# Liraglutide and semaglutide improve cardiovascular and renal outcomes across most BMI categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 trials

**Subodh Verma[1]; Stephen Bain[2]; Deepak L. Bhatt[3]; Lawrence A. Leiter[1]*; C. David Mazer[1]; Darren K. McGuire[4]; Richard Pratley[5]; Bernard Zinman[6]; Søren Lindberg[7]; Søren Rasmussen[7]; Hrvoje Vrazic[7]; John Buse[8]**

[1]St. Michael's Hospital and University of Toronto, Toronto, ON, Canada; [2]Institute of Life Science, Swansea University, Swansea, UK; [3]Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA; [6]Lunenfeld–Tanenbaum Research Institute, Mt. Sinai Hospital, University of Toronto, Toronto, ON, Canada; [7]Novo Nordisk A/S, Søborg, Denmark; [8]University of North Carolina School of Medicine, Chapel Hill, NC, USA

**- on behalf of the LEADER and SUSTAIN 6 investigators**

*Presenting author

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## Background

- In the LEADER[1] and SUSTAIN 6[2] cardiovascular (CV) outcomes trials, major adverse CV events (MACE) and renal events were evaluated in patients with type 2 diabetes (T2D) and at high CV risk who were randomised to receive liraglutide or semaglutide versus placebo.
  - Both liraglutide (in LEADER) and semaglutide (in SUSTAIN 6) resulted in fewer MACE compared with placebo. For liraglutide versus placebo, the hazard ratio (HR) was 0.87 (95% confidence interval [CI] 0.78–0.97), which demonstrated superiority ($p$=0.01).[1] A statistically significant reduction in MACE with semaglutide was shown *post hoc* (HR 0.74; 95% CI 0.58–0.95; $p$=0.02).[2]
  - Similar results were obtained in both trials for new or worsening nephropathy events (LEADER: HR 0.78; 95% CI 0.67–0.92; $p$=0.003,[1] SUSTAIN 6: HR 0.64; 95% CI 0.46–0.88; $p$=0.005).[2]
- Whether these cardiorenal benefits of liraglutide and semaglutide are consistent across patients within different body mass index (BMI) categories is unknown.
- We performed *post hoc* analyses on LEADER and SUSTAIN 6 data to evaluate cardiorenal efficacy by BMI categories in patients with T2D and high CV risk.

## Methods

- LEADER[1] and SUSTAIN 6[2] were global, randomised, double-blind, placebo-controlled, CV outcomes trials of liraglutide and semaglutide, in 9340 and 3297 patients, respectively, with T2D and high CV risk.[1,2]
- In both trials, the first occurrence of MACE (CV death, non-fatal myocardial infarction or non-fatal stroke) was the primary composite outcome.[1,2]
- Secondary outcomes included a composite renal outcome of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level, the need for continuous renal-replacement therapy or death from renal disease.[1,2]
- The effects of liraglutide and semaglutide on time to first primary CV and secondary renal outcomes were evaluated by baseline BMI category.
  - BMI was categorised as <25 kg/m$^2$, ≥25 to <30 kg/m$^2$, ≥30 to <35 kg/m$^2$ and ≥35 kg/m$^2$.
- The HR and 95% CI for treatment versus placebo were calculated using Cox regression with treatment and BMI category as fixed factors and the interaction between both, adjusted for baseline characteristics related to cardiorenal risk.
- Quadratic spline regression applied in a Cox regression was used to analyse the treatment differences in time to first MACE by continuous BMI.
- No adjustments for multiple testing were performed.

## Results

- In LEADER, 9%, 29%, 32% and 30% of patients had a baseline BMI of <25 kg/m$^2$, ≥25 to <30 kg/m$^2$, ≥30 to <35 kg/m$^2$ and ≥35 kg/m$^2$, respectively; proportions for SUSTAIN 6 were 8%, 28%, 33% and 31% (Table 1).
- The baseline characteristics were mostly balanced across the trial groups within each BMI category (Table 1).

