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BRIEF REPORT

WILEY

The effect of glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on cardiovascular and renal outcomes across baseline blood pressure categories: Analysis of the LEADER and SUSTAIN 6 trials

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Abstract

It is unknown if the cardioprotective and renal effects of glucagon-like peptide-1 receptor agonists are consistent across blood pressure (BP) categories in patients with type 2 diabetes and at high risk of cardiovascular events. Using data from the LEADER (9340 patients) and SUSTAIN 6 (3297 patients) trials, we evaluated post hoc the cardiorenal effect of liraglutide and semaglutide on major adverse cardiovascular events (MACE) and nephropathy by baseline BP categories using a Cox proportional hazards model (treatment and subgroup as factors; adjusted for cardiorenal risk factors). Data from the two trials were analysed separately. In the LEADER and SUSTAIN 6 trials, the prevalence of stage 1 hypertension was 30% and 31%, respectively, and of stage 2 hypertension 41% and 43%, respectively. There was no statistical heterogeneity across the BP categories for the effects of liraglutide (P = .06 for MACE; P = .14 for nephropathy) or semaglutide (P = .40 for MACE; P = .27 for nephropathy) versus placebo. This implies that liraglutide and semaglutide may be beneficial for patients with type 2 diabetes, irrespective of their baseline BP.

KEYWORDS
blood pressure, cardiovascular, liraglutide, MACE, semaglutide

1 | INTRODUCTION

Elevated blood pressure (BP) is very common in people with type 2 diabetes (T2D), and increases the risk of cardiovascular (CV) and renal events in this population.[1,2] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been shown to reduce the incidence of CV and renal events in people with T2D or at risk of CV disease.[3,4] These agents have also been shown to reduce BP versus placebo, insulin and

sulphonylureas,[5] with greater reductions observed in those with higher baseline BP (liraglutide vs. placebo).[6] Whether GLP-1 RAs exert CV and renal event reduction in a consistent fashion across the spectrum of baseline BP remains unknown. Therefore, we studied this question in the LEADER[7] and SUSTAIN 6[8] trials, through separate post hoc analyses.

2 | METHODS

The design, baseline patient characteristics and primary results of the LEADER[7] and SUSTAIN 6[8] trials have been reported previously. Briefly, they were global, double-blind, placebo-controlled, randomized CV outcomes trials of subcutaneously injected liraglutide (LEADER) and semaglutide (SUSTAIN 6), in patients with T2D (HbA1c ≥ 7.0%) and high CV risk. Institutional review boards or ethics committees for each centre approved the trial protocols and all patients provided informed consent.[7,8] The key inclusion criteria were age ≥ 50 years with ≥1 co-existing CV condition (coronary heart disease, cerebrovascular disease, chronic kidney disease stage ≥3, or chronic New York Heart Association class II or III heart failure) or age ≥ 60 years with ≥1 CV risk factor. In both trials, CV risk factors included microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle-brachial index of <0.9.[7,8]

Patients were followed for up to 5 years in the LEADER trial (N = 9340; median time 3.8 years), and in the SUSTAIN 6 trial all patients were followed for 2 years (N = 3297; median time 2.1 years).[7,8] The primary composite outcome in both trials was the first occurrence of major adverse cardiovascular events (MACE: CV death, non-fatal myocardial infarction [MI] or non-fatal stroke).[7,8] 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. Expanded MACE included the events within primary MACE in addition to revascularization and hospitalization for heart failure or unstable angina. CV and renal events were adjudicated by an external, blinded, independent, expert committee. BP was measured at baseline and designated clinic visits (at least annually) according to the usual practice at the investigator's site[7,8] (further details are available in the Supplementary Appendix, see the supporting information).

2.1 | Statistics

In this post hoc analysis, the effects of liraglutide and semaglutide on the primary CV and secondary new or worsening nephropathy outcomes were evaluated by baseline American College of Cardiology/American Heart Association-defined BP categories[9]: 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). The mean of two BP measurements taken at the randomization visit (baseline) was used to assign the BP category. A Cox proportional hazards model, with treatment and BP category as factors and the interaction between both, was used to calculate the hazard ratio (HR) and 95% confidence interval (CI). The model was adjusted for baseline characteristics related to cardiorenal risk (age, antihyperglycaemic medications, diabetes duration, geographic region, history of MI or stroke, renal function as measured by estimated glomerular filtration rate, sex, and smoking status [smoking status was omitted for endpoints with low frequency in SUSTAIN 6]). An interaction *P*-value of <.05 was considered significant. Analysis of expanded MACE, hospitalization for heart failure, CV death and all-cause mortality was also performed using the Cox proportional hazards model as described. The analysis of MACE and nephropathy was repeated with patients further categorized by angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) use at baseline. For all tests, *P*-values were not adjusted for multiple comparisons. Quadratic spline regression applied using a Cox proportional hazard model was used to analyse the treatment differences in time to first MACE by systolic and diastolic BP on a continuous scale.

