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BRIEF REPORT

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Effects of glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on cardiovascular and renal outcomes across body mass index categories in type 2 diabetes: Results of the LEADER and SUSTAIN 6 trials

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Abstract

Associations between body mass index (BMI) and the cardiovascular (CV) and kidney efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients with type 2 diabetes (T2D) are uncertain; therefore, data analysed separately from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) were examined. These international, randomized, placebo-controlled trials investigated liraglutide and semaglutide (both subcutaneous) in patients with T2D and at high risk of CV events. In post hoc analyses, patients were categorized by baseline BMI (<25, ≥25-<30, ≥30-<35 and ≥35 kg/m^2), and CV and kidney outcomes with GLP-1 RA versus placebo were analysed. All baseline BMI data from LEADER (n = 9331) and SUSTAIN 6 (n = 3290) were included (91% and 92% of patients with overweight or obesity, respectively). In SUSTAIN 6, nominally significant heterogeneity of semaglutide efficacy by baseline BMI was observed for CV death/myocardial infarction/stroke (major adverse CV events, primary outcome of both; $P_{interaction}$ = .02); otherwise, there was no statistical heterogeneity for either GLP-1 RA versus placebo across BMI categories for key CV and kidney outcomes. The lack of statistical heterogeneity from these cardiorenal outcomes implies that liraglutide and semaglutide may be beneficial for many patients and is probable not to depend on their baseline BMI, but further study is needed.

KEYWORDS

body mass index, cardiovascular, liraglutide, major adverse cardiovascular events, semaglutide

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1 | INTRODUCTION

While some glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been shown to reduce major adverse cardiovascular (CV) events (MACE) in people with type 2 diabetes (T2D), they are also a recommended treatment when there is a compelling need for such patients to lose weight.[1,2] Several factors have been linked to these reported CV benefits, but their precise roles are unknown.[3] One such factor is baseline body mass index (BMI), whose impact has only been investigated on limited treatment outcomes with GLP-1 RAs.[4] Although weight loss associated with GLP-1 RA use increases with increasing BMI,[4] it is unknown if other effects vary by BMI. We investigated if the CV and kidney outcomes with GLP-1 RAs are consistent across the spectrum of BMI, using data from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER[5]) trial and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6[6]) analysed separately.

2 | MATERIALS AND METHODS

2.1 | Study design

The LEADER and SUSTAIN 6 trial designs have been published.[5,6] In brief, both trials were double-blind and placebo-controlled. Patients with T2D and at high risk of CV events were randomly assigned to the GLP-1 RA or placebo (once-daily subcutaneous [s.c.] liraglutide 1.8 mg or maximum tolerated dose vs. placebo in LEADER, 1:1 ratio; once-weekly s.c. semaglutide 0.5 or 1.0 mg vs. volume-matched placebo in SUSTAIN 6, 1:1:1:1 ratio [pooled as semaglutide vs. placebo for analyses]), with all patients otherwise treated according to standard of care.[5,6] Key inclusion criteria in both trials were being aged 50 years or older with established CV disease (previous coronary, cerebrovascular or peripheral vascular disease), heart failure (New York Heart Association class II or III), or chronic kidney disease stage 3 or higher; or being aged 60 years or older with at least one CV risk factor (microalbuminuria or proteinuria, hypertension with left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index of <0.9).[5,6] Major exclusion criteria included use of GLP-1 RAs, dipeptidyl peptidase-4 inhibitors, pramlintide or rapid-acting insulin, and recent history of an acute coronary or cerebrovascular event.[5,6]

The primary composite outcome in both trials was first occurrence of MACE (CV death, non-fatal myocardial infarction or non-fatal stroke). The key secondary expanded outcome (expanded MACE) also included hospitalization for unstable angina or heart failure, or revascularization. The secondary composite renal outcome (termed nephropathy) was comprised of new-onset or persistent macroalbuminuria, persistent doubling of serum creatinine level and creatinine clearance of less than 45 mL/min/1.73m^2, the need for continuous renal-replacement therapy or death from kidney disease. Both trials were approved by institutional review boards or ethics committees for each centre; all patients provided written informed consent.[5,6]

Weight and height were measured by investigators at baseline and BMI was calculated. BMI was also assessed at designated visits throughout both trials.[5,6]

