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Effect of semaglutide on mortality and cardiovascular events in patients at high cardiovascular risk: an updated systematic review and meta-analysis

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The SOUL trial marked a significant addition to the evidence supporting glucagon-like peptide-1 receptor agonists (GLP-1RAs). This randomized, double-blind, placebo-controlled trial enrolled 9650 participants and was the first dedicated cardiovascular outcomes superiority trial of oral semaglutide.[1] It demonstrated a significant reduction in adverse events among diabetic patients with atherosclerotic cardiovascular disease and/or chronic kidney disease (CKD), consistent with prior findings for injectable semaglutide and other GLP-1RAs.[2,3]

GLP-1RAs are recommended for diabetics and, increasingly, for non-diabetics with stable coronary artery disease and overweight/obesity, with semaglutide specifically indicated for weight and cardiovascular events reduction (Class IIb, Level of Evidence B).[4,5] However, further evidence is needed to establish definitive survival benefits and fully characterize its impact on cardiovascular outcomes.

To address these gaps, we performed a pairwise meta-analysis of semaglutide vs. placebo focused on mortality and major adverse cardiovascular events (MACE), including high-risk subgroups.

Following PRISMA guidelines, we searched MEDLINE, Cochrane, and Web of Science through March 2025. Because this was an expedited, time-sensitive analysis, the protocol was not prospectively registered in PROSPERO, which recommends that registration be completed prior to data extraction. Eligible studies were randomized trials comparing semaglutide with placebo. Study-level data were extracted, and risk of bias was assessed using the Cochrane tool. The primary endpoint was all-cause death; the secondary endpoint was MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke. Mean differences and odds ratios (OR) with 95% confidence intervals (CI) were estimated using a frequentist random-effects model. Incidence rate ratios (IRRs) accounted for differences in follow-up durations. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test, complemented by leave-one-out sensitivity analyses. Meta-regressions were conducted to explore subgroup effects. Trial sequential analysis (TSA) evaluated evidence conclusiveness, defining significance when the Z-curve crossed the sequential monitoring boundary (SMB) and the required information size (RIS), which was derived from pooled event rates, was met (type-I error 5%, power 90%). Analyses were performed using R version 4.4.2.

The search identified 347 unique records. After title- and abstract-level selection, 231 were excluded (commentaries, dose-finding studies, or non-cardiovascular investigations), leaving 116 articles for full-text assessment. Of these, 105 were excluded because they were secondary analyses ($n = 52$), active-comparator trials ($n = 31$), or lacked death/MACE data ($n = 22$). Consequently, five studies comprising 37 267 patients, were included.[1–3,6,7] Baseline characteristics are reported in *Figure 1*. All trials were at low risk of bias. The mean age was 63.9 years, 29.6% were female, 77.8% were Caucasian, and 12% were current smokers. The mean body mass index (BMI) was 32.4 kg/m^2, mean glycated haemoglobin among diabetics was 8.1%, and mean estimated glomerular filtration rate (eGFR) was 75.4 mL/min/1.73 m^2. Pooled median follow-up was 3.3 years.

Semaglutide significantly reduced all-cause death compared with placebo (OR 0.84; 95% CI, 0.77–0.92; $P < 0.001$; IRR = 0.85, 95% CI, 0.78–0.93, $P < 0.001$), with low heterogeneity (I^2 14.5 %, Q = 7.2, $P = 0.124$). In the TSA, the Z-curve crossed the SMB, but the RIS was not reached, suggesting that conclusions remain potentially pre-mature (*Figure 1*).

MACE risk was significantly lower with semaglutide (OR 0.81; 95% CI, 0.76–0.87; $P < 0.001$; IRR 0.83; 95% CI, 0.77–0.89, $P < 0.001$), with no heterogeneity (I^2 0 %, Q = 1.4, $P = 0.842$). TSA confirmed conclusive evidence, with the Z-curve crossing the SMB and RIS lines. Reductions were observed for the individual components cardiovascular death and non-fatal MI, with the latter reaching TSA thresholds. Non-fatal stroke was reduced but did not reach significance (*Figure 1*).

Subgroup analyses showed consistent MACE reductions across patients with or without established cardiovascular disease, diabetes, older age (>65 years), obesity (BMI >30), CKD (eGFR <60), and heart failure. Greater benefits were observed in patients not receiving SGLT2 inhibitors and in those with prior MI or stroke (*Figure 1*).

This is the first study incorporating the SOUL trial to comprehensively assess semaglutide survival benefits. Semaglutide reduced all-cause death and MACE in high-risk patients, despite optimal medical