To further test potential interactions between BP categories and treatment, the Gail-Simon test (for qualitative interactions) was applied in the Cox proportional hazard model, where a *P*-value of <.05 would indicate that the direction of treatment effect differed in one or more subgroups versus the remaining subgroups, e.g. that a treatment increased the risk in one subgroup, while simultaneously decreasing risk in another subgroup for an endpoint. The Gail-Simon test differed from the interaction test (which measured quantitative interactions), wherein small *P*-values would indicate that the magnitude of the treatment effects differed between subgroups. All analyses were performed using the statistical software package SAS version 9.4.

3 | RESULTS

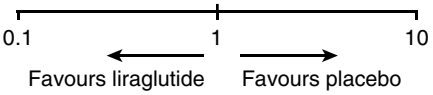
All patients randomized in the LEADER (n = 9340) and SUSTAIN 6 (n = 3297) trials were included in these analyses. The baseline characteristics of patients in each BP category in LEADER and SUSTAIN 6 are shown in Tables **S1** and S2, respectively. In the LEADER and SUSTAIN 6 trials, the prevalence of stage 1 hypertension was 30% and 31%, respectively, and the prevalence of stage 2 hypertension was 41% and 43%, respectively.

3.1 | Cardiorenal efficacy across BP categories in LEADER and SUSTAIN 6

Figure 1 depicts the HRs for the primary MACE and renal outcomes in LEADER (Figure 1A) and SUSTAIN 6 (Figure 1B) trials across the BP categories studied. In both instances, treatment with liraglutide or semaglutide versus placebo was associated with a consistent

(A)

	N with event (%) Liraglutide	Placebo	HR (95% CI)	*P*-interaction	(*P*-interaction Gail-Simon)
Primary MACE†					
LEADER overall[7]	608 (13.0)	694 (14.9)	0.87 (0.78–0.97)		
BP normal	98 (14.2)	100 (14.2)	1.00 (0.75–1.32)	0.06	0.39
BP elevated	80 (12.1)	64 (9.9)	1.21 (0.87–1.68)		
BP stage 1 hypertension	156 (11.2)	208 (14.8)	0.73 (0.60–0.90)		
BP stage 2 hypertension	274 (14.3)	322 (16.9)	0.84 (0.72–0.99		
Nephropathy‡					
LEADER overall[7]	268 (5.7)	337 (7.2)	0.78 (0.67–0.92)		
BP normal	26 (3.8)	31 (4.4)	0.81 (0.48–1.36)	0.14	0.70
BP elevated	33 (5.0)	28 (4.3)	1.12 (0.68–1.86)		
BP stage 1 hypertension	61 (4.4)	102 (7.2)	0.58 (0.42–0.79)		
BP stage 2 hypertension	148 (7.7)	176 (9.2)	0.80 (0.65–1.00)		



(B)

	N with event (%) Semaglutide	Placebo	HR (95% CI)	*P*-interaction	(*P*-interaction Gail-Simon)
Primary MACE†					
SUSTAIN 6 overall[8]	108 (6.6)	146 (8.9)	0.74 (0.58–0.95)		
BP normal	15 (6.9)	19 (8.7)	0.79 (0.40–1.56)	0.40	0.88
BP elevated	9 (4.1)	22 (10.0)	0.43 (0.20–0.95)		
BP stage 1 hypertension	24 (4.8)	37 (7.2)	0.62 (0.37–1.03)		
BP stage 2 hypertension	60 (8.4)	68 (9.8)	0.85 (0.60–1.21)		
Nephropathy‡§					
SUSTAIN 6 overall[8]	62 (3.8)	100 (6.1)	0.64 (0.46–0.88)		
BP normal	4 (1.8)	12 (5.5)	0.34 (0.11–1.05)	0.27	0.88
BP elevated	3 (1.4)	14 (6.3)	0.24 (0.07–0.84)		
BP stage 1 hypertension	19 (3.8)	25 (4.8)	0.69 (0.38–1.26)		
BP stage 2 hypertension	36 (5.1)	49 (7.1)	0.72 (0.47–1.11)		

