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Semaglutide and cardiovascular outcomes by baseline and changes in adiposity measurements: a prespecified analysis of the SELECT trial

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The SELECT trial demonstrated that semaglutide reduced major adverse cardiovascular events (MACE) by 20% in patients with overweight or obesity and cardiovascular disease, but without diabetes. However, the relationship between baseline adiposity measures, treatment-induced weight changes, and cardiovascular outcomes remained unclear. This prespecified analysis aimed to determine whether cardiovascular benefits depended on baseline adiposity or the magnitude of weight loss achieved.

SELECT was a randomized, double-blind, placebo-controlled trial conducted across 804 sites in 41 countries. The study enrolled 17,604 patients ≥45 years with BMI ≥27 kg/m² and established atherosclerotic cardiovascular disease (prior MI, stroke, or symptomatic peripheral artery disease), but without diabetes (HbA1c <6.5%). Patients were randomized to weekly subcutaneous semaglutide 2.4 mg or placebo, with mean follow-up of 39.8 months. The primary outcome was time to first MACE (cardiovascular death, non-fatal MI, or non-fatal stroke).

Semaglutide significantly reduced MACE compared to placebo (HR 0.80, 95% CI 0.72-0.90), with consistent benefits across all baseline weight and waist circumference categories. Within the semaglutide group, lower baseline weight was associated with a 4% reduction in MACE risk per 5 kg lower bodyweight (HR 0.96, p=0.001), and smaller waist circumference was associated with a 4% lower risk per 5 cm (HR 0.96, p=0.004). In the placebo arm, only smaller baseline waist circumference was predictive of outcomes (HR 0.96, p=0.007), while baseline weight showed no significant association.

At 20 weeks, mean weight change was -6.4% with semaglutide versus -0.8% with placebo. In the semaglutide group, there was no linear association between weight loss at week 20 and subsequent MACE risk (HR 0.95, p=0.31). In the placebo group, weight loss paradoxically associated with increased MACE risk, with non-linear effects (p=0.007) driven by higher rates in patients losing ≥5% weight.

Waist circumference decreased -5.0 cm with semaglutide versus -1.1 cm with placebo at 20 weeks. Greater waist circumference reduction at week 20 was linearly associated with lower subsequent MACE risk in the semaglutide group (HR 0.91, 95% CI 0.84-0.98; p=0.02) but not placebo (HR 0.94, 95% CI 0.86-1.02; p=0.13).

Time-varying covariate analysis showed that waist circumference reduction mediated only 33% of semaglutide's MACE benefit (adjusted HR 0.86, 95% CI 0.77-0.97), while weight loss showed no mediation effect.

No substantial differences in serious adverse events were observed across weight or waist circumference change categories in semaglutide-treated patients. However, placebo patients with ≥5% weight loss had higher all-cause mortality (7.3% vs. 5.1% and 4.9% in other groups).

Summary

The cardiovascular benefits of semaglutide were independent of baseline adiposity and weight loss magnitude. While waist circumference reduction showed some association with outcomes, it explained only one-third of the treatment effect, suggesting mechanisms beyond adiposity reduction drive most of the cardiovascular benefit.

These findings have important implications: prescribing restrictions based on BMI thresholds or weight-loss targets may be inappropriate, as patients benefit regardless of weight-loss response. The results support reconceptualizing GLP-1 receptor agonists as cardiovascular disease-modifying agents rather than primarily weight-loss medications.

The study population was predominantly White (82%) and male (72%), which may limit generalizability. Also, the analysis at week 20 excluded early MACE events (11.2% of total), though sensitivity analyses including all events showed similar patterns. The temporal relationship between adiposity changes and cardiovascular benefits requires further investigation.

References:

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