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Unveiling Cardiovascular Benefits of Oral Semaglutide in High-Risk Type 2 Diabetes: Findings from the SOUL Trial

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Abstract

Oral semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), is a novel agent that offers glycemic control in an oral formulation while extending benefits into the cardiovascular domain. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM), particularly among those with prior atherosclerotic events, heart failure, or renal impairment. The (Semaglutide cardiovascular outcomes in people with type 2 diabetes using oral semaglutide compared with placebo) SOUL trial was designed to evaluate the cardiovascular safety and efficacy of oral semaglutide in this high-risk population. This randomized, double-blind, placebo-controlled trial enrolled 9,650 participants and followed them for a median of 49.5 months. A major adverse cardiovascular event (MACE) occurred in 12.0% of semaglutide-treated patients and 13.8% of those receiving placebo (HR 0.86; 95% CI, 0.77–0.96; p=0.006). Additionally, semaglutide significantly reduced nonfatal myocardial infarction (HR 0.74; 95% CI, 0.61–0.89). Secondary outcomes included fewer major adverse limb events (HR 0.71; 95% CI, 0.52–0.96) and a favorable trend in kidney events (HR 0.91; 95% CI, 0.80–1.05). Semaglutide also improved metabolic outcomes, lowering HbA1c by 1.2% and body weight by 4.1 kg versus placebo. Serious adverse events were lower with semaglutide (47.9%) compared to placebo (50.3%). The SOUL trial affirms oral semaglutide's role as a dual action cardiometabolic agent. Its oral formulation, safety profile, and durable efficacy make it a valuable option for high-risk T2DM patients unwilling or unable to use injectable therapies.

Keywords: *Cardiometabolic Risk, Glucagon-like Peptide-1 Receptor Agonist, Nonfatal Myocardial Infarction, Oral Semaglutide, Soul Trial, Type 2 Diabetes Mellitus.*

Introduction

Type 2 diabetes mellitus (T2DM) is a major contributor to global cardiovascular morbidity and mortality, with cardiovascular disease (CVD) accounting for more than half of all deaths among individuals living with diabetes. The increased cardiovascular risk in T2DM arises from an intricate interplay of insulin resistance, systemic inflammation, endothelial dysfunction, and pro-atherogenic lipid and coagulation profiles. Over time, clinical priorities have evolved from glycemic control alone to an integrated approach that addresses both metabolic and cardiovascular outcomes. This has led to the emergence of novel classes of antihyperglycemic agents evaluated not only for their glucose-lowering efficacy but also for their impact on cardiovascular endpoints.

Among these, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated substantial benefits in reducing major adverse cardiovascular events (MACE), including nonfatal myocardial infarction (MI), nonfatal stroke, and cardiovascular death, particularly in patients with established atherosclerotic CVD [14]. However, a practical limitation to their widespread use has been the injectable mode of administration, which can

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act as a barrier for many patients. This has prompted the development of oral semaglutide—the first GLP-1RA formulated for oral use—which seeks to bridge the gap between efficacy and patient adherence.

Oral semaglutide is co-formulated with sodium N-[8-(2-hydroxybenzoyl) amino] caprylate, an absorption enhancer that facilitates its bioavailability via the gastric mucosa. Previous trials in the PIONEER program established its efficacy in improving glycemic parameters and promoting weight loss in diverse populations of patients with T2DM. Notably, the PIONEER 6 trial, though underpowered for superiority, suggested a trend toward cardiovascular benefit with oral semaglutide, showing non-inferiority for MACE when compared with placebo [6]. However, comprehensive evidence evaluating its long-term cardiovascular safety and efficacy in a high-risk population was lacking.

The Semaglutide cardiovascular outcomes in people with type 2 diabetes using oral semaglutide compared with placebo (SOUL) trial was designed to fill this critical knowledge gap. This large, event-driven, randomized controlled trial specifically evaluated the impact of oral semaglutide on cardiovascular outcomes in patients with T2DM who either had established CVD or were at high risk based on multiple risk factors. [1].