2.2 | Statistical methods

Details of the primary statistical analyses conducted in these trials have been described.[5,6] For the present post hoc analyses, the effects of liraglutide and semaglutide on the time-to-first primary MACE, expanded MACE, CV death and nephropathy were evaluated by baseline BMI category, separately for the two trials. BMI was categorized based on cut-off values described by the World Health Organization (<25, ≥5 to <30, ≥30 to <35 and ≥35 kg/m^2, defining overweight as BMI ≥25 kg/m^2 and obesity as BMI ≥30 kg/m^2).[7] The significance of the differences between the baseline characteristics across these BMI categories was assessed using a Kruskal–Wallis test for continuous variables and a chi-square test for categorical variables regardless of treatment group. The Cochran–Armitage trend test was used to analyse event rates across BMI groups in the placebo groups of both trials. The hazard ratios (HRs) and 95% confidence intervals (CIs) for treatment versus placebo were calculated using Cox proportional hazard regression models with treatment and BMI category as fixed factors and included a treatment-by-BMI term to test for quantitative interaction between both. The models were adjusted for baseline characteristics related to cardiorenal risk (sex, smoking status, antihyperglycaemic treatments, prior CV events, geographic region, age, diabetes duration, estimated glomerular filtration rate), with a *P*-interaction of less than .05 considered significant. No adjustments for multiple testing were performed.

Quadratic spline regression was applied using Cox proportional hazard regression to analyse treatment differences in time-to-first MACE by continuous baseline BMI. The percentage weight loss by BMI category was calculated over 3 years for LEADER and 104 weeks for SUSTAIN 6, including *P*-interaction for both. All analyses were performed using the software package SAS (version 9.4).

3 | RESULTS

The disposition and baseline characteristics of trial participants have been published.[5,6] In LEADER, a total of 9340 patients were randomized (4668 to liraglutide; 4672 to placebo), with a median follow-up of 3.8 years.[5] In SUSTAIN 6, 3297 patients were randomized (1648 to semaglutide; 1649 to placebo), with a median follow-up of 2.1 years.[6]

The proportions of patients in LEADER with a baseline BMI of less than 25 kg/m^2, of 25 to less than 30 kg/m^2, of 30 to less than 35 kg/m^2, and of 35 kg/m^2 or higher, were 9%, 29%, 32%, and 30%, respectively, and in SUSTAIN 6 these were 8%, 28%, 33%, and 31%, respectively (**Table** S1). Baseline characteristics varied across the BMI categories within each trial (**Table** S1). Notably, in LEADER, the mean diabetes duration was longest in

the BMI less than 25 kg/m^2 category versus the other BMI categories, with a similar trend in SUSTAIN 6. As expected, a greater percentage of patients were treated with insulin at baseline with increasing baseline BMI in both trials (**Table** S1). The percentage of patients with established CV disease was similar across the BMI categories in LEADER (P = .30; range: 80.3%-82.2%; **Table** S1), while, in SUSTAIN 6, it differed (P = .02; range: 78.7%-84.7%; **Table** S1). Within both trials, the mean estimated glomerular filtration rates were similar across the BMI categories (P = .27 for LEADER; P = .14 for SUSTAIN 6; **Table** S1).

The placebo event rates for MACE, expanded MACE and CV death were similar across BMI categories within each trial (**Table** S2). In SUSTAIN 6, the risk of nephropathy declined with increasing BMI category (P_{trend} = .0002) and, although the nephropathy event rate declined in LEADER, it did not reach significance (P_{trend} = .18) (**Table** S2).

When analysing data from the treatment groups, only the interaction for MACE in SUSTAIN 6 showed significance; for all others, there was no statistically significant heterogeneity of the treatment effects of liraglutide or semaglutide versus placebo across baseline BMI groups (Figure 1). Correspondingly, P-interaction values for treatment-by-BMI for MACE, expanded MACE and CV death in LEADER were .34, .22 and .79, respectively; and in SUSTAIN 6 these were .02, .27 and .82, respectively.

For new-onset or worsening nephropathy, there was no heterogeneity of treatment efficacy across the BMI categories, with P-interaction values of .92 for LEADER and .21 for SUSTAIN 6 (Figure 2).

In the regression analysis of baseline BMI as a continuous variable, liraglutide showed consistent benefits across BMI categories in analysis of time-to-first MACE, within the quartile boundaries, where 50% of the events occurred. Semaglutide also showed similar results across baseline BMI values for MACE (Figure S1).

