NEWSLETTER 19

SOUL Trial: Oral Semaglutide and MACE Reduction

Cardiovascular protection from an oral GLP-1 in high-risk type 2 diabetes

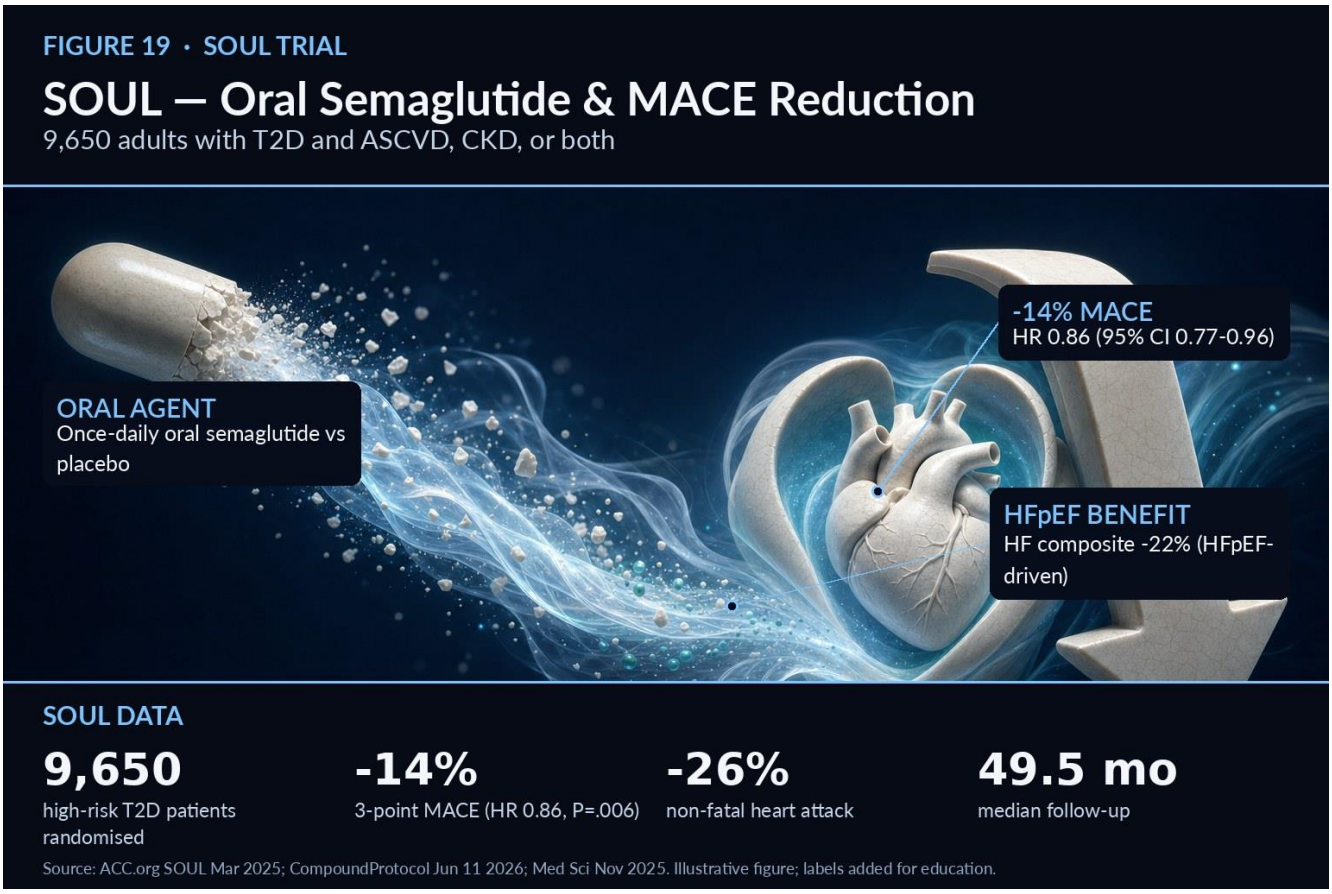

Figure 19. SOUL Trial: Oral Semaglutide and MACE Reduction — mechanism overview (illustrative; labels added for education).

The SOUL trial tested whether oral semaglutide could reduce cardiovascular events in high-risk type 2 diabetes. It randomised 9,650 patients—4,825 to semaglutide and 4,825 to placebo—all with type 2 diabetes and atherosclerotic cardiovascular disease, CKD, or both.[1] The design directly reflects the CKM population.

The primary result was positive. The three-point MACE outcome—all-cause death, non-fatal myocardial infarction, or non-fatal stroke—occurred in 12.0% of the semaglutide group versus 13.8% of placebo (HR 0.86, 95% CI 0.77–0.96, P = 0.006) over a median 49.5 months.[1] An oral GLP-1 thus delivered cardiovascular protection comparable to injectable agents.

A 2026 secondary analysis in *JAMA Internal Medicine* refined the picture, reporting a 14% MACE reduction and a 26% reduction in non-fatal heart attack, underscoring myocardial infarction as a key driver of benefit.[2]

Heart-failure findings were particularly instructive. In patients with existing heart failure, the heart-failure composite outcome fell 22% (HR 0.78, 95% CI 0.63–0.96), a benefit driven by HFpEF (HR 0.59) rather than HFrEF (HR 0.98).[2] This phenotype-specific signal aligns with the emerging role of GLP-1 therapies in obesity-related HFpEF.

SOUL's enrolment criteria make it directly relevant to CKM practice: every participant had type 2 diabetes plus established atherosclerotic disease, CKD, or both—the multi-organ overlap that defines the syndrome.[1] The long median follow-up of nearly 50 months lends durability to the MACE benefit, and the availability of an oral formulation matters for patients who are needle-averse or who face barriers to cold-chain storage, broadening who can realistically access GLP-1 cardiovascular protection.[3]

Safety and provenance are reassuring. The main SOUL trial was published in the *New England Journal of Medicine* in 2025, and oral semaglutide did not increase serious adverse events.[1,2] Independent syntheses confirm the headline: SOUL demonstrated that oral semaglutide reduced the composite of cardiovascular death, myocardial infarction, and stroke by 14% in high-risk type 2 diabetes with ASCVD and/or CKD.[3] For clinicians and patients who prefer or require an oral option, SOUL provides robust evidence that the cardiovascular benefits of the GLP-1 class extend to a once-daily tablet—an important consideration for adherence and access.

References

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