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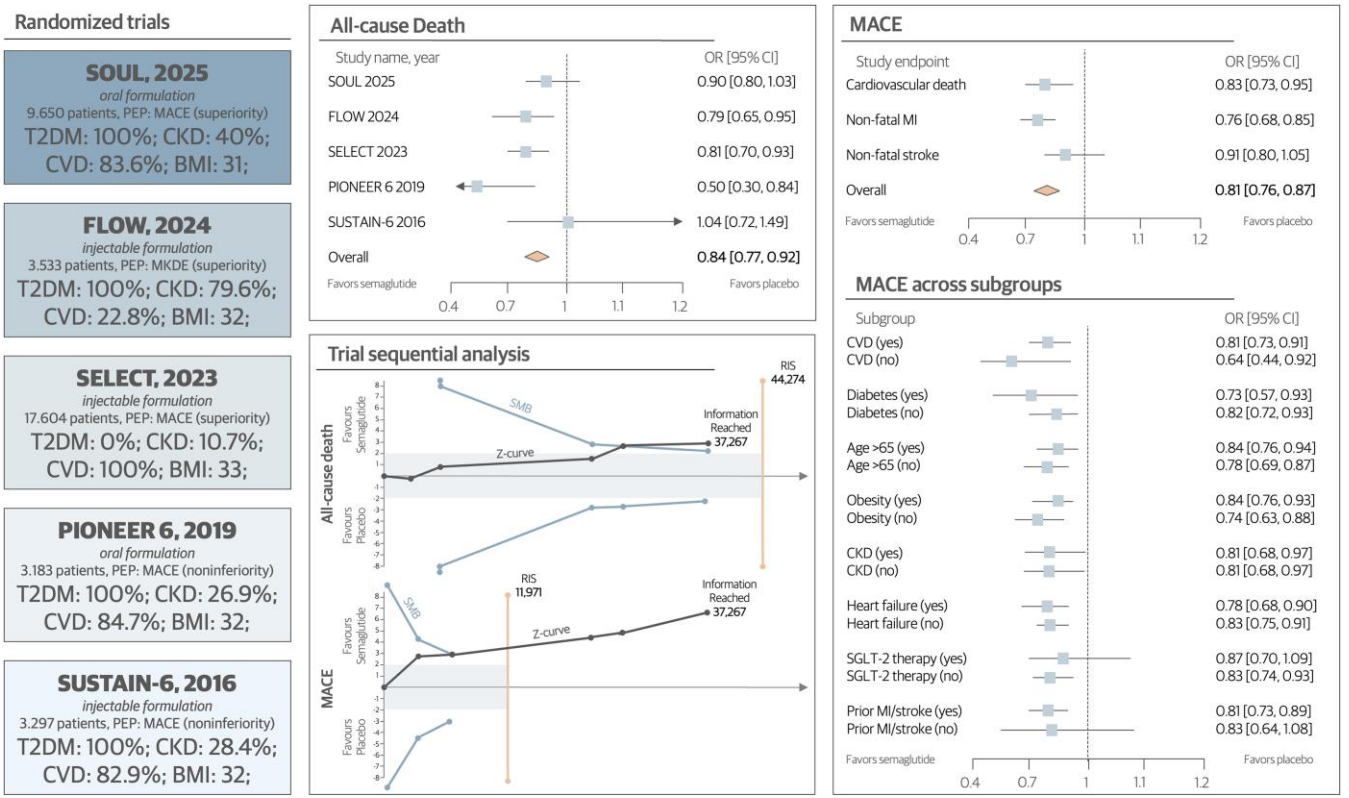

Figure 1 Forest plot and trial sequential analysis plot for all-cause death and major adverse cardiovascular events. The figure displays trial characteristics and forest plots comparing semaglutide vs. placebo for all-cause death, major adverse cardiovascular events (MACE), and MACE in high-risk subgroups, alongside trial sequential analysis (TSA) plots for death and MACE. In TSA, the cumulative Z-curve reflects accumulating evidence; crossing the SMB indicates sufficient evidence to reject the null hypothesis. This occurs for both endpoints, but the required information size (RIS) was reached only for MACE—suggesting that the evidence for MACE, driven primarily by a reduction in non-fatal MI, is robust and unlikely to change. Meta-regression analyses comparing MACE across subgroups defined by high-risk features yielded no significant *P* values for interaction. BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; CKD, chronic kidney disease (defined as estimated glomerular filtration rate < 60); MACE, major adverse cardiovascular events); MI, myocardial infarction; PEP, primary endpoint; RIS, required information size; SMB, sequential monitoring boundary; T2DM, type 2 diabetes mellitus; TSA, trial sequential analysis.

therapy. The Z-curve crossed the SMB, but the RIS was not reached, indicating that findings for this outcome should be interpreted with caution. On the other hand, semaglutide robustly reduced MACE, notably non-fatal MI, a finding unlikely to be altered by future studies. These results clarify previous inconsistencies in the literature and support the role of GLP-1RAs in attenuating atherosclerosis progression, an evolving therapeutic concept warranting further research. Importantly, the benefits of semaglutide were consistent across key subgroups, including patients without overt diabetes or obesity.

Limitations of this study include those inherent to study-level meta-analyses, the exclusion of the FLOW trial from subgroup analyses due to unavailable stratified data, and minor differences in subgroup definitions that may have minimally affected estimates. Importantly, the lack of individual patient-level data precluded a direct comparison between oral and injectable semaglutide, limited our ability to adjust for potential confounders influencing the observed mortality reduction, and prevented analysis of incremental benefit across risk indicators such as BMI and eGFR. These limitations highlight the value of adopting individual patient data in future studies.

In conclusion, semaglutide confers a significant reduction in MACE, driven mainly by non-fatal MI, among high-risk individuals receiving optimal medical therapy, with consistent benefits across subgroups. Although a statistically significant reduction in all-cause mortality was detected, the current evidence base falls short of the threshold for conclusiveness to confirm a definitive survival benefit. These findings support a reconsideration of the role of semaglutide in guideline recommendations for cardiovascular risk management, particularly for patients at higher risk of developing adverse cardiovascular events.

Author contribution

M.S. contributed to the conception and design of the work, extracted and analysed the data, and drafted the manuscript. D.C. contributed to the writing of the manuscript, critically revised it for important intellectual content, and approved the final version. Both authors agree to be accountable for all aspects of the work, ensuring its integrity and accuracy.

Conflict of interest: D.C. reports honoraria from Bristol-Myers Squibb, Daiichi Sankyo, Novo Nordisk, sanofi-aventis, Terumo. M.S. reports no conflicts of interest.

Data availability

The data underlying this article are derived from publicly available randomized trial publications, as referenced in the manuscript. These are accessible through the New England Journal of Medicine (https://www.nejm.org) to subscribers, in accordance with its access policies.

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