Heart and SOUL – oral semaglutide demonstrates cardiovascular benefit in high-risk people with type 2 diabetes

Oral semaglutide up to a dose of 14 mg demonstrated a 14% reduction in major adverse cardiovascular events in people aged 50 years or older with type 2 diabetes at high risk of cardiovascular disease in the SOUL (Semaglutide Cardiovascular Outcomes Trial), published in the *New England Journal of Medicine*. In this event-driven trial, 9650 people were followed for a median of 49.5 months, during which time 12.5% suffered a primary outcome event (cardiovascular death, non-fatal myocardial infarction or stroke) in the oral semaglutide group, compared with 13.8% in those receiving placebo, with the reduction largely driven by a lower rate of non-fatal myocardial infarction with oral semaglutide. The incidence of serious adverse events was similar in both groups but, as expected, there were more gastrointestinal adverse events in those receiving oral semaglutide. There was no significant difference demonstrated between the groups in the confirmatory secondary composite renal outcome. This will reassure clinicians that, as with the injectable formulation, oral semaglutide is effective at reducing cardiovascular events in this high-risk population with type 2 diabetes.

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The cardiovascular safety of oral semaglutide has been confirmed previously in the PIONEER 6 trial; however, this study was not designed to detect cardiovascular benefits. The randomised, placebo-controlled cardiovascular safety study enrolled 3183 people with a high risk of cardiovascular disease (age ≥50 years with established cardiovascular disease [CVD] or chronic kidney disease [CKD], or age ≥60 years with CVD risk factors only), and the primary outcome was the time to first occurrence of major adverse cardiovascular events (MACE) (Husain et al, 2019). People were followed for a median of 15.9 months until the event rate was reached. The study was designed to rule out an 80% excess risk of MACE compared with placebo, which it successfully demonstrated. In addition, death from any cause occurred in 1.4% of participants in the oral semaglutide arm and 2.8% in the placebo group, a hazard ratio of 0.51 (95% CI 0.31–0.84), thus raising the possibility that oral semaglutide might in fact reduce mortality risk.

The cardiovascular outcomes trial for oral semaglutide, SOUL, assessed the cardiovascular efficacy in people with type 2 diabetes at high cardiovascular risk; that is, those with established atherosclerotic CVD, CKD or both.

SOUL

Published in the *New England Journal of Medicine*, SOUL was a double-blind, placebo-controlled, event-driven superiority trial, enrolling 9650 participants who were randomised to receive oral semaglutide (up to 14 mg once daily) or placebo, alongside standard care for diabetes and CVD (McGuire et al, 2025). Of the participants, 70% had coronary artery disease, 23% heart failure, 21% cerebrovascular disease and 16% peripheral artery disease. A significant proportion were already treated with SGLT2 inhibitors, balanced across both groups. The primary outcome was a composite of non-fatal myocardial infarction or stroke, or cardiovascular death (3-point MACE).

Confirmatory secondary outcomes were tested in hierarchical order and looked at time to first event:

- Major kidney disease events (5-point composite of death from cardiovascular causes, death from kidney causes, persistent reduction of eGFR of

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≥50%, persistent eGFR <15 mL/min/1.73 m^2, or long-term renal replacement therapy with dialysis or transplantation).
- Death from cardiovascular causes.
- Major adverse limb events (2-point composite of hospitalisation for acute limb ischemia or hospitalisation for chronic limb ischaemia).

A variety of other supportive secondary outcomes were also specified.

Results

The study was event-driven, and the median follow-up was approximately 48 months, during which there were:
- 579 primary events in the oral semaglutide group (3.1 events per 100 person-years; 12.0% incidence).
- 668 primary events in the placebo group (3.7 events per 100 person-years; 13.8% incidence).

The hazard ratio for the primary outcome was 0.86 (95% CI 0.77–0.96; *P*=0.006), demonstrating a significant 14% reduction in MACE in those treated with oral semaglutide versus placebo. This was comparable to the benefits seen with injectable semaglutide, dulaglutide and liraglutide, although results should not be compared across the different populations enrolled in different cardiovascular outcome trials. Primary outcome benefits appeared similar across different age groups and appeared greater in those with higher baseline HbA_{1c}; however, the study was not powered to demonstrate differences between subgroups.

