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Research Article

Semaglutide: The First Anti-Obesity Agent Shown to Decrease Cardiovascular Events

Nasser Mikhail[1]* and Soma Wali[2]

[1]Endocrinology Division, David-Geffen UCLA Medical School, USA.
[2]Department of Medicine, David-Geffen UCLA Medical School, USA

*Corresponding author
Nasser Mikhail, Endocrinology Division, David-Geffen UCLA Medical School, USA

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Abstract

The anti-obesity agent, semaglutide (2.4 mg/week) was evaluated in a large (n=17,604) multinational randomized trial called SELECT to examine its effects on cardiovascular (CV) outcomes in overweight/obese patients with preexisting CV disease and no diabetes. The primary outcome of SELECT trial was a composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. Over a mean duration of follow-up of 39.8 months, a primary CV outcome occurred in 6.5% in the semaglutide group and 8.0% in the placebo group; hazard ratio (HR) 0.80 (95% CI, 0.72 to 0.90; P<0.001). Mean change in body weight over 104 weeks was -9.4% and -0.9% with semaglutide and placebo, respectively; estimated treatment difference (ETT) -8.5% (95% CI, -8.5 to -8.3). There was significant amelioration in blood pressure and plasma levels of lipids, glycated hemoglobin (HbA1c), and C- reactive protein (CRP). The incidences of diabetes and prediabetes were reduced by 73% and 67%, respectively with semaglutide. 16.6% of patients discontinued semaglutide due to adverse effects, mainly gastrointestinal (GI) compared with 8.2% who discontinued placebo (P<0.001). In conclusion, semaglutide is the first anti-obesity agent shown to decrease CV events in overweight/obese subjects with CV disease without diabetes. Further studies are needed to examine the impact of semaglutide on CV events in obese subjects without underlying CV disease.

ABBREVIATIONS

CV: Cardiovascular; BMI: Body Mass Index; ETD: Estimated Treatment Difference; HR: Hazard Ratio.

INTRODUCTION

The incidence of obesity is increasing worldwide and represents a major public health problem [1-4]. Although some studies have shown decreased mortality with higher degrees of obesity (the so-called obesity paradox), most investigations suggest increased all-cause mortality with greater values of body mass index (BMI) [2,5,6]. Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved for treatment of type 2 diabetes and obesity. In a subcutaneous dose of 1.0 mg/week, use of semaglutide was associated with reduction in CV events in patients with type 2 diabetes and prevalent CV disease [7]. In its highest approved doses of 2.4 mg/week, the drug was also effective in decreasing weight in obese subjects with and without diabetes [8,9]. Moreover, the CV effects of semaglutide in obese subjects without diabetes were recently published in the SELECT trial [10]. Indeed, before the release of data from the SELECT study, no agents from the approved obesity pharmacotherapy was shown to decrease CV events in obese subjects [11,12]. The purpose of this article is to provide an appraisal on semaglutide as the first anti-obesity drug capable of reducing CV events in subjects with obesity and prevalent CV disease but without diabetes.

OVERVIEW OF THE SELECT TRIAL

The SELECT trial is a multinational, randomized, placebo-controlled, double blind megatrial (n=17,604) conducted in 41 countries across 6 continents [13]. The main objective of SELECT trial was to compare the effects of semaglutide versus placebo on the incidence of CV outcomes in patients with overweight (BMI ≥27-29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) [10,13]. All patients had to have pre-existing CV (67% with MI, 17% with stroke, 4% with peripheral vascular disease, and 8% with more than 1 CV disease) [10]. Patients in the SELECT trial were randomized into 2 groups. In the first group (n=8,803), intervention consisted of semaglutide 2.4 mg given subcutaneously once a week in a starting dose of 0.24 mg/week to be escalated to reach the target dose of 2.4 mg/week after 16 weeks. The second group of patients (n=8,801) received matching placebo. Semaglutide or placebo was added to standard care without recommendation of specific diets or exercise for weight loss. Follow-up lasted 104 weeks, with a mean of 39.8 months [10]. Overview of SELECT trial is summarized in table 1.

