Exploring the impact of liraglutide on diabetic foot ulcers in patients with type 2 diabetes and increased risk of cardiovascular events: results from the LEADER trial

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on behalf of the LEADER Trial Steering Committee and Investigators

Introduction

- Diabetic foot syndrome, which includes diabetic foot ulcer (DFU), is a leading cause of hospitalisation among all possible complications in patients with type 2 diabetes (T2D),[1,2] with >10% of these patients ultimately requiring an amputation.[3] Mortality rates 5 years post-amputation range from 39% to 68%.[1]
- In general, there is a lack of published long-term data assessing the impact of glucagon-like peptide-1 receptor agonists on DFU outcomes.
- Amputation is a late-stage complication which the population of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial provides a unique opportunity to assess.
- The LEADER trial reported a cardiovascular (CV) risk reduction with liraglutide compared with placebo (both in addition to standard of care) in patients with T2D and at high risk of CV events (hazard ratio [HR]: 0.87, 95% confidence interval [CI]: 0.78–0.97, p=0.01 for superiority) with up to 5 years of follow-up.[4] DFU was a prespecified secondary endpoint in the trial.
- The aim of this analysis was to investigate the incidence of DFU and its associated complications in patients treated with liraglutide compared with placebo in the LEADER trial.

Methods

Study design and oversight

- LEADER was a double-blind, placebo-controlled trial in which patients with T2D and at high risk for CV events were randomly assigned in a 1:1 ratio to liraglutide or placebo, both in addition to standard of care. The disposition and baseline characteristics of trial participants have been published previously.[4]
  - Information on diabetes complications and risk factors for DFU was collected at baseline.
- In the LEADER trial, a selective and targeted approach to safety-data collection was applied, and reporting was required only for events meeting the definition of a serious adverse event (SAE) or a prespecified Medical Event of Special Interest (MESI). DFU was a MESI and defined as an open skin wound on the foot. Complications of DFU events were collected on a specific DFU MESI form.
- Identification of DFU events was based on a search using prespecified terms from the Medical Dictionary for Regulatory Activities (MedDRA).
  - A blinded review of the case narratives of the events identified by this search was used to establish the nature of the DFU and any associated complications (i.e., infections, involvement of underlying structures, amputations, peripheral revascularisations).

Statistical methods

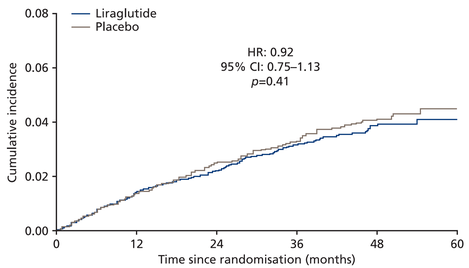
- Summary statistics were calculated for baseline data.
- The HR for time to first DFU event was estimated using a Cox regression model with treatment as a fixed factor, and cumulative incidence was estimated using the Aalen-Johansen method with death as a competing risk.

Table 1 Baseline characteristics of patients with DFU compared with the full analysis set.

	Patients with DFU*		Full analysis set	
	Liraglutide (N=176)	Placebo (N=191)	Liraglutide (N=4668)	Placebo (N=4672)
Age, years	64.7 ± 7.0	64.6 ± 7.8	64.2 ± 7.2	64.4 ± 7.2
Male, n (%)	130 (73.9)	140 (73.3)	3011 (64.5)	2992 (64.0)
Diabetes duration, years	15.6 ± 7.2	16.4 ± 8.4	12.8 ± 8.0	12.9 ± 8.1
HbA_{1c}, %	9.2 ± 1.9	9.1 ± 1.7	8.7 ± 1.6	8.7 ± 1.5
Body weight, kg	98.0 ± 27.1	97.4 ± 23.6	91.9 ± 21.2	91.6 ± 20.8
BMI, kg/m^2	33.2 ± 7.8	32.9 ± 6.8	32.5 ± 6.3	32.5 ± 6.3
SBP, mmHg	138.3 ± 22.6	135.9 ± 20.6	135.9 ± 17.8	135.9 ± 17.7
DBP, mmHg	76.1 ± 11.8	76.2 ± 10.7	77.2 ± 10.3	77.0 ± 10.1
LDL cholesterol, mmol/L	2.4 ± 0.9	2.4 ± 1.1	2.3 ± 0.9	2.3 ± 0.9
Smoking status, n (%)				
Current smoker	28 (15.9)	27 (14.1)	567 (12.1)	563 (12.1)
Previous smoker	66 (37.5)	66 (34.6)	1950 (41.8)	1920 (41.1)
Never smoked	82 (46.6)	98 (51.3)	2151 (46.1)	2189 (46.9)
Medical history of DFU, n (%)	71 (40.3)	69 (36.1)	208 (4.5)	196 (4.2)
Antidiabetic medication, n (%)				
1 OAD	28 (15.9)	20 (10.5)	916 (19.6)	894 (19.1)
>1 OADs	40 (22.7)	50 (26.2)	1520 (32.6)	1481 (31.7)
Insulin with OAD(s)	71 (40.3)	89 (46.6)	1677 (35.9)	1754 (37.5)
Insulin without OADs	29 (16.5)	27 (14.1)	361 (7.7)	377 (8.1)
None	8 (4.5)	5 (2.6)	194 (4.2)	166 (3.6)
Antihypertensive medication, n (%)	160 (90.9)	169 (88.5)	4329 (92.7)	4302 (92.1)
Statins	124 (70.5)	137 (71.7)	3405 (72.9)	3336 (71.4)