MACE reduction remained significant in those already receiving an SGLT2 inhibitor when oral semaglutide was added. However, *post hoc* analysis failed to show additional benefits in those receiving both classes of drug compared with use of oral semaglutide alone.

The rate of the first confirmatory secondary event outcome, major kidney disease events, did not differ between the oral semaglutide and placebo groups; thus, the hierarchical testing stopped at that point.

Adverse events

Serious adverse events were reported by around 50% in each group, with no significant difference between groups. Gastrointestinal events occurred in 5.0% of the semaglutide group and 4.4% in the placebo group. These are similar to the adverse event rates seen with injectable semaglutide. No new safety concerns were identified. Overall, 27% of those taking semaglutide discontinued due to side effects compared with 28.5% of those taking placebo.

Other effects

Average weight loss was 4.22 kg with oral semaglutide versus 1.27 kg with placebo. HbA_{1c} was reduced by 0.71% (7.8 mmol/mol), 0.56% more than placebo despite intensification of glucose-lowering therapy being available in both groups during the study.

Discussion

The FLOW (Evaluate Renal Function with Semaglutide Once Weekly) study of injectable semaglutide 1 mg in people with type 2 diabetes and CKD differed from SOUL, in that it demonstrated a significantly improved composite renal outcome (hazard ratio 0.76) (Perkovic et al, 2024). The authors propose that this might be due to higher eGFR in SOUL, lower bioavailability of the oral preparation of semaglutide or, indeed, chance.

The authors warn that a limitation of SOUL is that the trial population was at higher cardiovascular risk than the general type 2 diabetes population, in whom around one third have established CVD and 25–40% have CKD; therefore, the results may not be directly applicable to lower-risk populations with type 2 diabetes. Likewise, only 28.9% of the trial population were women, who are at higher risk of CVD and mortality than men, and only 2.6% were Black, who are at greater risk of type 2 diabetes than the White population.

Implications for practice

This study reassures us that in people with type 2 diabetes at high risk of cardiovascular events due to established CVD or CKD, oral semaglutide offers similar benefits to injectable semaglutide. Up to this point, we may have been cautious about prescribing the oral preparation in this high-risk group.

Unfortunately, benefits in slowing progression of CKD were not demonstrated in this study, so

the results with weekly injectable semaglutide seen in FLOW cannot be extrapolated to oral semaglutide as a result of this study, which was undertaken in a different population with a different primary outcome.

Some people with type 2 diabetes may have needle phobia or may prefer an additional oral drug rather than adding a once-weekly injectable therapy to their regimen. We can now reassure them that, if they are at high risk of MACE, they can achieve similar benefits with daily oral semaglutide – provided it is taken exactly as directed, in order to optimise absorption and bioavailability.

However, in my experience, there are many reasons why people do not take oral semaglutide as directed, despite us believing we have delivered dosing instructions carefully. This is often identified when HbA_{1c} fails to reduce at the first or subsequent 3-month repeat testing and, although this gives us another opportunity to share dosing directions, the person has already spent precious time with elevated glucose levels. A telephone call to ask people how they are getting on with their oral semaglutide after 3–4 weeks, at the time of dose escalation, offers the opportunity to subtly explore how oral semaglutide is being taken and also identifies those who have had initial side effects and have stopped the drug but not yet informed us. Many of those with side effects can be encouraged to restart therapy and gain the long-term benefits, including cardiovascular protection as seen in this trial. ■

Husain M, Birkenfeld AL, Donsmark M et al; PIONEER 6 investigators (2019) Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* **381**: 841–51

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Practice points

1. For people with type 2 diabetes at high cardiovascular risk, once-daily oral semaglutide offers similar cardiovascular benefits to the once-weekly injectable formulation.
2. Effects on slowing renal progression, however, have not been demonstrated with the oral formulation in this study, whereas they have previously with subcutaneous semaglutide.
3. Remind people of the need to take oral semaglutide exactly as directed if the effects on glycaemia, weight and cardiovascular outcomes are to be realised.
4. Contact people 3–4 weeks after initiating oral semaglutide to explore whether it is being taken correctly, to monitor side effects and to discuss dose escalation.

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