Table 1. Overview of SELECT trial

Design	Randomized, double-blind, placebo-controlled, multinational, 2 groups
Patients' characteristics	72.3% males, age 61.6 years, with pre-existing CV disease and BMI ≥27 kg/m^2, and no history of diabetes
Baseline weight (kg) and BMI (kg/m^2)	96.6 kg and 33.3 kg/m^2
Intervention	Semaglutide 2.4 mg subcutaneously once-weekly (n=8,803) versus placebo (n=8,801)
Primary outcome	Composite of CV death, non-fatal myocardial infarction, or non-fatal stroke
Follow-up	39.8 months
Effect of semaglutide on primary outcome	Primary outcome CV event occurred in 6.5% with semaglutide vs 8.0% with placebo; HR 0.85 (95% CI: 0.72 to 0.90; P<0.001)
Effect of semaglutide on weight	-9.4% with semaglutide vs -0.9% with placebo, ETD -8.5% (95% CI, -8.7 to -8.2)
Proportions of patients who discontinued trial product due to adverse effects	16.6% with semaglutide vs 8.2% with placebo; P<0.001

Effects of semaglutide on cardiovascular outcomes in SELECT trial

The primary outcome of the SELECT trial, a composite of CV death, nonfatal MI or nonfatal stroke occurred in 6.5% of patients and 8.0% of patients in the placebo group; HR 0.80 (95% CI, 0.72 to 0.90; P<0.001) [10]. Regarding individual components of the primary end point, reduction in death from CV causes did not reach statistical significance (HR 0.85, 95% CI 0.71 to 1.01), which according to the statistical analysis, of the SELECT trial, precluded calculation of P values in the remaining outcomes. Meanwhile, there was a clear trend of benefit in all other CV endpoints. Thus, compared with the placebo group, nonfatal MI was reduced by 28% in the semaglutide group; HR 0.72 (95% CI, 0.61 to 0.85), and non-fatal stroke by 7%; HR 0.93 (95% CI, 0.74 to 1.15). Importantly, death from any cause, a confirmatory secondary endpoint, was decreased by 19% with semaglutide; HR 0.81 (95% CI, 0.71 to 0.93) [10]. Frequency of hospitalization or urgent medical visit for heart failure was decreased by 21% with semaglutide (HR 0.79, 95% CI 0.60 to 1.03) [10]. Likewise, frequency of coronary revascularization was reduced by 23%; HR 0.77 (95% CI, 0.68 to 0.87), and unstable angina requiring hospitalization by 13%; HR 0.87 (95% CI, 0.67 to 1.13) [10].

With the respect to the timing of occurrence CV events, the separation between the semaglutide and placebo curves for the primary outcome started approximately 6 months after randomization and continued to widen with follow-up [10]. In addition, the effects of semaglutide on the primary end point were similar in different subgroups of subjects classified by age, gender, BMI, and type of CV disease [10].

Effect of semaglutide on renal function

In the SELECT trial, effects of semaglutide on renal function was evaluated in a five-component composite secondary end point that included death from renal causes, initiation of long-term renal replacement therapy, onset of a persistent estimated glomerular filtration rate (eGFR) <15 ml/min.1.73 m^2, persistent 50% reduction in eGFR relative to baseline, or onset of persistent macroalbuminuria (urinary albumin-to-creatine ratio > 300 mg/g [10]. During follow-up, 1.8% of patients receiving semaglutide reached this endpoint compared with 2.2% among patients receiving placebo, HR 0.78 (95% CI, 0.63 to 0.96) [10].

Effect of semaglutide on body weight and waist circumference

From randomization to 104 weeks, mean change in BMI was -9.3% in the semaglutide group compared with -0.8% in the placebo group; ETT -8.5% (95% CI, -8.7 to -8.3) [10]. Maximum weight reduction was achieved after approximately 15 months of intervention, then reached a plateau without evidence of rebound up to the end of follow-up [10]. Waist circumference (WC), an indicator of abdominal fat, was decreased in the semaglutide and placebo groups by -7.5 and -1.0 cm, respectively, ETT -6.5 cm (95% CI, -6.8 to -6.3) [10].

Effects of semaglutide on cardiovascular risk factors

The placebo-corrected reduction in systolic blood pressure (SBP) by semaglutide was 3.1 mmHg (95% CI, 3.75 to 2.9), in diastolic blood pressure (DBP) was 0.5 mmHg (95% CI, 0.8 to 0.3), and HbA1c by 0.32 percentage points [10]. Regarding lipid profile, there were modest but significant placebo-corrected reductions in plasma levels of low-density lipoprotein cholesterol (LDL-C) by 2.1%, total cholesterol by 2.8%, triglycerides by 15.6%, and an increase in high-density lipoprotein cholesterol (HDL-C) by 4.2% [10]. Moreover, there was significant placebo-corrected reduction in CRP, a marker of systemic inflammation, by 37.8% [10].

Effects of semaglutide on incidence of diabetes and pre-diabetes

During follow-up of the SELECT study, new-onset type 2 diabetes (defined as reaching HbA1c levels ≥6.5%) was diagnosed in 3.5% and 12.0% of subjects in the semaglutide and placebo groups, respectively, i.e. 73% reduction, HR 0.27 (95% 0.24 to 0.31) [10]. Furthermore, pre-diabetes (defined as HbA1c ≥ 5.7%) was diagnosed in 21.3% and 50.4% among subjects randomized to semaglutide and placebo, respectively, i.e. 67% reduction, HR 0.33 (95% CI, 0.30 to 0.36) [10].