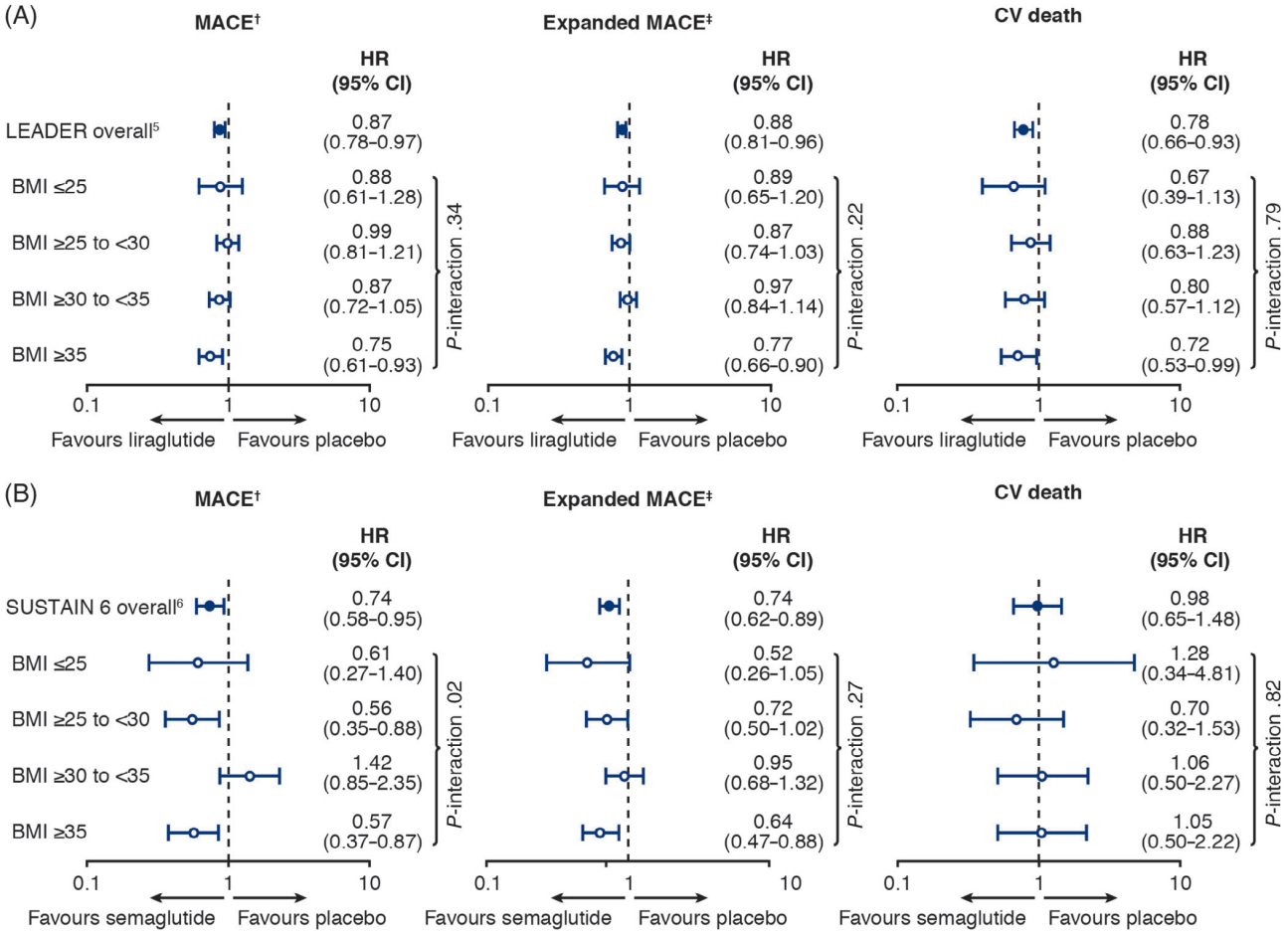

FIGURE 1 Cardiovascular outcomes by baseline body mass index category in A, LEADER and B, SUSTAIN 6. Primary and expanded MACE analyses adjusted for sex, smoking status, antihyperglycaemic treatments, prior cardiovascular (CV) events, geographic region, age, diabetes duration, estimated glomerular filtration rate. Smoking status was not adjusted for in the SUSTAIN 6 analysis for CV death because of low event numbers. †Primary major adverse cardiovascular events (MACE): composite of CV death, non-fatal myocardial infarction (MI) and non-fatal stroke. ‡Expanded MACE: components of primary MACE plus revascularization (coronary only in LEADER; coronary or peripheral in SUSTAIN 6) or hospitalization for unstable angina pectoris or heart failure. BMI, body mass index (in kg/m^2); CI, confidence interval; HR, hazard ratio

