For Heart Health Semaglutide Dose may Matter more than Weight Loss

The amount of semaglutide patients receive may matter more for long-term heart health than the amount of weight they lose.

Study

Obesity, characterized by excessive fat accumulation in the body, is a major risk factor for cardiovascular disease and related mortality. Glucagon-Like Peptide-1 (GLP-1) receptor agonists, including semaglutide, have shown immense promise in reducing body weight, improving blood glucose control, and providing cardiometabolic benefits.

These diverse therapeutic effects of semaglutide raise a vital mechanistic question, namely whether these effects align along a single axis, or whether the drug provides separable cardiovascular benefits that are independent of the magnitude of weight reduction achieved.

Semaglutide-mediated weight loss does not only depend on the drug dose. Several factors can potentially contribute to the final treatment outcome, including treatment adherence, tolerability, metabolic profile, and pre-existing health conditions of patients.

Given this multifactorial involvement and the fact that weight loss represents a composite physiological response, researchers at nference, a US-based health technology company, hypothesized that semaglutide-mediated weight loss and cardiovascular protection are not necessarily inter-connected responses, and that the magnitude of weight loss may not predict cardiovascular outcomes.

To investigate this hypothesis, the researchers analyzed longitudinal clinical data from a federated, de-identified U.S. electronic health record network comprising 47,199 patients with at least one documented baseline cardiovascular condition who initiated semaglutide.

A total of 12,519 patients met the inclusion criteria for the primary dose analysis, and their clinical data on dose escalation and weight change during the first two years after semaglutide initiation were assessed in relation to cardiovascular outcomes during the subsequent two years.

Findings

The analysis showed that patients who attained higher semaglutide doses during the first two years of treatment also lost more weight, with each 1 mg increase in dose associated with an additional 3.15% reduction in body weight.

More importantly, patients who reached a higher maximum semaglutide dose (1.7 mg or greater) during this period experienced significantly lower risks of all-cause mortality, composite cardiovascular events, cerebrovascular disease, and heart failure over the following two years than those whose maximum dose remained between 0.25 mg and 1.0 mg.

The researchers then examined whether these cardiovascular benefits were explained by the amount of weight patients lost. While greater maximum achieved weight loss during the first two years was strongly associated with improved glycemic control and lower blood pressure during subsequent follow-up, it was not significantly associated with a lower risk of all-cause mortality or composite cardiovascular events. These findings suggest that the cardiovascular benefits observed in the study were more closely associated with attained semaglutide dose than with weight loss alone.

To place these findings into a broader clinical context, the researchers also compared semaglutide with other commonly prescribed anti-diabetic medications. In propensity-matched analyses, semaglutide treatment was associated with lower rates of several cardiovascular outcomes than treatment with metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors.

Because attained semaglutide dose appeared to align more closely with cardiovascular outcomes than maximum achieved weight loss, the researchers explored whether the drug might exert direct effects on the heart. Analysis of a whole-body single-cell atlas and publicly available transcriptomic datasets revealed relatively high GLP1R transcript expression in cardiac tissue, particularly in cardiomyocytes and cardiac endothelial cells. While these findings provide biological plausibility for a direct cardiac mechanism, they do not demonstrate functional receptor activity or confirm that semaglutide acts directly on these cells.

Conclusion

The findings suggest that the cardiovascular benefits associated with semaglutide may not be fully explained by the amount of weight patients lose while taking the drug. Instead, the results indicate that therapeutic exposure, reflected by the maximum dose patients attained, may better capture the mechanisms underlying long-term cardiovascular protection.

These observations support growing evidence that semaglutide's effects extend beyond weight management and glucose control, while also highlighting that weight loss alone may not be an adequate surrogate for predicting cardiovascular benefit. However, because this was a retrospective observational study, the findings cannot establish that higher semaglutide doses directly caused the improved cardiovascular outcomes, and unmeasured confounding factors may have influenced the observed associations.

While the findings raise the possibility that semaglutide's cardiovascular benefits extend beyond its effects on weight loss, the authors stress that the underlying mechanisms remain unclear. They suggest that future studies should investigate how cumulative drug exposure, peak drug concentrations, and treatment adherence contribute to cardiovascular protection, as well as whether GLP-1 signaling in cardiac and epicardial adipose tissues plays a direct role.

The study has several limitations. As a retrospective analysis of electronic health records, it is susceptible to selection and ascertainment bias, and cardiovascular conditions and outcomes were identified primarily using ICD diagnostic codes, which may not always reflect specialist-confirmed diagnoses. In addition, all participants had at least one documented cardiovascular condition at baseline, limiting the generalizability of the findings to patients without pre-existing cardiovascular disease.

The researchers also did not directly account for treatment duration or adherence, both of which are known to influence long-term outcomes. Furthermore, laboratory and physiological measurements, including body weight, hemoglobin A1c, and blood pressure, were only available for subsets of patients, which may have affected some analyses. Prospective studies will be needed to determine whether the observed associations reflect a direct effect of semaglutide exposure or other factors linked to treatment patterns and patient characteristics.

Source:

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