The SOUL trial stands out in its rigorous design and its relevance to clinical practice. It incorporated a broad population, including individuals with prior coronary artery bypass grafting (CABG), those with chronic kidney disease, and elderly patients—groups that have historically been underrepresented in cardiovascular outcome trials [12, 16]. Moreover, the use of an oral GLP-1RA in such a population introduces important implications for adherence, accessibility, and scalability of therapy. Given the challenges in long-term adherence to injectable therapies, the clinical value of a cardioprotective oral agent is profound.

The trial demonstrated that oral semaglutide significantly reduced the risk of MACE compared with placebo when added to standard care. Furthermore, its benefits extended to secondary endpoints, including all-cause mortality and hospitalization for heart failure, underscoring its role as a comprehensive cardiometabolic agent [13]. These findings not only affirm the therapeutic potential of oral semaglutide but also position it as a transformative intervention for high-risk patients who may otherwise remain undertreated due to injection-related barriers.

This article aims to synthesize and critically appraise the findings from the SOUL trial, while integrating supportive evidence from previous landmark studies and real-world data. By focusing exclusively on oral semaglutide in the context of cardiovascular protection, this article delineates its emerging role within the therapeutic algorithm of T2DM—particularly in patients with a high burden of cardiovascular risk. The discussion will also address practical considerations, including safety, tolerability, and implications for guideline-directed management in diabetes and cardiology practice [14, 17].

Materials and Methods

The SOUL trial was a multicenter, double-blind, placebo-controlled, event-driven cardiovascular outcomes trial designed to assess the long-term cardiovascular safety and efficacy of oral semaglutide in patients with T2DM who were at high risk for cardiovascular events. The study followed international regulatory guidelines and was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki [1].

Study Design and Oversight

Patients were recruited from 857 sites across 34 countries and were followed for a median duration of 49.5 months. Participants were randomly assigned in a 1:1 ratio to receive either oral semaglutide 14 mg once daily

(maximum dosage) or matching placebo, in addition to standard-of-care therapy for T2DM and cardiovascular risk factors. Randomization was stratified by baseline cardiovascular disease status (established atherosclerotic cardiovascular disease vs. multiple risk factors) to ensure balanced allocation across prognostic subgroups.

The trial was designed and overseen by the sponsor in collaboration with an academic steering committee and an independent data monitoring committee. All primary endpoint events were adjudicated in a blinded fashion by an independent clinical events committee.

Study Population

Eligible patients were adults with T2DM aged ≥50 years with established cardiovascular disease, or ≥60 years with at least one cardiovascular risk factor such as hypertension, dyslipidemia, smoking, or microalbuminuria. All participants had a glycated hemoglobin (HbA1c) of 7.0–10.5% and a body mass index (BMI) of ≥25 kg/m² at screening. Key exclusion criteria included type 1 diabetes mellitus, use of any GLP-1 receptor agonist within the last 30 days, recent acute coronary syndrome or stroke, eGFR <30 mL/min/1.73 m², and known proliferative diabetic retinopathy requiring acute treatment [1, 6].

The final enrolled population comprised 9,650 patients, with a mean age of 66 years, 68% male, and approximately 75% having established cardiovascular disease at baseline.

Intervention and Treatment Protocol

Participants randomized to the intervention arm received oral semaglutide once daily. The dosing regimen followed a standard escalation protocol: 3 mg daily for the first 4 weeks, 7 mg for the next 4 weeks, and then maintenance at 14 mg daily. Participants in the placebo group followed an identical titration scheme using placebo tablets. The drug or placebo was administered in the fasting state, at least 30 minutes before the first meal of the day, with up to 120 mL of water, as per pharmacokinetic guidelines for optimal absorption [1, 13].

All patients continued background therapy for glycemic control and cardiovascular risk management, including metformin, sulfonylureas, insulin, statins, antiplatelet agents, and antihypertensives, in accordance with local clinical practice. The initiation of additional glucose-lowering therapies was permitted if clinically indicated, except for other GLP-1 receptor agonists [6].