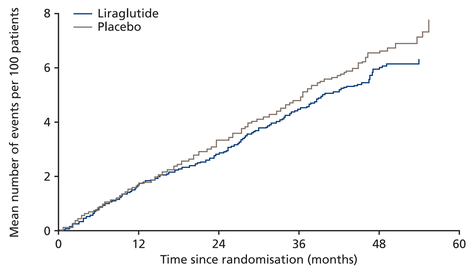
Values are mean ± SD unless stated otherwise.
*A total of 21 events in 21 patients identified by the MedDRA search, but subsequently found to be unrelated to DFU, or reported as complications to a previously reported DFU were excluded from the analysis. BMI, body mass index; DBP, diastolic blood pressure; DFU, diabetic foot ulcer; HbA_{1c}, glycated haemoglobin; LDL, low-density lipoprotein; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; OAD, oral antidiabetic drug; SBP, systolic blood pressure; SD, standard deviation.

Figure 1 Cumulative incidence plot of time to first DFU events among all patients in the LEADER trial.



Aalen-Johansen plot, with death as a competing risk factor.
This figure includes data from the first DFU events in 176 liraglutide-treated and 191 placebo-treated patients. CI, confidence interval; DFU, diabetic foot ulcer; HR, hazard ratio.

Figure 2 Mean number of DFU events per 100 patients during the LEADER trial.



This figure includes data from 260 DFU events in 176 liraglutide-treated patients and 291 DFU events in 191 placebo-treated patients. DFU, diabetic foot ulcer.

Table 2 Complications associated with DFU events.

	Liraglutide (N=4668) (PYO=17,822)				Placebo (N=4672) (PYO=17,741)				*p*-value
	N	%	E	R	N	%	E	R	
Number of patients with DFU events	176	100	260	1.46	191	100	291	1.64	
Infection	107	60.8	146	0.82	131	68.6	162	0.91	0.12
Involvement of underlying structures	64	36.4	86	0.48	80	41.9	98	0.55	0.28
Amputation	44	25.0	60	0.34	67	35.1	78	0.44	0.04
Minor	34	19.3	45	0.25	46	24.1	50	0.28	0.27
Major	11	6.3	13	0.07	22	11.5	24	0.14	0.08
Unknown	1	0.6	2	0.01	4	2.1	4	0.02	–
Peripheral revascularisation	20	11.4	24	0.13	23	12.0	26	0.15	0.84

Based on review of case narratives, *p*-value was calculated using chi-square test for number of patients with events.
'Infection': presence of clinical signs of infection, including redness, warmth, pain, purulence or discharge. 'Involvement of underlying structures': tendon, joint capsule or bone. 'Minor amputations': midtarsal or distal amputations.[5] 'Major amputations': any resection proximal to midtarsal level.[5] 'Unknown amputations': case narratives contained insufficient information for classification as major or minor.
DFU, diabetic foot ulcer; E, number of events; N, number of patients; %, proportion of patients with events; PYO, patient-years of observation; R, event rate per 100 PYO.

- The numbers of patients with complications were compared for the liraglutide and placebo groups using Chi-square tests.
- Due to the exploratory nature of these *post hoc* analyses, there were no corrections for multiple testing.

Results

- In LEADER, 9340 patients were randomised (full analysis set: 4668 to liraglutide and 4672 to placebo) with a median follow-up of 3.8 years.[4]
- At baseline, 4.5% of patients in the liraglutide group and 4.2% in the placebo group had a medical history of DFU; 1.5% and 1.3% of patients, respectively, had ongoing DFU.
- Among patients with DFU events during the trial compared with the full analysis set, more were male, had longer diabetes duration and poorer glycaemic control, were receiving insulin and had a medical history of DFU at baseline. Within the group of patients who reported at least one DFU event, baseline characteristics were overall similar between the liraglutide and placebo treatment groups (Table 1).
- The proportions of patients with DFU events during the trial were 3.8% in the liraglutide group (n=176) and 4.1% in the placebo group (n=191).
- The HR for time to first DFU event was 0.92 (95% CI: 0.75–1.13; p=0.41; Figure 1).
- The mean number of DFU events per 100 patients appeared lower with liraglutide compared with placebo from Month 18 onwards (Figure 2) and a similar pattern was seen for the time to first DFU event (Figure 1).
- Analysis of DFU complications demonstrated that (Table 2):
  - There were similar proportions of patients with a DFU-related infection, DFU involving underlying structures and DFU requiring peripheral revascularisation between the liraglutide and placebo groups.
  - Treatment with liraglutide resulted in a lower proportion of patients with DFU events leading to amputations compared with placebo (p=0.04); non-significant differences were seen when minor and major amputations were considered separately.

References

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Conclusions

- During the LEADER trial, the proportions of patients with DFU events were similar for liraglutide and placebo.
- The data suggest a reduced risk of DFU-associated amputations with liraglutide versus placebo in patients with T2D and at increased risk of CV events.

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

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The trial and this analysis were sponsored by Novo Nordisk (NCT01179048)
Presenter Ketan Dhatariya is on the Clinical Endpoint Adjudication Committee for the Sotagliflozin trials implemented by Lexicon pharmaceuticals and has received consulting fees and honoraria from Novo Nordisk
The authors are grateful to Bernt Johan von Scholten, Novo Nordisk, for review of and input to the poster, and to Watermeadow Medical (supported by Novo Nordisk) for writing assistance
Presented at the European Association for the Study of Diabetes, 11-15 September 2017, Lisbon, Portugal