Liraglutide and semaglutide improve cardiovascular and renal outcomes across baseline BP categories: analysis of LEADER and SUSTAIN 6

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- on behalf of the LEADER and SUSTAIN 6 investigators

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Background

- High blood pressure (BP) is prevalent in patients with type 2 diabetes (T2D) and is a risk factor for cardiovascular (CV) disease and microvascular complications.[1]
- In the LEADER[2] and SUSTAIN 6[3] CV outcomes trials, major adverse CV events (MACE) and renal events were evaluated in patients with T2D and high CV risk who received liraglutide or semaglutide versus placebo.
  - Overall, in LEADER, there were 608 (13.0%) events of primary MACE with liraglutide and 694 (14.9%) events with placebo (hazard ratio [HR] 0.87; 95% confidence interval [CI] 0.78–0.97; $p<0.001$ for noninferiority; $p=0.01$ for superiority).[2] There were also 268 (5.7%) and 337 (7.2%) events of new or worsening nephropathy with liraglutide and placebo, respectively (HR 0.78; 95% CI 0.67–0.92; $p=0.003$).[2]
  - In SUSTAIN 6 overall, there were 108 (6.6%) events of primary MACE with semaglutide and 146 (8.9%) events with placebo (HR 0.74; 95% CI 0.58–0.95; $p<0.001$ for noninferiority).[3] Additionally, there were 62 (3.8%) and 100 (6.1%) events of new or worsening nephropathy with semaglutide and placebo, respectively (HR 0.64; 95% CI 0.46–0.88; $p=0.005$).[3]
- Whether these cardiorenal benefits of liraglutide and semaglutide are consistent across patients within different BP categories is unknown.
- *Post hoc* analyses were performed on LEADER and SUSTAIN 6 data to evaluate cardiorenal efficacy by BP categories in patients with T2D and high CV risk.

Methods

- LEADER[2] and SUSTAIN 6[3] were global, double-blind, placebo-controlled, randomised CV outcomes trials of liraglutide and semaglutide, in 9340 and 3297 patients, respectively, with T2D and high CV risk.
- The primary composite outcome in both trials was the first occurrence of MACE (CV death, non-fatal myocardial infarction or non-fatal stroke).[2,3]
- The 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.[2,3]
- The effects of liraglutide and semaglutide on the primary CV and secondary renal outcomes were evaluated by baseline BP category.
  - BP was categorised as normal (<120/80 mmHg), elevated (systolic 120–129 mmHg and diastolic <80 mmHg), stage 1 hypertension (systolic 130–139 mmHg or diastolic 80–89 mmHg), and stage 2 hypertension (systolic ≥140 mmHg or diastolic ≥90 mmHg) as per American College of Cardiology/American Heart Association clinical practice guidelines.[4]
- A Cox proportional hazards model, with treatment and BP category as factors and the interaction between BP category and treatment, was used to calculate the treatment HR and 95% CI, adjusted for baseline characteristics related to cardiorenal risk.
- Quadratic spline regression applied in a Cox regression was used to calculate the treatment HR in time to first MACE by systolic and diastolic BP on a *continuous* scale.

Results

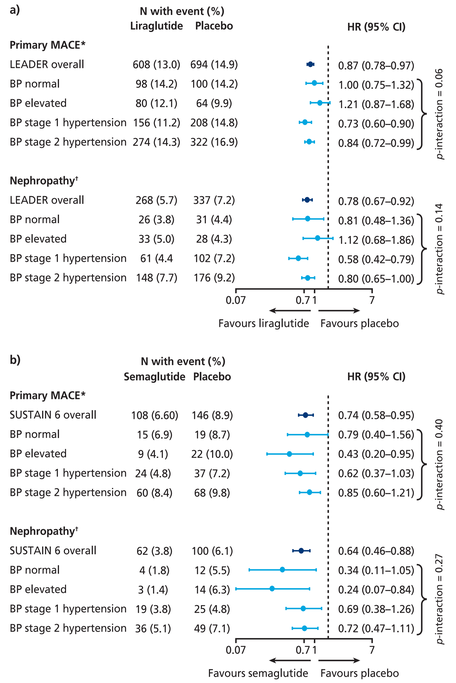
- In LEADER, 15%, 14%, 30% and 41% of patients had normal BP, elevated BP, stage 1 or stage 2 hypertension, respectively; proportions in SUSTAIN 6 were 13%, 13%, 31% and 43%, respectively (Table 1).
- The baseline characteristics were balanced across the treatment groups within each BP category.
- Liraglutide decreased the risk of both CV and renal endpoints across all four BP categories (Figure 1a). Semaglutide demonstrated a similar effect in SUSTAIN 6, even though the CIs were wider due to the small sample size (Figure 1b).
- No significant interactions ($p<0.05$) were found across risk groups for primary MACE or nephropathy with either treatment (Figure 1).
- Analysis of BP at baseline as a continuous variable revealed no indication of differential effect with either liraglutide or semaglutide, within the quartile boundaries, where 50% of the events occurred (Figure 2).A higher proportion of patients reported ≥1 treatment-emergent adverse event (AE) in the liraglutide group than the placebo group (66.3 vs 47.0%, respectively [Table 2]).
  - Nausea was the most commonly reported AE (26.2% and 6.0% for liraglutide versus placebo, respectively) and was predominately early-onset and transient.
  - The proportion of patients reporting hypoglycaemia was similar across liraglutide (8.9%) and placebo (8.0%) groups, and none of these episodes were severe (defined as requiring assistance from another person according to the American Diabetes Association criterion).[1]
  - Serious AEs were reported by a low proportion of patients in both liraglutide (2.5%) and placebo (1.0%) groups and there were no fatalities, reports of acute renal failure, DKA, diabetic foot ulcers or amputations with liraglutide in combination with an SGLT2i.