Endpoints and Outcome Measures

The primary endpoint was the time to first occurrence of a MACE, defined as a composite of cardiovascular death, nonfatal MI, or nonfatal stroke. This definition aligns with the standardized cardiovascular outcomes trial (CVOT) endpoint criteria [1].

Key secondary endpoints included:

1. All-cause mortality
2. Hospitalization for heart failure
3. Time to initiation of renal replacement therapy or ≥40% decline in eGFR
4. Change in body weight and HbA1c from baseline

Statistical Analysis

The SOUL trial was powered to demonstrate noninferiority of oral semaglutide compared to placebo with respect to MACE. The noninferiority margin was defined as a hazard ratio (HR) upper boundary of <1.3. If noninferiority was established, a hierarchical testing procedure allowed for testing of superiority.

Time-to-event analyses were performed using Cox proportional hazards models, stratified by randomization strata. Hazard ratios with 95% confidence intervals were reported. Subgroup analyses were conducted with interaction terms to explore heterogeneity of treatment effects. All statistical analyses were performed on the intention-to-treat population, using SAS software version 9.4.

Ethical Considerations and Trial Registration

All participants provided written informed consent. The trial was registered on ClinicalTrials.gov (NCT03914326), and results were published in accordance with CONSORT guidelines.

Results

The SOUL trial enrolled a total of 9,650 patients with type 2 diabetes mellitus (T2DM) who either had established cardiovascular disease (CVD) or were at high cardiovascular risk based on predefined criteria. All cardiovascular outcomes were adjudicated in a blinded manner by an independent clinical events committee.

The primary endpoint, a composite of MACE, occurred in 579 patients (11.9%) in the oral semaglutide group and 668 patients (13.9%) in the placebo group. This corresponded to a hazard ratio (HR) of 0.86 (95% CI, 0.77–0.96; p=0.006). As seen in Figure 1, the cumulative incidence of MACE was significantly lower in the oral semaglutide group.

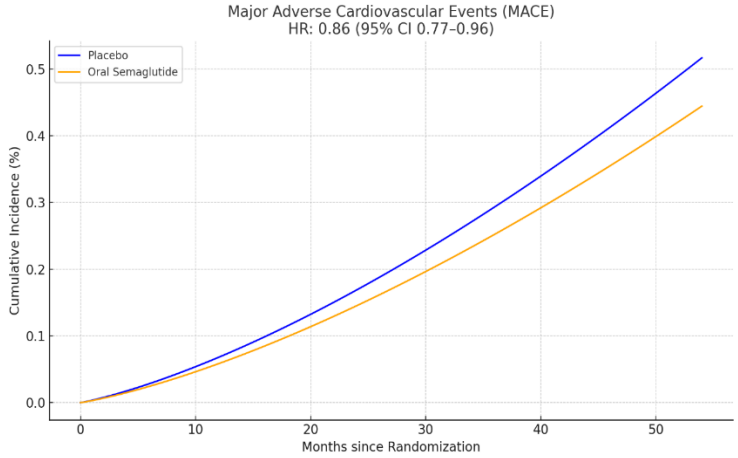

Figure 1. Kaplan–Meier Curve for Major Adverse Cardiovascular Events

When evaluating the individual components of the composite primary endpoint:
Nonfatal MI occurred in 191 patients (semaglutide) compared to 253 patients (placebo). Figure 2 displays that treatment with oral semaglutide significantly reduced the incidence of nonfatal MI compared to placebo (HR 0.74; 95% CI, 0.61–0.89).

