later confirmed in a mouse model, where stimulation of GLP-1 receptors on atrial cells induced a chronotropic effect, but only when neuronal input was present [30].

Most new drugs are also tested for their effect on the QT interval, as QT prolongation is a marker for potential ventricular fibrillation. Compared with placebo, subcutaneous semaglutide did not affect this electrocardiogram measurement in healthy volunteers at doses above those used in daily practice [31].

Recent randomized clinical trials have demonstrated that glucagon-like peptide-1 receptor agonists (GLP-1RA) reduce cardiovascular events in at-risk individuals with type 2 diabetes. Despite these findings, GLP-1RA are underutilized in eligible patients, particularly by cardiologists. To date, randomized clinical trials of albiglutide, dulaglutide, liraglutide, and injectable semaglutide have reported favorable cardiovascular outcomes. Most recently approved for clinical use, oral semaglutide has a favorable safety profile and is currently undergoing regulatory review and additional studies for cardiovascular outcomes. Professional society guidelines now recommend GLP-1RA therapy for cardiovascular risk mitigation in patients with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD) or multiple ASCVD risk factors, regardless of glucose control or background antihyperglycemic therapy (other diabetes medications being used). Additional conditions suitable for GLP-1RA therapy include obesity and advanced chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2), for which cardiovascular risk reduction options are limited [32].

Also, GLP-1RA therapy has a favorable safety profile. Its most common adverse effect is gastrointestinal discomfort, which typically decreases during the first few weeks of therapy and can be mitigated by starting with the lowest dose and increasing as tolerated. Depending on baseline glycemic control, sulfonylureas, and insulin may need to be tapered before initiating GLP-1RA; without concomitant use of insulin or sulfonylureas, GLP-1RAs are not associated with hypoglycemia. Multidisciplinary management and collaborative care with primary care physicians and/or endocrinologists are important [32].

In this regard, it is important to consider the safety profile of semaglutide for patients with type 2 diabetes and cardiovascular risk reduction when selecting the most appropriate treatment option for each patient. This can help ensure that patients achieve an optimal response, that those who experience adverse events are appropriately managed, and that treatment is personalized for those with pre-existing conditions. The American Diabetes Association and the American Association of Clinical Endocrinologists/American College of Endocrinology recommend a glucagon-like peptide-1 receptor agonist (GLP-1RA) or sodium-glucose cotransporter 2 inhibitor with proven cardiovascular (CV) benefit in patients with established CVD or those at high risk of CVD [33].

Besides, injectable semaglutide is approved by the FDA to reduce the risk of major CV events in adults with T2DM and established CVD. In PIONEER 6, the CV safety of the first GLP-1RA tablet, oral semaglutide, was non-inferior to placebo, and a long-term study (SOUL; NCT03914326) powered to assess a potential CV benefit is ongoing. The safety and tolerability profile of oral semaglutide across the PIONEER clinical trial program was consistent with the GLP-1RA class. The most common adverse events were gastrointestinal events (e.g., nausea, diarrhea, and vomiting), which were typically mild to moderate and transient. In clinical practice, oral semaglutide expands the treatment options available for patients with T2D and may be considered in patient populations suitable for injectable GLP-1RAs [33].

Since 2022, a single-blind randomized clinical trial called "Study of Antiatherosclerotic Mechanisms of Action of Semaglutide (SAMAS)" with a total of 100 consecutive patients with T2D and a disease duration of up to 10 years, without overt cardiovascular disease, who are treated with metformin (± sulfonylurea) and optimal cardioprotective therapy, is being recruited. After 1:1 randomization, patients received oral semaglutide 14 mg daily or placebo for 1 year. The primary outcome comprises changes in the structural and functional characteristics of the arterial wall related to atherosclerosis, which were: a reduction in carotid

intima-media thickness, improvement in endothelial function, and decrease in arterial stiffness. Secondary outcomes are changes in atherogenic small dense low-density lipoproteins, glucose control (HbA1c), and inflammatory markers (hsCRP). Possible correlations between primary outcomes and changes in lipids, HbA1c, and high-sensitivity C-reactive protein were analyzed **[34]**.

Finally, a study developed by authors Niu et al. (2024) **[35]** compared the adverse event profiles of semaglutide across different routes of administration by analyzing the US Food and Drug Administration (FDA) adverse event reporting system. The findings of this analysis provided valuable data for clinical practice and drug surveillance. A total of 22,287 records of semaglutide-related adverse reactions were identified in the FAERS database. A comparative analysis was performed on 16,346 records of subcutaneous administration and 2,496 records of oral administration. Different routes of administration may lead to varying adverse reaction outcomes. Compared with oral administration, subcutaneous injection is more likely to result in endocrine-related adverse events. Oral administration is more likely to induce gastrointestinal adverse events. Furthermore, it significantly accelerates the onset of adverse reactions. Comparative analysis of all relevant results indicates that semaglutide may lead to different adverse reaction events depending on the route of administration. Furthermore, there are significant differences in the time to onset of these adverse reactions.

Conclusion

It was concluded that subcutaneous injection is more likely to result in endocrine-related adverse events. Oral administration is more likely to induce gastrointestinal adverse events. Furthermore, it significantly accelerates the onset of adverse reactions. As one of the newest agents in the class, the safety of semaglutide in both subcutaneous and oral formulations has been examined in phase 3 programs and CVOTs. However, no major safety concerns have emerged to date, although definitive conclusions for pancreatic cancer, thyroid cancer, and complications of polycystic kidney disease cannot be drawn at this time. When weighed against the beneficial effects of these medications on glucose metabolism, blood pressure, body weight, and cardiovascular (and potentially even renal) outcomes, these agents have an overall beneficial risk/benefit profile for the treatment of patients with T2DM. GLP-1RAs are safe, well tolerated, and improve cardiovascular outcomes, largely independent of their antihyperglycemic properties, but they remain underutilized by cardiologists, requiring therapy management in patients with T2DM and established atherosclerotic cardiovascular disease or at high risk for established atherosclerotic cardiovascular disease.

CRediT

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate@.

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It was performed.

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