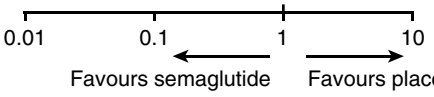


FIGURE 1 Cardiorenal outcomes by baseline blood pressure (BP) category, adjusted for baseline variables related to cardiorenal risk, in the LEADER (A) and SUSTAIN 6 trials (B). †Primary major adverse cardiovascular events (MACE): composite of cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke. Analysis adjusted for baseline characteristics related to cardiorenal risk (age, antihyperglycaemic medications, diabetes duration, geographic region, history of MI or stroke, renal function as measured by estimated glomerular filtration rate, sex, and smoking status). ‡Nephropathy (new or worsening): new or persistent macroalbuminuria, doubling of serum creatinine, end-stage kidney disease or death from kidney disease. §Analysis adjusted as for MACE, with the omission of smoking status because of a low number of events. BP categories were defined as follows: normal = systolic blood pressure (SBP) < 120 mmHg, diastolic blood pressure (DBP) 80 mmHg; elevated = SBP 120-129 mmHg and DBP < 80 mmHg; stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg; stage 2 hypertension = SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. CI, confidence interval; HR, hazard ratio

reduction in cardiorenal outcomes with no evidence of statistical heterogeneity. Although there appeared to be a trend with liraglutide versus placebo towards a lower relative risk reduction in those with normal BP (compared with those with stage 1 or 2 hypertension), this was not statistically significant (*P*-interaction = .06). The Gail-Simon test for qualitative interaction revealed no significant interaction for the primary MACE or nephropathy outcomes in LEADER or SUSTAIN 6, respectively (Figure 1A,B).

Additional outcomes, including expanded MACE, hospitalization for heart failure and all-cause mortality, are depicted in Tables S3 and S4, and generally supported a conclusion of consistent benefit for liraglutide and semaglutide across the BP categories. For the expanded MACE outcome (which included CV death, non-fatal MI, non-fatal stroke, coronary revascularization, hospitalization for unstable angina or heart failure), the *P*-value for interaction was .048 in LEADER, and was non-significant in SUSTAIN 6. Analysis by ACEi/

ARB use at baseline in both trials also revealed a consistent benefit across all categories (Figures **S1** and S2).

Analysis of systolic and diastolic BP at baseline as continuous variables confirmed a consistent benefit of liraglutide or semaglutide within the quartile boundaries (i.e. end of Q1 to beginning of Q3), in which 50% of the events occurred (Figure 2).

4 | DISCUSSION

GLP-1 RAs are known to have multiple favourable cardiometabolic effects on glycaemia, weight and blood pressure.[3,7,8] While the CV benefits of these therapies are unlikely to be solely dependent on these effects[10,11] and are also suggested to be modulated by direct vasculoprotective/antiatherosclerotic pathways,[12,13] questions have been raised about whether these therapies exert cardiorenal benefits in the setting of adequate risk factor control. The present analyses, from two large and contemporary randomized controlled trials, suggest that liraglutide and semaglutide provide similar benefits, both quantitatively and qualitatively, on major cardiorenal outcomes in people with T2D across the spectrum of baseline BP values. Even in patients with normal BP on entering both of these trials, these benefits were seen for both GLP-1 RAs. These data, taken together with prior analyses from LEADER and SUSTAIN 6 showing efficacy across the spectrum of lipid levels[11,13] and body mass index,[14] suggest that these therapies should be considered as complementary to traditional risk factor modification for risk reduction in people with T2D.

Indeed, when examining data related to BP, it can be important to consider traditional risk factor modifications in terms of medications frequently prescribed for this purpose, such as ACEis and ARBs. We noted that the benefits with GLP-1 RAs were consistently observed in users and non-users of ACEis/ARBs, suggesting that the cardiorenal benefits of liraglutide and semaglutide are probably additive to that of renin-angiotensin system blockade. Future studies could further