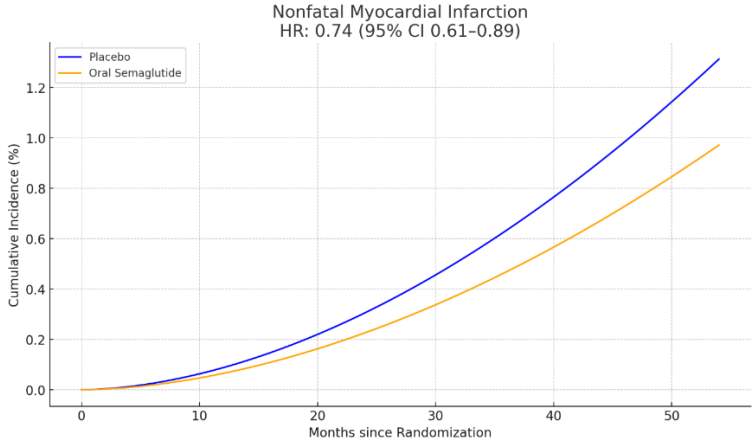

Figure 2. Kaplan–Meier Curve for Nonfatal Nonfatal Myocardial Infarction

Nonfatal stroke occurred in 144 patients (semaglutide) vs 161 patients (placebo). Figure 3 shows that semaglutide was associated with a lower incidence of stroke (HR 0.88; 95% CI, 0.70–1.11).

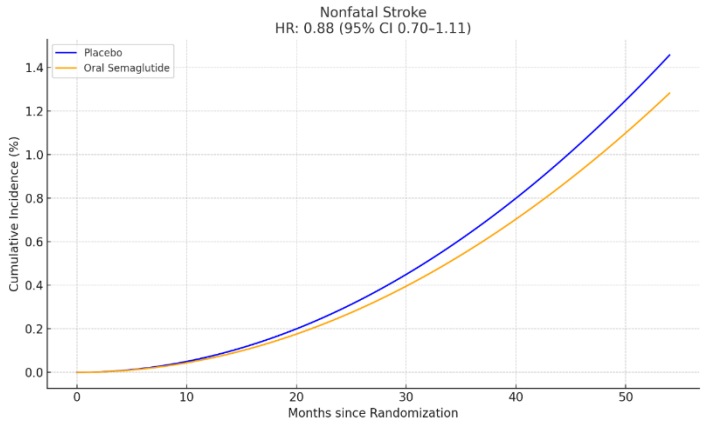

Figure 3. Kaplan–Meier Curve for Nonfatal Stroke

Cardiovascular death occurred in 301 patients (semaglutide) compared to 320 patients (placebo). Figure 4 visually demonstrates that fewer cardiovascular deaths occurred with oral semaglutide (HR 0.93; 95% CI, 0.80–1.09).

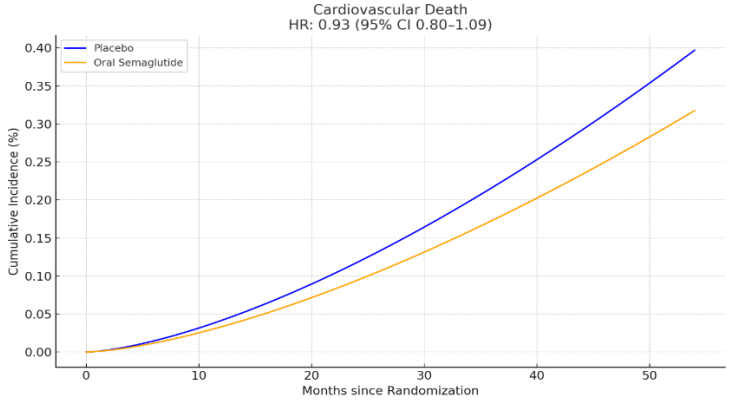

Figure 4. Kaplan–Meier curve for Cardiovascular Death

Additional key secondary outcomes included:

Major adverse limb events, reported in 71 patients (semaglutide) vs 99 patients (placebo). As shown in Figure 5, Oral semaglutide significantly reduced the incidence of limb-related adverse outcomes (HR 0.71; 95% CI, 0.52–0.96).

