Impact of microvascular disease on cardiorenal outcomes in type 2 diabetes: an analysis from the LEADER and SUSTAIN 6 clinical trials

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– on behalf of the LEADER and SUSTAIN 6 investigators

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Background

- Microvascular complications in type 2 diabetes (T2D) may increase the risk of cardiovascular (CV) complications,[1,2] but data from large-scale trials are lacking.
- Liraglutide and semaglutide are human glucagon-like peptide-1 analogues used for the treatment of patients with T2D.
- LEADER and SUSTAIN 6 were large-scale outcomes trials designed to assess the CV safety and efficacy of liraglutide and semaglutide, respectively.[3,4] Treatment with these GLP-1 analogues was shown to reduce the risk of CV events versus placebo in patients with T2D.[3,4]
- We present the results of *post hoc* analyses of LEADER and SUSTAIN 6 data evaluating cardiorenal risk, and the effects of liraglutide and semaglutide in patients with a history of microvascular disease.

Methods

Study design

- LEADER and SUSTAIN 6 were multinational, randomised, double-blind, CV outcomes trials of once-daily liraglutide (up to 1.8 mg) and once-weekly semaglutide (0.5–1.0 mg) respectively, versus placebo, in addition to standard of care therapy, in patients with T2D and at high risk of CV disease.[3,4] Median follow-up was 3.8 years in LEADER, and 2.1 years in SUSTAIN 6.[3,4]
- Both trials enrolled patients with glycated haemoglobin (HbA_{1c}) ≥7.0% who were aged ≥50 years with established CV disease/chronic renal failure, or aged ≥60 years with risk factors for CV disease.
- The primary outcome in LEADER and SUSTAIN 6 was time to first major cardiovascular event (MACE), a composite of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke.
- Secondary endpoints included:
  - Expanded MACE (MACE + coronary revascularisation, or hospitalisation for unstable angina pectoris or heart failure).
  - A nephropathy composite endpoint (new onset of macroalbuminuria or doubling of serum creatinine level and an estimated glomerular filtration rate [eGFR] ≤45 mL/min/1.73 m^2, or the need for continuous renal-replacement therapy or death from renal disease).
- These endpoints were assessed by an independent event adjudication committee.

Statistical analysis

- We analysed time to first MACE, expanded MACE and the nephropathy composite endpoint according to history of microvascular disease at baseline, and concomitant microvascular and macrovascular disease at baseline.
- Microvascular disease at baseline was defined as an investigator-reported history of nephropathy (microalbuminuria, macroalbuminuria or overt proteinuria with normal serum creatinine/creatinine clearance; or chronic renal failure [elevated serum creatinine or reduced creatinine clearance]), retinopathy, or peripheral neuropathy.
- Macrovascular disease at baseline was defined as a history of MI, ≥50% coronary artery stenosis, percutaneous coronary intervention (PCI) or coronary artery bypass grafting, angina pectoris, asymptomatic cardiac ischaemia, stroke, transient ischaemic attack, or ≥50% intracranial, carotid or peripheral artery stenosis.
- Risk of CV events (hazard ratio [HR] and 95% confidence interval [CI]) by microvascular disease at baseline was calculated using a Cox proportional hazards model with risk group as a factor, adjusted for treatment.
- Treatment effects of liraglutide and semaglutide versus placebo, respectively, within risk groups were estimated using a Cox proportional hazards model with treatment, risk group, and the interaction of both as factors, adjusted for important CV risk factors.
  - Furthermore, for SUSTAIN 6 the model was stratified for factors used for randomisation (CV disease status, insulin treatment and eGFR at screening).[3]

Results

- A history of microvascular disease at baseline was reported in 62% (5761/9340) patients in LEADER and 71% (2356/3297) patients in SUSTAIN 6 (Figure 1).
- Patients with microvascular disease at baseline were older, with a longer duration of diabetes, had more frequent insulin use, higher systolic blood pressure and a lower eGFR than those without (Table 1).
- Patients with ≥1 microvascular disease at baseline had a higher risk of MACE (HR [95% CI] in LEADER: 1.15 [1.03;1.29]; SUSTAIN 6: 1.56 [1.14;2.17]) and there was a stepwise increase in risk with increasing number of microvascular diseases (Figure 2).
  - A similar effect was seen for expanded MACE and nephropathy.
- Compared with placebo, liraglutide and semaglutide reduced the risk of:
  - MACE and expanded MACE in patients with and without microvascular disease (Figure 3).
  - Nephropathy in patients with microvascular disease (Figure 3).
- A history of both microvascular and macrovascular disease at baseline was reported in 41% (3835/9340) patients in LEADER and 50% (1640/3297) patients in SUSTAIN 6.
- The risk of MACE was higher in patients with both microvascular and macrovascular disease, irrespective of treatment, compared with macrovascular disease alone: placebo event rates (per 100 patient-years observation) were 5.0 vs 3.8 in LEADER and 5.4 vs 4.1 in SUSTAIN 6.