**Table 1**: Proportion of patients at baseline in each BMI category

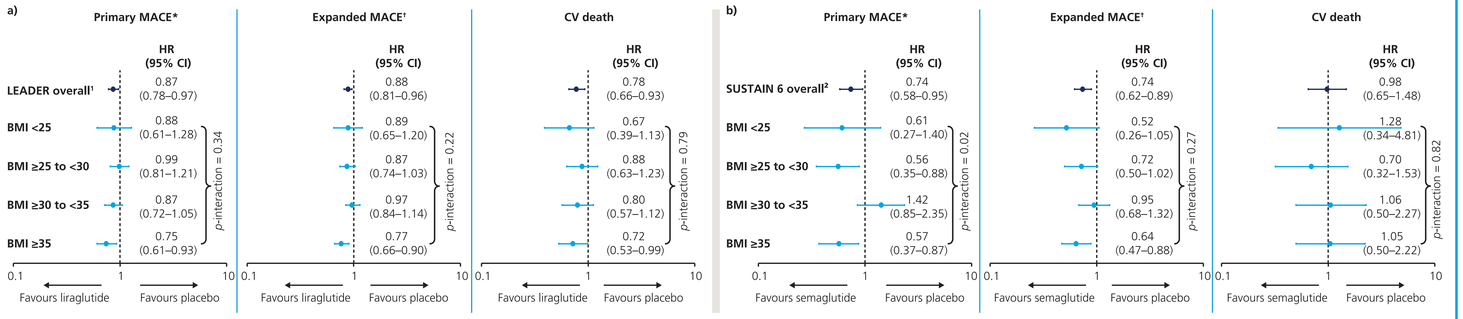
| | LEADER, n (%) N=9340 | | | | SUSTAIN 6, n (%) N=3297 | | | |
|---|---|---|---|---|---|---|---|---|
| **BMI (kg/m$^2$)** | **<25** | **≥25 to <30** | **≥30 to <35** | **≥35** | **<25** | **≥25 to <30** | **≥30 to <35** | **≥35** |
| **n (%)** | 832 (9) | 2684 (29) | 2993 (32) | 2822 (30) | 254 (8) | 926 (28) | 1080 (33) | 1030 (31) |
| **Age, years** | 64.7 ± 7.8 | 65.4 ± 7.4 | 64.4 ± 7.2 | 63.0 ± 6.7 | 65.6 ± 7.7 | 65.6 ± 7.6 | 64.6 ± 7.2 | 63.7 ± 7.1 |
| **Male, n (%)** | 578 (69.5) | 1868 (69.6) | 1995 (66.7) | 1559 (55.2) | 159 (62.6) | 637 (68.8) | 670 (62.0) | 529 (51.4) |
| **$HbA_{1c}$, %** | 9.0 ± 1.8 | 8.6 ± 1.5 | 8.6 ± 1.5 | 8.7 ± 1.5 | 9.0 ± 1.7 | 8.7 ± 1.5 | 8.6 ± 1.4 | 8.7 ± 1.5 |
| **Duration of diabetes, years** | 14.2 ± 8.9 | 13.5 ± 8.2 | 12.5 ± 7.8 | 12.1 ± 7.7 | 15.6 ± 8.1 | 15.1 ± 8.5 | 13.3 ± 8.1 | 13.1 ± 7.7 |
| **Insulin use at baseline, n (%)** | 304 (36.5) | 1161 (43.3) | 1348 (45.0) | 1351 (47.9) | 139 (54.7) | 520 (56.2) | 615 (56.9) | 636 (61.7) |
| **Established CV disease, n (%)** | 673 (80.9) | 2154 (80.3) | 2459 (82.2) | 2304 (81.6) | 200 (78.7) | 748 (80.0) | 915 (84.7) | 866 (84.1) |
| **eGFR, mL/min/1.73 m$^2$** | 82.1 ± 29.4 | 80.2 ± 27.1 | 80.1 ± 26.6 | 80.3 ± 27.8 | 77.5 ± 29.9 | 77.0 ± 27.3 | 76.5 ± 25.4 | 74.6 ± 26.2 |

CV, cardiovascular; BMI, body mass index; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, glycated haemoglobin

- In LEADER, the mean diabetes duration was longest in the <25 kg/m$^2$ BMI category (14.2 years) and slightly shorter (12.1–13.5 years) in the other three BMI categories. A similar trend was seen in SUSTAIN 6, with the mean diabetes duration being 15.6 years, 15.1 years, 13.3 years and 13.1 years in the <25 kg/m$^2$, ≥25–<30 kg/m$^2$, ≥30–<35 kg/m$^2$ and ≥35 kg/m$^2$ BMI categories, respectively.
- There were 608 (13.0%) events of primary MACE with liraglutide and 694 (14.9%) events with placebo in LEADER.[1] Due to the smaller trial size, these numbers were lower in SUSTAIN 6, with 108 (6.6%) events of primary MACE with semaglutide and 146 (8.9%) events with placebo.[2]

