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Reducing cardiovascular outcomes with semaglutide: a metabolic route for a SELECT few

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Comment on the article 'Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes' presented at the American Heart Association Scientific Sessions on 11 November 2023, and simultaneously published in the *New England Journal of Medicine;* DOI: 10.1056/NEJMoa2307563.

Key Points

- In the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity trial, the SELECT Investigators tested the hypothesis that the addition of semaglutide, a glucagon-like peptide-1 receptor agonist (GLP1-RA), to standard care would reduce the risk of major adverse cardiovascular events (MACE) among patients with overweight or obesity and pre-existing cardiovascular disease (CVD) who did not have diabetes.[1]
- SELECT was a company-funded, multicentre, double-blind, randomized, placebo-controlled, event-driven superiority trial. Patients were eligible if they were 45 years of age or older, had a body mass index (BMI) of 27 kg/m^2 or higher, and had established CVD [defined as previous myocardial infarction (MI), previous stroke, or symptomatic peripheral arterial disease]. Key exclusion criteria were a previous diagnosis of diabetes, a baseline glycated haemoglobin (HbA1c) level of 6.5% or higher, treatment with any glucose-lowering medication or GLP1-RA within the previous 90 days, New York Heart Association class IV heart failure (HF), or end-stage kidney disease or dialysis.
- Patients were randomly assigned in a 1:1 ratio, without stratification, to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg (to be escalated from a starting dose of 0.24 mg over 16 weeks) or placebo. Patients were treated for the underlying CVD according to evidence-based recommendations. If diabetes mellitus developed during the trial, the patient continued to take the assigned trial product, and the use of glucose-lowering medications was at the discretion of the Investigator, with the exception of open-label treatment with a GLP1-RA that was prohibited by the protocol.
- The primary efficacy endpoint was a composite of death from CV causes, non-fatal MI, or non-fatal stroke, assessed in a time-to-first-event analysis. Confirmatory secondary endpoints, tested in hierarchical order, were CV death, a composite HF endpoint (CV death or hospitalization or an urgent medical visit for HF), and death from any cause. The basic assumptions for the sample size calculation were a 2.2% annual rate of MACE in the placebo group and a 17% relative risk reduction in the semaglutide group. A minimum of 1225 primary endpoint events were required for 90% power to detect such a benefit.
- From October 2018 through March 2021, a total of 17 604 patients (mean [± SD] age, 62 ± 9 years; 72% male) underwent randomization. The mean BMI was 33.3 ± 5.0 kg/m^2, and about three out of four patients met the BMI criterion for obesity (≥30). The mean HbA1c level was 5.8 ± 0.3%, and two out of three patients met the glycated haemoglobin criterion for pre-diabetes (defined as a mean level of 5.7% to 6.4%). More than three-quarters of the patients had had a previous MI, and nearly one-quarter had chronic HF. About 90% of the patients were receiving lipid-lowering medications and antiplatelet agents, 70% were taking beta-blockers, 45% angiotensin-converting-enzyme inhibitors, and 30% angiotensin-receptor blockers. Patients were followed up for a mean of 40 ± 9 months. The mean duration of exposure to semaglutide or placebo in the overall trial population was 34 ± 14 months. The mean change in body weight over the first two years after randomization was −9.4% with semaglutide and −0.9% with placebo.
- A primary endpoint event occurred in 569 of the 8803 patients (6.5%) in the semaglutide group and 701 of the 8801 patients (8.0%) in the placebo group [hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.72 to 0.90; $P < .001$]. Death from cardiovascular causes occurred in 223 patients (2.5%) in the semaglutide group and in 262 patients (3.0%) in the placebo group (HR, 0.85; 95% CI, 0.71 to 1.01; $P = .07$). Because this difference did not meet the required P value for hierarchical testing, superiority testing was not performed for the remaining confirmatory secondary endpoints. The effects of semaglutide on the primary endpoint appeared to be similar across all pre-specified subgroups. Adverse events leading to treatment discontinuation occurred twice more frequently with semaglutide than placebo (16.6% vs. 8.2%; $P < .001$), largely due to gastrointestinal and gallbladder disorders. Permanent premature discontinuation of study drug occurred in 27% of the semaglutide group and 24% of the placebo group.