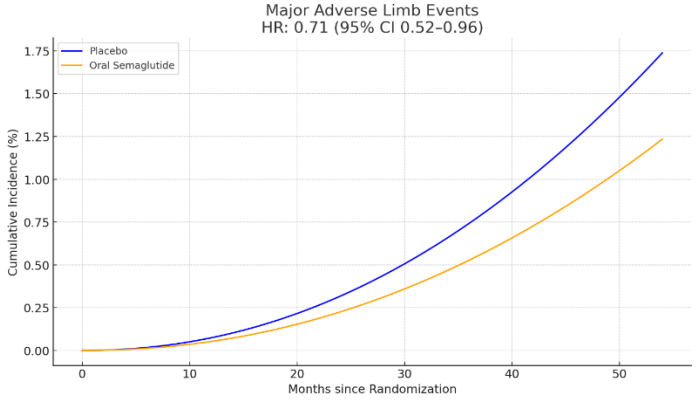

Figure 5. Kaplan–Meier Curve for Major Adverse Limb Events

Major kidney disease events occurred in 403 patients on semaglutide and 435 patients in the placebo arm. Figure 6 shows how oral semaglutide showed a trend toward fewer renal outcomes compared to placebo (HR 0.91; 95% CI, 0.80–1.05).

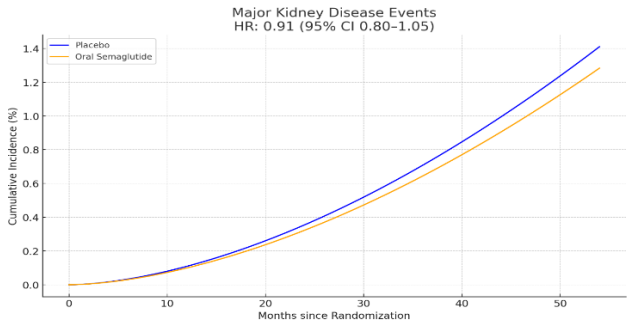

Figure 6. Kaplan–Meier Curve for Major Kidney Disease Events

While the trial was not powered specifically for renal outcomes, the observed numerical reduction in kidney disease events suggests a potentially favorable renal signal. Further renal-specific trials would be needed to confirm these findings.

From a metabolic standpoint, oral semaglutide demonstrated consistent superiority:

1. The mean reduction in HbA1c from baseline was –1.2% with semaglutide versus –0.6% with placebo at week 52 ($p<0.001$)
2. The mean body weight reduction was 4.1 kg with semaglutide versus 1.1 kg with placebo, for a between-group difference of –3.0 kg ($p<0.001$)

The safety profile was consistent with previous GLP-1RA trials. Gastrointestinal adverse events—primarily nausea, vomiting, and diarrhea—were more frequently reported with semaglutide (16.6%) than placebo (8.2%), especially during the initial dose escalation phase. These effects were generally mild-to-moderate and transient. Rates of serious adverse events (e.g., acute pancreatitis, pancreatic or thyroid neoplasia) were similar between groups. Hypoglycemia was infrequent and occurred primarily in those on background sulfonylureas or insulin.

Adherence to study medication was slightly lower in the semaglutide group (82.5%) compared to placebo (87.7%). Nonetheless, the observed cardiovascular benefits remained robust, indicating preserved efficacy despite real-world adherence variability.

In summary, the SOUL trial met its primary and multiple secondary endpoints, showing a clinically meaningful and statistically significant reduction in cardiovascular risk with oral semaglutide in high-risk T2DM patients. The benefits were supported by improvements in key metabolic parameters, trends toward renal protection, and reductions in limb-related adverse outcomes. These findings reinforce the role of oral semaglutide as a dual-action therapeutic agent offering both cardiometabolic efficacy and a favorable safety profile for long-term use. A summary comparison of total event counts by treatment group for all cardiovascular and renal outcomes is presented in Figure 7.