Figure 1: Microvascular disease at baseline in LEADER and SUSTAIN 6

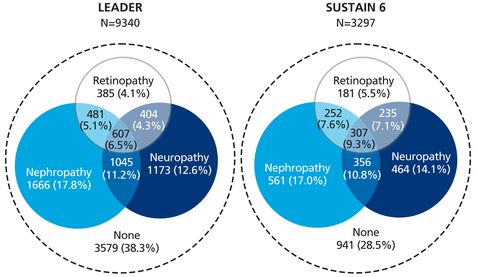
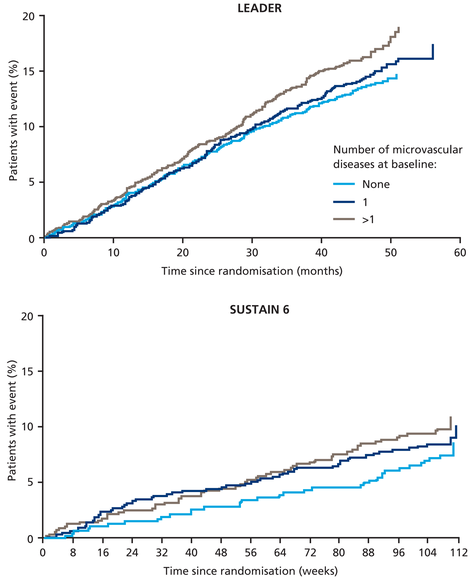


Table 1: Baseline characteristics by history of microvascular disease in LEADER and SUSTAIN 6

Characteristic	LEADER		SUSTAIN 6	
	≥1 microvascular disease (N=5761)	No microvascular disease (N=3579)	≥1 microvascular disease (N=2356)	No microvascular disease (N=941)
Age, years	64.9 ± 7.2	63.2 ± 7.2	65.1 ± 7.4	63.5 ± 7.2
Female	37%	35%	41%	35%
HbA_{1c}, %	8.8 ± 1.6	8.6 ± 1.5	8.7 ± 1.5	8.6 ± 1.4
Duration of T2D, years	14.0 ± 8.1	10.9 ± 7.4	14.9 ± 8.2	11.4 ± 7.2
Insulin use	50%	35%	52%	33%
BMI, kg/m^2	32.6 ± 6.3	32.4 ± 6.2	33.0 ± 6.3	32.3 ± 5.8
SBP, mmHg	136.6 ± 18.2	134.7 ± 16.9	136.4 ± 17.7	133.8 ± 15.6
DBP, mmHg	76.7 ± 10.4	77.7 ± 9.9	77.0 ± 10.2	77.2 ± 9.6
eGFR, mL/min/1.73m^2	76.1 ± 28.0	87.2 ± 24.8	72.2 ± 27.2	86.1 ± 22.0

Data are mean ± standard deviation, or proportion of patients (%). Microvascular disease at baseline: diabetic retinopathy, diabetic neuropathy or diabetic nephropathy. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure; T2D, type 2 diabetes

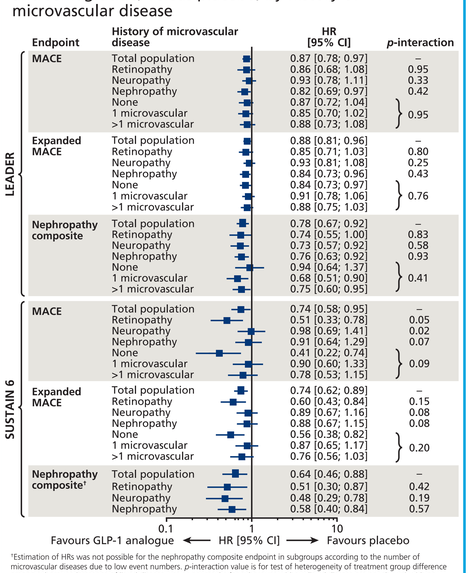
Figure 2: MACE by history of microvascular disease in LEADER and SUSTAIN 6



Cumulative incidences were estimated using the Kaplan–Meier method. Microvascular disease at baseline: diabetic retinopathy, diabetic neuropathy or diabetic nephropathy. MACE, major adverse cardiovascular events

Figure 3: Cardiorenal events with liraglutide and semaglutide, versus placebo, by history of microvascular disease

Key result



†Estimation of HRs was not possible for the nephropathy composite endpoint in subgroups according to the number of microvascular diseases due to low event numbers. *p*-interaction value is for test of heterogeneity of treatment group difference among subgroups (presence of listed disease, yes or no; results for subgroups without listed disease are not shown) with no adjustment for multiple tests. CI, confidence interval; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MACE, major adverse cardiovascular events

Conclusions

- In this *post hoc* analysis of data from LEADER and SUSTAIN 6, patients with a history of microvascular disease were:
  - Older, with a longer duration of T2D and lower eGFR, and used insulin more frequently.
  - At higher risk of cardiorenal events.
- The risk of CV events, irrespective of treatment, was higher in patients with microvascular and macrovascular disease versus macrovascular disease alone.
- Liraglutide and semaglutide reduced the risk of cardiorenal events versus placebo, irrespective of microvascular disease at baseline.

The analysis was sponsored by Novo Nordisk. Both trials are registered with ClinicalTrials.gov (LEADER: NCT01179048; SUSTAIN 6: NCT01720446).
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References: (**1**) Beckman *et al. Circ Res* 2016;118:1771–85; (**2**) Brownrigg *et al. Lancet Diabetes Endocrinol* 2016;4:588–97; (**3**) Marso *et al. N Engl J Med* 2016;375:1834–44; (**4**) Marso *et al. N Engl J Med* 2016;375:311–22.