Table 1: Proportion of patients at baseline in each blood pressure category

Blood pressure (mmHg)	LEADER, n (%) N=9340	SUSTAIN 6, n (%) N=3297
Normal (<120/80)	1397 (15)	436 (13)
Elevated (systolic 120–129 *and* diastolic <80)	1310 (14)	439 (13)
Stage 1 hypertension (systolic 130–139 *or* diastolic 80–89)	2806 (30)	1018 (31)
Stage 2 hypertension (systolic ≥140 *or* diastolic ≥90)	3827 (41)	1404 (43)

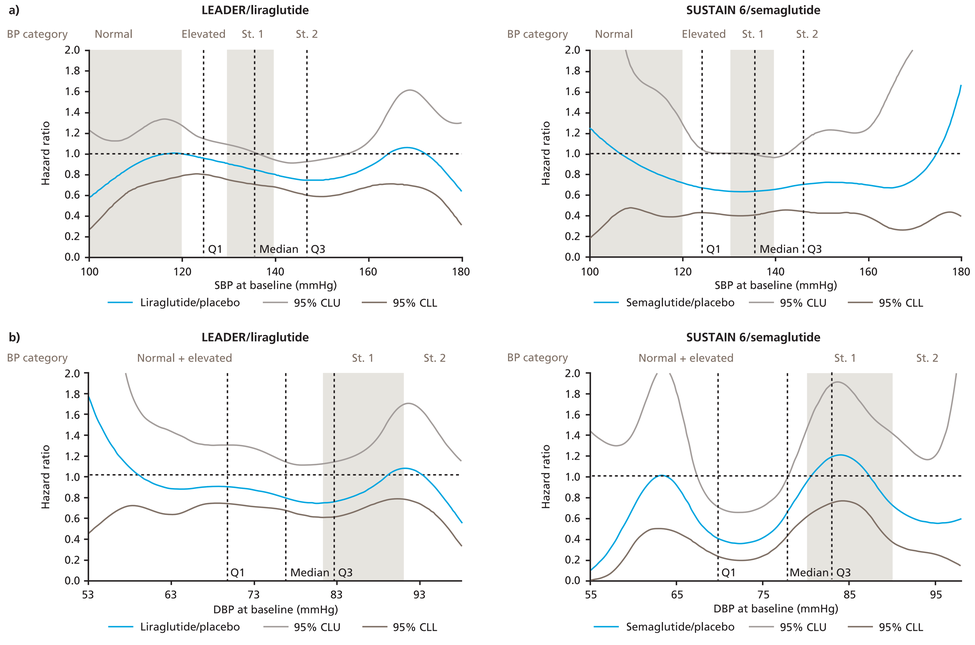
Figure 1: Cardiorenal outcomes by baseline BP category, adjusted for baseline variables in a) LEADER and b) SUSTAIN 6

Key result



*Primary MACE: composite of cardiovascular death, non-fatal MI and non-fatal stroke. †Nephropathy: new or persistent macroalbuminuria, doubling of serum creatinine, end-stage kidney disease or death from kidney disease. BP, blood pressure; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

Figure 2: Treatment ratios (liraglutide or semaglutide vs placebo) in time to first MACE using quadratic spline regression according to a) SBP and b) DBP



Primary MACE: composite of cardiovascular death, non-fatal MI and non-fatal stroke. Q1, one quarter of patients with events had a lower BP value than this; median, half of patients with events had a lower BP value than this; Q3, three quarters of patients with events had a lower BP value than this. BP, blood pressure; CLL, confidence limit lower; CLU, confidence limit upper; DBP, diastolic blood pressure; MACE, major adverse cardiovascular events; MI, myocardial infarction; Q, quartile; SBP, systolic blood pressure; St., stage

Conclusions

- In LEADER and SUSTAIN 6, liraglutide and semaglutide demonstrated improvements in CV and renal outcomes irrespective of baseline BP categories.

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References: (**1**) American Diabetes Association. *Diabetes Care* 2016;39 Suppl 1:S60–71; (**2**) Marso *et al. N Engl J Med* 2016;375:311–22; (**3**) Marso *et al. N Engl J Med* 2016;375:1834–44; (**4**) Whelton *et al. J Am Coll Cardiol* 2018;71:e127–248.