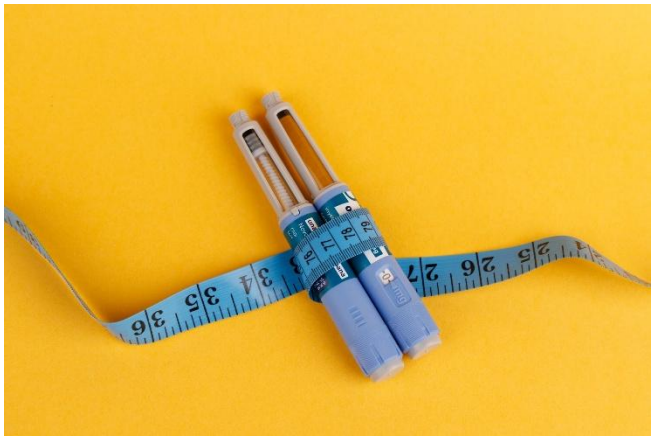
Even without Major Weight Loss Semaglutide Lowers Cardiovascular Events

Researchers examined whether baseline waist circumference and body weight, and treatment-induced changes in these measures, were associated with the risk of major adverse cardiovascular events (MACE) in adults.

Semaglutide reduced MACE consistently across all baseline adiposity levels. However, cardiovascular benefits were not associated with the degree of weight loss; reductions in waist circumference were associated with lower MACE risk and accounted for approximately one-third of the treatment effect, although this likely reflects a risk marker rather than a proven causal mediator.



Study

Researchers sought to determine whether baseline adiposity and treatment-related changes in weight or waist circumference influenced cardiovascular outcomes, and to explore the potential mechanisms underlying semaglutide's cardioprotective effects.

SELECT was a randomized, double-blind, placebo-controlled, and event-driven trial conducted across 41 countries. Adults aged 45 years or older with a BMI of 27 kg/m2 or more, and established cardiovascular disease, but without diabetes, were randomly assigned to once-weekly subcutaneous semaglutide (target dose 2.4 mg) or placebo, in addition to standard cardiovascular care. Randomization used block sizes of four, and participants and investigators were masked to treatment allocation.

Body weight was measured at baseline, every four weeks to week 20, and every 13 weeks thereafter; waist circumference was measured at baseline, week 20, and annually. The primary endpoint was time to first MACE, defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, adjudicated by an independent committee.

This prespecified analysis assessed associations between baseline adiposity and MACE risk and examined whether early (week 20) and longer-term (week 104) changes in weight or waist circumference predicted subsequent MACE. A landmark analysis was used to evaluate events occurring after week 20, acknowledging that a proportion of cardiovascular events occurred before substantial weight or waist changes had developed, which may complicate interpretation of mediation analyses.

Cox proportional hazards models were used to evaluate trends and treatment interactions. Time-varying covariate models estimated the extent to which adiposity changes statistically mediated or marked semaglutide's effect on MACE.

Findings

Among 17,604 participants, semaglutide significantly reduced the composite of MACE compared with placebo, with consistent effects across all baseline weight and waist circumference categories. In both treatment groups, lower baseline waist circumference was associated with a lower risk of MACE.

In the semaglutide group, lower baseline body weight and waist circumference were each associated with a 4% lower MACE risk per 5 kg or 5 cm decrement, respectively. In the placebo group, only waist circumference, and not body weight, showed a similar association.

By week 20, semaglutide produced substantially greater reductions in body weight (–6.4%) and waist circumference (–5.0 cm) than placebo. However, early weight loss did not predict subsequent MACE risk in the semaglutide group. Notably, in the placebo group, greater early weight loss was paradoxically associated with higher subsequent MACE risk, likely reflecting unintentional weight loss or underlying illness.

In contrast, greater reductions in waist circumference at week 20 were associated with a lower subsequent risk of MACE. At longer follow-up through week 104, greater waist circumference reduction and, to a lesser extent, a modest trend toward lower MACE with greater weight loss in the semaglutide group were associated with lower in-trial MACE incidence, whereas no consistent linear relationship was observed in the placebo group.

Mediation analysis indicated that weight loss did not attenuate the treatment effect on MACE, while changes in waist circumference accounted for approximately one-third of the cardiovascular benefit. The authors emphasized that these post-randomization associations are observational and do not establish causality. Adverse event rates were broadly similar across adiposity change categories.

Conclusion

These findings demonstrate that semaglutide reduces cardiovascular events independently of baseline adiposity and largely independently of the magnitude of weight loss. Although reductions in waist circumference, a marker of central adiposity, were associated with improved outcomes and explained part of the treatment effect, most of the cardiovascular benefit appeared unrelated to measurable changes in adiposity.

This suggests that semaglutide's cardioprotective mechanisms extend beyond weight reduction, potentially involving anti-inflammatory effects, improvements in endothelial function, blood pressure, and lipid modulation, or direct vascular and central nervous system pathways, although these mechanisms were not directly tested in this analysis.

Strengths include a large sample size, a long follow-up period, a broad BMI range, standardized adiposity measurements, and rigorous event adjudication. Limitations include limited demographic diversity (predominantly White and male participants) and the non-causal, post-randomization nature of analyses linking adiposity change to outcomes, which precludes definitive mechanistic inference and may limit generalisability to more diverse populations.

These results support reconceptualizing GLP-1RAs such as semaglutide as cardiovascular disease-modifying therapies rather than solely weight-loss treatments, with implications for prescribing practices and health policy.

Source:

https://www.news-medical.net/news/20260211/Semaglutide-lowers-cardiovascular-events-even-without-major-weight-loss-researchers-report.aspx