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SELECT semaglutide to improve outcomes in patients with obesity and cardiovascular disease, also without diabetes

Grzegorz Gajos[1, 2]

[1]Department of Coronary Artery Disease and Heart Failure, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[2]St. John Paul II Hospital, Kraków, Poland

More than half the world population is expected to be overweight or obese by the year 2035 [1]. Obesity and atherosclerotic cardiovascular disease have always been a fatal combination. There is evidence on the causal relationships between obesity and cardiovascular diseases (CVD), and most of obese patients die because of cardiovascular complications. Moreover, obesity is related to increased mortality in patients with CVD. Unfortunately, the incidence of obesity in patients with CVD is increasing. In this Journal, Jankowski et al. showed a gradual and alarming increase in BMI and waist circumference in patients with established coronary artery disease over the course of 2 decades in Poland [2]. Moreover, the COVID-19 pandemic revealed that obese people infected with SARS-CoV-2 were at a higher risk of developing more severe and fatal disease [3].

Given these effects of obesity, lowering body mass is recommended as an essential component of cardiovascular risk reduction strategies. However, the use of pharmacotherapies in treating obesity has been hampered by the lack of evidence from cardiovascular outcome trials indicating that such interventions can improve cardiovascular outcomes. In those trials, weight-loss agents (e.g. sibutramine, rimonabant, naltrexone/bupropion, lorcaserin) that were administered in high-risk cardiovascular patients helped them to reduce body weight successfully but did not improve cardiovascular outcomes. On the contrary, since some of those drugs were related to significant side effects, they have been withdrawn from the market. Only glucagon-like peptide-1 (GLP-1) receptor agonists have been recently shown to produce substantial weight loss — comparable to bariatric surgery — and to lower the risk of cardiovascular disease in patients with diabetes [1, 3].

Therefore, I consider the results of the recently published SELECT study (Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes) groundbreaking [1]. The study evaluated whether treatment with semaglutide (once-weekly subcutaneous 2.4 mg) in comparison to matching placebo would reduce the risk of major cardiovascular events among 17 604 patients with pre-existing cardiovascular disease and overweight or obesity who did not have diabetes. The trial was a collaborative effort at 804 clinical sites in 41 countries. I had the privilege of being the national leader of the study in Poland, where we enrolled 640 patients, were a member of the Global Expert Panel, and co-authored some major publications with trial results.

Most of the patients in the trial had previous MI (76%) and obesity (71%). The average HbA1c was approx. 5.8%. Of note, before randomization, prior heart failure occurred in 24% of participants and stroke in 18%. Therefore, it was a high-risk population for both cardiovascular and metabolic events. SELECT was a cardiovascular outcome trial, not a weight loss study- patients received standard-of-care recommendations for secondary CVD prevention (but without a focus on targeting weight loss). Over a mean of approximately 40 months, semaglutide reduced the risk of the

Address for correspondence: Prof. Grzegorz Gajos, Department of Coronary Artery Disease and Heart Failure, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland, e-mail: grzegorz.gajos@uj.edu.pl.

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composite cardiovascular endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke by 20% (hazard ratio, 0.80; 95% confidence interval, 0.72–0.90; $p < 0.001$). On average, semaglutide treatment resulted in a substantial 9.4% reduction in body weight. There was no increase in rates of serious safety events with semaglutide [1].

The difference in cardiovascular disease incidence between semaglutide and placebo arms emerged very early after initiation of the treatment, even before significant weight loss appeared. Consistent trends were seen for each component of the composite outcome as well as for death from any cause. However, confirmatory secondary endpoints (heart failure events, all-cause mortality) were tested with a hierarchical strategy using a separate alpha-spending function. As the reduction in the first secondary confirmatory endpoint (cardiovascular death) was nonsignificant ($p = 0.065$), we could not apply statistical testing to other secondary endpoints. However, confidence intervals were well below 1.0 for both heart failure composite (HR 0.82; 95% CI, 0.71 to 0.96) and death from any cause (HR 0.81; 95% CI, 0.71 to 0.93) strongly suggestive of a clinical benefit [1]. The observation of a more pronounced reduction in all-cause mortality compared to cardiovascular mortality may be strongly related to the fact that the SELECT trial was performed at the peak of the COVID-19 pandemic. In my opinion, probably, the classification of the causes of death (CVD vs. non-CVD) could be hampered during that period [1, 3].

Mechanisms of cardiovascular benefit with semaglutide remain speculative but likely involve multiple pathways relating to weight reduction, improvements in glycaemia and other cardiovascular risk factors, potential beneficial effect on visceral/ /ectopic fat formation, reductions in inflammation, and perhaps direct pharmacologic effects on cardiomyocytes, vascular and platelet function [4].

We have recently published interesting data on metabolic outcomes in the SELECT trial [5, 6]. Firstly, as most (66.4%) of participants in SELECT had prediabetes (HbA1c ≥ 5.7%), we have demonstrated that with the use of semaglutide, there was a 73% reduction in the relative risk of developing diabetes. This is a breakthrough in the treatment of patients with prediabetes because, until now, we can only offer them lifestyle interventions and metformin [5]. Secondly, we have shown that the cardiovascular benefits of semaglutide are independent of baseline or magnitude of change in HbA1c, suggesting important pleiotropic factors besides its glucose-lowering effect [6].

Irrespective of the mediators of benefit, the groundbreaking SELECT trial establishes obesity as a modifiable risk factor for cardiovascular disease. SELECT demonstrates that the use of semaglutide in those with established cardiovascular disease who are overweight or obese, even without diabetes, should take its place alongside other standard evidence-based practices of secondary atherosclerotic cardiovascular disease prevention. Therefore, semaglutide should be considered the new statin of the 21st century and should join the list of established and guideline-recommended therapies necessary to reduce cardiovascular disease risk.

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