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Comment

In a collaborative analysis of individual participant data from almost 900 000 adults in 57 prospective studies, overall mortality was lowest at a BMI in the range of 22.5 to 25 kg/m^2 in both sexes and at all ages.[2] Above this range, each 5 kg/m^2 higher BMI was associated with ~30% higher all-cause mortality (40% for vascular, and 10% for cancer mortality).[2] Although BMI and waist circumference are not directly causal, both are closely correlated with aspects of adiposity that directly affect blood pressure, lipid levels, and diabetes mellitus.[2] Effective interventions for weight loss lower blood pressure, favourably affect lipoprotein particles, and increase insulin sensitivity. Therefore, at least some of the major adverse effects of obesity are reversible.[2]

The results of the SELECT trial are consistent with these premises by showing that body weight reduction by semaglutide was associated with small reductions in HbA1c (and fewer patients developed a HA1c level ≥ 6.5%), blood pressure, LDL-cholesterol and triglyceride levels, and high-sensitivity C-reactive protein. Furthermore, this study convincingly showed that exposure to a GLP1-RA for ~3 years reduced the incidence of MACE by 20%, largely due to a 28% reduction in non-fatal MI, with a similar time frame as the body weight reduction, i.e. an early effect persisting for the duration of follow-up. Although a reduction in mortality would be expected from appreciable body weight reduction based on the epidemiological association, and SELECT mortality data trend in this direction, the trial was not powered to detect and reliably quantitate a mortality benefit. The favourable trend of mortality data is reassuring from a perspective of long-term safety.

The magnitude of the effect of semaglutide in the current trial was similar to that among patients with type-2 diabetes and pre-existing CVD or cardiovascular risk factors, in previous studies.[3] However, given the ~2.5% annual rate of MACE in the SELECT control population, the cardioprotective effect of semaglutide translated into five vascular events avoided per 1000 patients treated for one year (number-needed-to-treat, 200). How this benefit compares to those of other body weight or cardiovascular risk lowering strategies[4,5] in a similar secondary prevention population without diabetes, both in terms of effect size and cost, remains to be investigated.

Mechanisms of cardiovascular risk reduction by semaglutide remain speculative, and may include direct, though uncharacterized, effects of semaglutide and those related to physiological benefits from the reduction of excess abnormal body fat. The latter has been shown to improve the systemic proinflammatory and prothrombotic milieu associated with obesity.[6,7] GLP1-RA have been shown to reduce ectopic adipose tissue depots, such as perivascular and epicardial adipose tissue, that impose direct adverse effects on the vascular endothelium and myocardium.[8,9] Limited evidence for direct inhibition of atherosclerotic plaque progression through the down-regulation of multiple inflammatory and metabolic pathways comes from animal models.[10] It should be noted that in the placebo group, there was no apparent relationship between baseline BMI and risk of MACE during follow-up (8.1% at BMI < 30 and 8.1% at BMI > 45), with 71% of patients at BMI < 35 experiencing numerically larger risk reductions than those with higher BMI values.

The major strength of the SELECT trial is related to the large population and 3-year follow-up, that combined with a realistic sample size calculation preserved the planned statistical power of the study. Weaknesses of SELECT are represented by the fact that only patients with pre-existing CVD were studied, and by the limited generalizability of the findings given that only 28% of the participants were women, precluding a reliable assessment of the effects of semaglutide, and only 4% were Black persons.

We conclude that the present study confirms the well-established cardioprotective effect associated with GLP1-receptor agonism in other settings, but fails to identify a specific clinical phenotype of high-risk patients without diabetes in whom the absolute benefit of semaglutide may justify favouring this particular pharmacological intervention *vis-à-vis* other competing preventive strategies.

Declarations

Disclosure of Interest

G.L. reports personal fees for speaker bureau from Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Daiichi Sankyo, Sanofi, and Novartis, outside the submitted work. C.P. reports personal fees from AbbVie, Acticor Biotech, Bayer, Eli Lilly, and Tremeau, and grant support (to the Institution) for investigator-initiated research from AIFA (Italian Drug Agency), Bayer, Cancer Research UK, and European Commission; he chaired the Scientific Advisory Board of the International Aspirin Foundation.

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