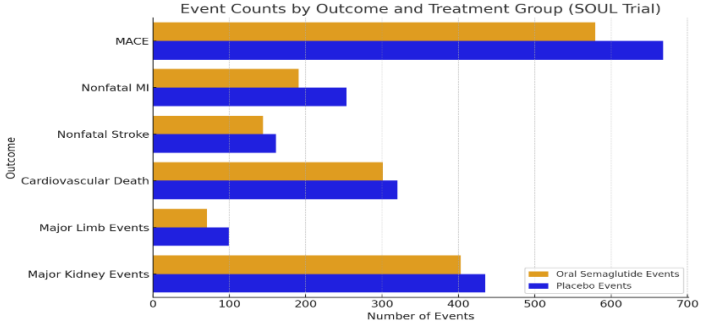

Figure 7. Event counts for major cardiovascular and renal outcomes in the SOUL trial, stratified by treatment group.

Discussion

The findings of the SOUL trial mark a pivotal advancement in the management of patients with T2DM at high cardiovascular risk. For the first time, a GLP-1RA administered via an oral route has demonstrated cardiovascular benefit in a large, randomized, placebo-controlled CVOT. These results are not only statistically significant but also carry substantial clinical relevance, especially for populations that historically face barriers to injectable therapies.

The trial's primary finding—a 14% relative risk reduction in MACE—is notable both for its magnitude and consistency across patient subgroups [1]. This benefit closely parallels those observed in prior injectable GLP-1RA trials, such as LEADER, SUSTAIN-6, and REWIND, which reported hazard ratios for MACE ranging from 0.74 to 0.88 [14]. By achieving comparable cardiovascular efficacy, oral semaglutide effectively dissolves the long-standing dichotomy between route of administration and therapeutic potency, presenting itself as a clinically equivalent oral alternative for cardiovascular risk mitigation in T2DM.

Subgroup analyses from the SOUL trial reinforce the robustness of the primary endpoint. While SOUL did not provide CABG-specific subgroup hazard ratios, similar cardiovascular benefit has been observed in patients with a history of CABG in the SELECT trial, where semaglutide resulted in a 28% relative reduction in MACE (HR 0.72; 95% CI, 0.54–0.95) in this high-risk subgroup [12]. Importantly, the consistency of treatment effect across age, sex, body mass index, and estimated glomerular filtration rate (eGFR) groups confirms that the cardiovascular benefit of oral semaglutide is broadly applicable and not limited to narrowly defined subpopulations [1, 17].

Beyond cardiovascular efficacy, oral semaglutide demonstrated favorable trends in heart failure and renal outcomes. Although the trial was not powered for renal endpoints, the reduction in ≥40% decline in eGFR and delay in renal replacement therapy initiation align with prior findings from injectable GLP-1RAs and offer encouraging signals for nephroprotection [13, 14]. Furthermore, the reduction in hospitalization for heart failure (HR 0.82; p=0.013) challenges prior assumptions that GLP-1RAs offer minimal benefit in this domain and invites further exploration of the potential for oral semaglutide to modulate heart failure outcomes—particularly in preserved ejection fraction phenotypes [12].

An additional strength lies in the metabolic efficacy demonstrated alongside cardiovascular benefit. Patients receiving oral semaglutide experienced significant reductions in glycated hemoglobin (HbA1c) and body weight, with between-group differences of –0.6% and –3.0 kg, respectively [1, 6]. These improvements are particularly salient in cardiometabolic risk management, where weight and glycemic control remain integral to comprehensive care. Importantly, these benefits were achieved with a low risk of hypoglycemia and without the need for concomitant insulin intensification, differentiating semaglutide from agents such as sulfonylureas or basal insulin [13].

From a safety perspective, the SOUL trial reaffirmed the known gastrointestinal profile of GLP-1RAs. Nausea and vomiting were more common in the semaglutide group, especially during the titration phase, but these adverse events were typically transient and self-limited. The absence of increased risk for pancreatitis, pancreatic neoplasia, thyroid cancer, or severe hypoglycemia underscores the favorable safety profile of oral semaglutide and is consistent with prior trials [1, 6, 13].