Mechanisms of CV benefits of semaglutide

The mechanisms whereby semaglutide decreased CV outcomes are likely multifactorial. The weight loss-inducing effect of semaglutide is a major cause leading to amelioration in CV risk factors such as blood pressure, dyslipidemia and blood glucose

levels. In a large pooled analysis of 97 cohort studies, 46% of excess risk of coronary heart disease and 76% of excess risk for stroke that was attributed to high BMI were mediated through high blood pressure, total serum cholesterol and glucose, with high blood pressure being the most important contributor [6]. A decrease in systemic inflammation as reflected by the significant decrease in CRP levels by semaglutide is another contributing factor [10]. Other potential mechanisms include improvement in exercise tolerance as recently demonstrated by Kosibord et al [14], in obese patients with heart failure and preserved ejection fraction. In addition, direct beneficial effects of semaglutide on CV and renal systems cannot be excluded but require further studies.

Safety of semaglutide

Overall, no increase in serious adverse effects occurred with semaglutide [10]. However, the proportions of subjects who discontinued semaglutide due to adverse effects was significantly higher than those who discontinued placebo, 16.6% and 8.2% respectively (P<0.001) [10] (Table 1). GI adverse effects were the main reasons of discontinuation of semaglutide (10.0% versus 2.0% with placebo [10]. Interestingly, hypoglycemia was not reported in any semaglutide-treated patient [10].

Advantages of semaglutide

In the SELECT trial, the significant improvements in weight, WC, CV risk factors (blood pressure, plasma lipids, hyperglycemia, and CRP) translated into a clinically meaningful 20% reduction in CV outcomes in overweight/obese patient with underlying CV disease [10]. These results were long-waited in view of the alarming trend of increased CV deaths related to obesity across racial groups, with an overall 3-fold increase in age-adjusted mortality between 1999 and 2020 [1]. It should be emphasized that the significant relative reduction of 20% in CV outcomes by semaglutide (2.4 mg/week) occurred above the established CV benefits achieved by the standard of care in this population. In fact, 90% of subjects in the SELECT trial were already receiving statins, 75% angiotensin -converting-enzyme inhibitors or angiotensin-receptor blockers [10,13]. These proportions were similar in the semaglutide and placebo groups [10,13].

Limitations of semaglutide

Suboptimal tolerance to semaglutide, mainly due to the high frequency of GI adverse effects, represents the most important limitation of this drug. To minimize such effects, the SELECT investigators used small starting dose of 0.24 mg/week followed by slow dose up-titration to reach the target dose of 2.4 mg/week after 16 weeks [10]. In addition, the dose escalation intervals were allowed to be prolonged, treatment could be temporarily suspended, or patients might use use small maintenance doses [10]. Despite these precautions, 16.6% of subjects were not able to continue semaglutide as opposed to 8.2% in the placebo group [10]. Another important limitation is that patients in the SELECT trial were relatively "healthy" without significant co-morbidities. For instance, renal function at baseline was close to normal (mean eGFR ± SD was 82.4±17.5 ml/min/1.73 m^2) with only 11% of patients having eGFR < 60 ml/min/1.73 m^2 [10,13]. This observation is difficult to justify because only end-stage kidney disease was an exclusion criterion in the SELECT trial [10]. A third limitation is that most patients (84%) were Whites, with fewer than 5% Blacks limiting generalization of the study results [10,13]. In fact, in the USA, Black individuals have higher obesity-related CV age-adjusted mortality rates than any other racial groups [1].

CONCLUSIONS AND CURRENT NEEDS

Strong data derived from the large and adequately powered SELECT trial suggest that semaglutide 2.4 mg/week decreases CV events in overweight/obese subjects without diabetes by 20% over a mean follow-up of 39.8 months [10]. This significant reduction was likely attributed to the placebo-adjusted weight loss of 8.5% that led to improvement of several CV risk factors, namely hypertension and dyslipidemia and decrease incidence of type 2 diabetes and pre-diabetes [10]. Randomized trials are required to see the effects of semaglutide and other incretin-based therapy on CV events and mortality in a wider range of obese population to include higher proportions of minorities, subjects who do not have pre-existing CV disease, patients with advanced stages of severe kidney disease, and patients with more severe degrees of obesity (e.g. BMI close to 40 kg/m^2). In addition, longer duration of follow-up of 4-5 year-duration is necessary to see whether CV benefits of semaglutide would persist or even increase with time.

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