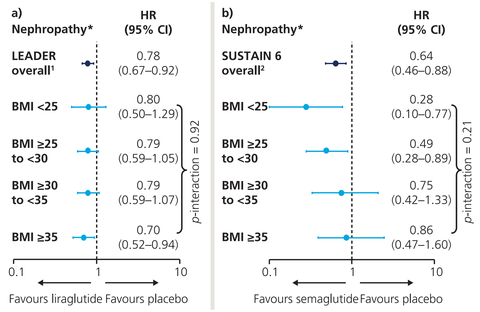
**Figure 1**: Cardiovascular outcomes by baseline BMI category in a) LEADER and b) SUSTAIN 6

Key result



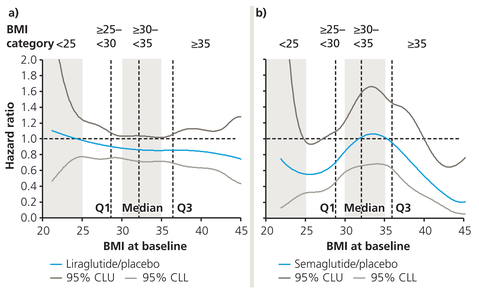

*Primary MACE: composite of CV death, non-fatal MI and non-fatal stroke. †Expanded MACE: components of primary MACE plus coronary revascularisation or hospitalisation for unstable angina pectoris or heart failure. BMI, body mass index (kg/m$^2$); CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

**Figure 2**: Renal outcomes by baseline BMI category in a) LEADER and b) SUSTAIN 6




*New or worsening nephropathy: new or persistent macroalbuminuria, doubling of serum creatinine, end-stage kidney disease or death from kidney disease. BMI, body mass index (kg/m$^2$); CI, confidence interval; HR, hazard ratio

**Figure 3**: Treatment difference in time to first MACE across continuous BMI using spline regression in a) LEADER and b) SUSTAIN 6




Primary MACE: composite of CV death, non-fatal MI and non-fatal stroke. Q1, one quarter of patients with events had a lower BMI value; median, half of patients with events had a lower BMI value; Q3, three quarters of patients with events had a lower BMI value. BMI, body mass index (kg/m$^2$); CLL, confidence limit lower; CLU, confidence limit upper; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; Q, quartiles for patients with an event

- Overall, liraglutide reduced the risk of CV and renal endpoints across BMI categories (Figures 1 and 2). The analysis of SUSTAIN 6 data demonstrated a similar effect with semaglutide, even though the CIs were wider due to the small sample size.
- In addition to the improvements in MACE and new or worsening nephropathy outcomes, more weight loss was observed with liraglutide at year 3 (<25 kg/m$^2$: –0.85 kg; ≥25–<30 kg/m$^2$: –1.93 kg; ≥30–<35 kg/m$^2$: –2.06 kg; ≥35 kg/m$^2$: –3.25 kg; $p$-interaction: <0.001) and semaglutide at week 104 (<25 kg/m$^2$: –3.13 kg; ≥25–<30 kg/m$^2$: –2.89 kg; ≥30–<35 kg/m$^2$: –3.96 kg; ≥35 kg/m$^2$: –3.99 kg; $p$-interaction: 0.14) versus placebo.
- When analysing BMI at baseline as a continuous linear variable, there was no indication of a differential effect with liraglutide or semaglutide, within the quartile boundaries, where 50% of the events occurred (Figure 3). Again, there was greater variability in the semaglutide than liraglutide HRs due to the small number of MACE analysed in SUSTAIN 6.

## Conclusions

- The *post hoc* analyses from LEADER and SUSTAIN 6 show that the CV and renal benefits of liraglutide and semaglutide versus placebo are consistent across baseline BMI categories.
- These data reaffirm the cardioprotective role of liraglutide and semaglutide in patients with T2D, irrespective of baseline BMI.

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**References:** (**1**) Marso *et al. N Engl J Med* 2016;375:311–22; (**2**) Marso *et al. N Engl J Med* 2016;375:1834–44.