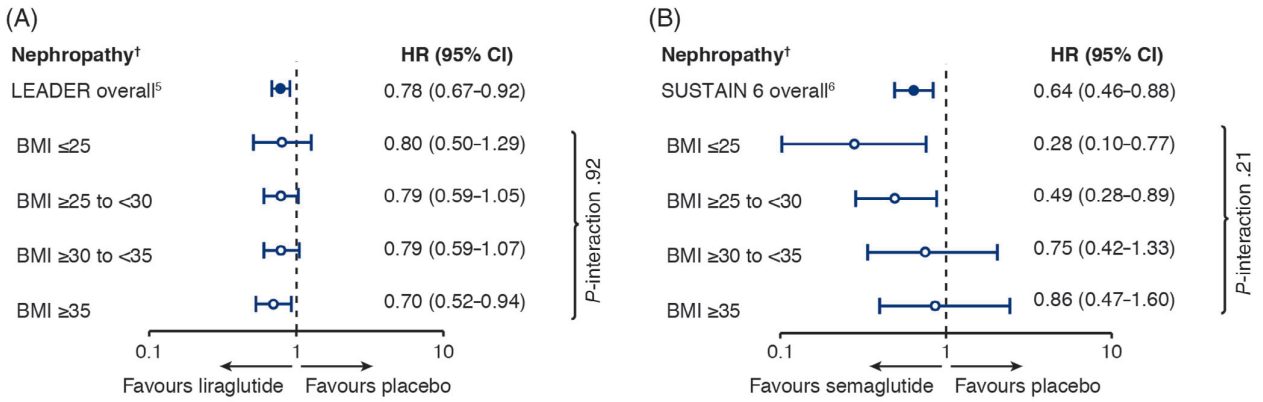

FIGURE 2 Renal outcomes by baseline body mass index category in A, LEADER and B, SUSTAIN 6. LEADER analysis adjusted for sex, smoking status, antihyperglycaemic treatments, prior cardiovascular events, geographic region, age, diabetes duration, estimated glomerular filtration rate. SUSTAIN 6 analysis adjusted for sex, antihyperglycaemic treatments, prior cardiovascular events, geographic region, age, diabetes duration, estimated glomerular filtration rate (smoking status was omitted because of low event numbers). †Nephropathy: new or persistent macroalbuminuria, doubling of serum creatinine, creatinine clearance of less than 45 mL/min/1.73m^2, end-stage kidney disease or death from kidney disease. BMI, body mass index (in kg/m^2); CI, confidence interval; HR, hazard ratio

There was no significant interaction between treatment and BMI category for percentage weight loss with either liraglutide ($P_{interaction}$ = .07; Figure S2A) or semaglutide ($P_{interaction}$ = .51; Figure S2B).

4 | DISCUSSION

The present results of post hoc analyses from LEADER and SUSTAIN 6 show that there was no heterogeneity in the CV and renal benefits of liraglutide and semaglutide versus placebo across the spectrum of baseline BMI evaluated either categorically or continuously, excepting a nominally significant interaction observed by baseline BMI category for the effect of semaglutide on MACE. These data should be considered by prescribers when choosing these agents for CV risk reduction in appropriate patients.

The exact nature of the relationship between any baseline characteristic, including BMI, and CV benefit of liraglutide and semaglutide (via glycaemic control and/or weight loss and/or other mechanisms) remains difficult to establish,[3,8] with published meta-analysis results showing that baseline BMI was not associated with achieved glycaemic control across seven different antihyperglycaemic treatments.[9] Thus, the dose–response curves for any treatment may differ for MACE, glucose levels and weight, and our analyses have shown that there appeared to be generally no effect of baseline BMI on MACE.