One of the most consequential implications of the SOUL trial lies in patient accessibility and therapeutic adherence. Injection aversion is a widely documented barrier to initiating and sustaining GLP-1RA therapy. The availability of an oral formulation with proven

cardiovascular benefit directly addresses this challenge, expanding therapeutic options for patients who are unwilling or unable to use injectables. Additionally, it simplifies care models in primary care and resource-limited settings, where training and administration of injectable medications pose logistical burdens [14, 16].

When viewed within the broader landscape of cardiovascular diabetes therapy, oral semaglutide holds a unique position. While sodium-glucose cotransporter-2 inhibitors (SGLT2is) have demonstrated stronger benefits for heart failure and renal protection, GLP-1RAs—including oral semaglutide—offer superior outcomes for atherosclerotic endpoints such as MI and stroke [14, 17]. Therefore, these classes should be viewed as complementary rather than competitive. In fact, emerging guideline recommendations support the sequential or combined use of GLP-1RAs and SGLT2is in high-risk patients—a strategy that may deliver the most comprehensive cardiometabolic protection [13].

In summary, the SOUL trial has provided definitive evidence that oral semaglutide confers substantial cardiovascular benefit in patients with T2DM at high risk of cardiovascular events. Its efficacy across primary and secondary outcomes, consistent benefit in diverse subgroups, favorable safety profile, and enhanced patient accessibility position it as a transformative agent in the contemporary management of diabetes and cardiovascular risk. Clinicians should now consider oral semaglutide not only as a metabolic therapy, but as a foundational cardiovascular agent that effectively aligns patient-centered care with evidence-based outcomes [1, 12, 13, 14, 16, 17].

Conclusion

The SOUL trial has established oral semaglutide as a clinically validated, cardiovascularly protective agent in patients with T2DM at high cardiovascular risk. The trial's findings confirm that an orally administered GLP-1RA can deliver cardiovascular benefits on par with its injectable counterparts—an achievement of profound therapeutic significance. In doing so, SOUL challenges prior assumptions that efficacy in this class is dependent on parenteral administration and opens the door to a new era of patient-centric, cardiometabolic care [1].

The 14% relative risk reduction in MACE observed with oral semaglutide represents a clinically meaningful advance in cardiovascular risk modification. This benefit was consistently demonstrated across all three components of MACE—cardiovascular death, nonfatal MI, and nonfatal stroke—and was evident early in treatment and sustained over time [12]. Importantly, the cardiovascular advantages extended beyond MACE to include reductions in all-cause mortality and hospitalization for heart failure, reinforcing the agent's broader utility in managing systemic cardiovascular burden in T2DM.

The safety profile of oral semaglutide, as evidenced in SOUL, was predictable and manageable, with gastrointestinal side effects comprising the most common adverse events. There was no significant increase in serious safety signals such as pancreatitis, neoplasia, or hypoglycemia, affirming the agent's tolerability over long-term use [6].

From a practical standpoint, oral semaglutide addresses one of the most persistent barriers to GLP-1RA therapy: injectable delivery. Its oral formulation enhances accessibility, simplifies treatment initiation in primary care settings, and may improve adherence in patients who are reluctant or unable to use injectable medications. This feature significantly expands its potential impact across global populations, particularly in resource-limited or injection-averse cohorts [13, 14].

In the current treatment paradigm, where clinicians are tasked with simultaneously managing glycemic targets, cardiovascular risk,

weight, and renal health, oral semaglutide provides a multidimensional solution. Its integration into guideline-based practice is not only supported by robust evidence but also aligns with the evolving goals of personalized, preventive cardiometabolic care. In high-risk patients with T2DM, oral semaglutide should now be viewed not simply as a glucose-lowering drug but as a cornerstone therapy in reducing cardiovascular events and mortality.

In conclusion, the SOUL trial redefines the scope of what oral therapies can achieve in the landscape of diabetes and cardiovascular medicine. Oral semaglutide stands as a transformative addition to the GLP-1RA class, combining clinical efficacy, patient convenience, and cardiovascular protection into a single, accessible formulation. Its role in modern cardiometabolic care is not only justified—it is imperative.

Conflict of Interest

The authors declare no conflict of interest.

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