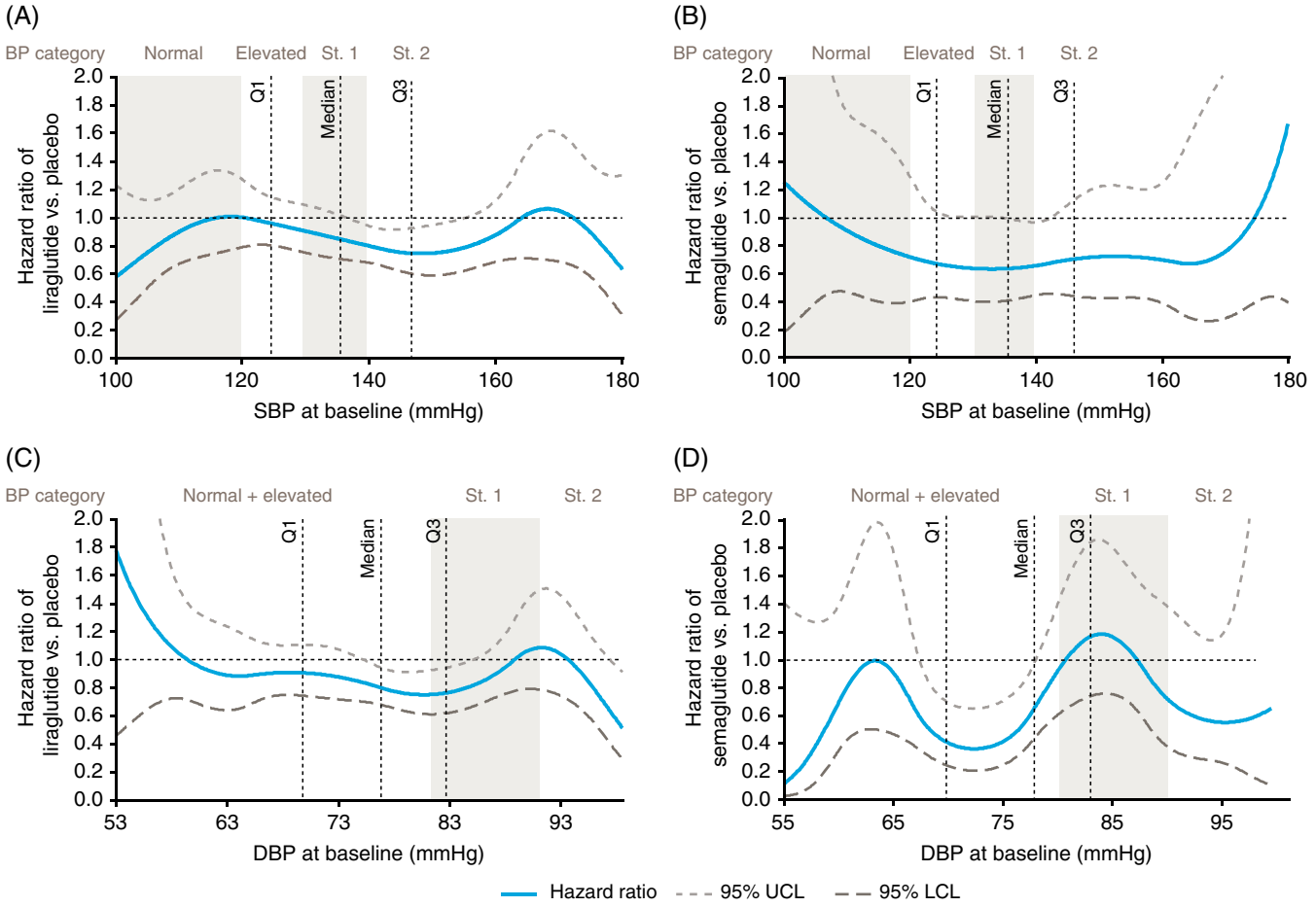


FIGURE 2 Quadratic spline regression treatment differences in time to first major adverse cardiovascular events (MACE), according to baseline systolic blood pressure (SBP) (A and B) and diastolic blood pressure (DBP) (C and D), in the LEADER (A and C) and SUSTAIN 6 (B and D) trials. Primary MACE: composite of cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke. Q1, one quarter of patients had a lower blood pressure (BP) value than this. Median, half of patients had a lower BP value than this. Q3, three-quarters of patients had a lower BP value than this. BP categories were defined as follows: normal = SBP < 120 mmHg, DBP 80 mmHg; elevated = SBP 120-129 mmHg and DBP < 80 mmHg; stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg; stage 2 hypertension = SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. LCL, lower confidence limit; Q, quartile; St., stage; UCL, upper confidence limit

explore this to determine exactly how GLP-1 RAs confer such cardiorenal benefits, independently of the renin-angiotensin system.

Limitations of this post hoc analysis include that it was a retrospective analysis of data from two different trials, not powered to look at endpoints in these subgroups, and only baseline and not in-trial BP categories were considered. Furthermore, BP was recorded using different techniques, as per the usual practice at each site, which may have had an impact on the measurements. In addition, the use of antihypertensive medication during the trial was at the discretion of the investigator and was not examined as a time-varying covariate. Competing risk factors (e.g. non-CV death) may have also impacted the results, and there was no adjustment for biomarkers in this analysis, as has been performed in other similar analyses.[15]

In conclusion, in both LEADER and SUSTAIN 6, liraglutide and semaglutide showed no heterogeneity of efficacy in CV and renal outcomes, irrespective of baseline BP categories and of ACEi/ARB use.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Design (of the post hoc analysis): SV, LAL, DLB, CDM, SR, MSR, HV, SCB, JBB and REP. Conduct/data collection: LAL, SCB, JBB and REP. Analysis: SR. Manuscript writing: LAL and SV, who contributed equally to writing the first full draft of this paper.

DATA ACCESSIBILITY

The data used for this manuscript are available on reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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