Also, prior data evaluating the associations of weight loss on CV outcomes are varied. The Look AHEAD trial randomized patients with overweight/obesity and T2D to intensive lifestyle (diet and exercise) intervention versus control.[10] Despite significantly greater weight loss achieved in the intervention group, there was no significant difference in CV disease-related morbidity and mortality.[10] Conversely, in the Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease (Harmony Outcomes) trial that randomized patients with T2D at high CV risk to the GLP-1 RA albiglutide or placebo, a statistically significant 22% reduction in first occurrence of CV death, myocardial infarction or stroke (HR, 0.78 [95% CI 0.68; 0.90]) was observed with albiglutide versus placebo. While weight loss was marginally greater in the albiglutide group versus placebo at 8 and 16 months, the differences were less than 1 kg (−0.66 and − 0.83 kg, respectively), and at 28 months, weight in both the placebo and albiglutide groups was similar to their baseline values.[11] Yet another type of association was evident in the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial, in which treatment of patients with T2D with dulaglutide resulted in a significant decrease in CV events (HR, 0.88 [95% CI 0.79; 0.99]) and a significant decrease in body weight (−1.46 kg [95% CI 1.25; 1.67]) versus placebo.[12] Mediation analyses utilizing data from such trials may provide evidence as to how weight loss impacts upon CV risk, but to date, it appears that the size of any such mediation of body weight on CV outcomes may be small with liraglutide.[13]

The many mechanisms that have been proposed to underlie the cardioprotective effects of GLP-1 RAs are complex. They include anti-inflammatory effects, attenuation of cardiac ischaemic injury through a variety of direct and indirect actions on the myocardium and coronary arteries, modification of lipid synthesis and secretion, and improvement in endothelial dysfunction, among others.[3] For example, in one study, liraglutide and semaglutide reduced plaque lesion development through altering inflammatory pathways in mouse models of atherosclerosis.[14] These pathways could be involved in the significant improvements in the carotid intima-media thickness of patients who were treated with liraglutide for 8 months versus baseline.[15] Such cardioprotective mechanisms of GLP-1 RAs appear to be independent of the lipid levels of patients.[15]

The renal protective effects of GLP-1 RAs have been less well studied than the cardioprotective effects, and may be linked to renal tubular effects, oxidative stress and haemodynamic effects.[16] For liraglutide and semaglutide, renal benefits were found in LEADER and SUSTAIN 6, where they were investigated as secondary, composite endpoints.[5,6] Analysis of the nephropathy components revealed that

the renal benefits were driven by new or persistent macroalbuminuria.[6,17] Within our post hoc analyses, the renal benefit with semaglutide appeared to decrease with increasing BMI, but this effect modification by BMI status was not statistically significant. However, in the placebo-treated population of SUSTAIN 6, it was evident that nephropathy decreased with increasing BMI, which may seem counterintuitive, but fits with some studies of patients with chronic kidney disease and end-stage renal disease.[18] The reason for the discrepancy between the LEADER and SUSTAIN 6 data in this particular regard remains unknown, but could be related to any of the baseline characteristics that varied by BMI category in SUSTAIN 6, but not in LEADER (e.g. established CV disease).

There were limitations to this study. These were post hoc analyses with numerous potential confounding factors (including not being powered to assess efficacy for CV and renal outcomes across baseline BMI strata and being of comparatively short follow-up), and the analyses were not adjusted for differences in insulin, sodium-glucose co-transporter-2 inhibitor and CV medication use. Baseline BMI categories were not corrected for application to Asian patients, who comprised 9.6% of the study population, and the BMI categories were not protected by the trial randomization, resulting in heterogeneous subgroups. Only baseline BMI was analysed, and results were more consistent with the larger, postapproval LEADER trial compared with the smaller, preapproval SUSTAIN 6 trial. With just one of the many interaction tests yielding a nominally significant *P*-value, the validity of this finding is uncertain and may be a spurious finding as these analyses were post hoc and did not include correction for multiplicity of testing. Given limited power in the present analyses for interaction testing, we are not able to exclude the possibility of effect modification by BMI. These analyses used data pertaining to liraglutide and semaglutide only; further analyses with datasets utilizing other GLP-1 RA data will help clinicians to understand if a class effect underpins these results. Although pooling data from the two trials may have increased the power of this analysis, because of the larger size of LEADER versus SUSTAIN 6, we chose to analyse the data separately, to provide a clear indication of what happened with each treatment.

In conclusion, these results from post hoc analyses of the LEADER and SUSTAIN 6 trials suggest that there are consistent CV and renal benefits of liraglutide and semaglutide across baseline BMI categories in patients with T2D and high CV risk, but they need to be confirmed in future studies.

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CONFLICT OF INTEREST

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