



The Impact of Liraglutide on Diabetes-Related Foot Ulceration and Associated Complications in Patients With Type 2 Diabetes at High Risk for Cardiovascular Events: Results From the LEADER Trial

Ketan Dhatariya,^{1,2} Stephen C. Bain,³ John B. Buse,⁴ Richard Simpson,⁵ Lise Tarnow,⁶ Margit Staum Kaltoft,⁷ Michael Stellfeld,⁷ Karen Tornøe,⁷ Richard E. Pratley,⁸ and the LEADER Publication Committee on behalf of the LEADER Trial Investigators

Diabetes Care 2018;41:2229–2235 | <https://doi.org/10.2337/dc18-1094>

OBJECTIVE

Diabetes-related foot ulcers (DFUs) and their sequelae result in large patient and societal burdens. Long-term data determining the efficacy of individual glucose-lowering agents on DFUs are lacking. Using existing data from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, we conducted post hoc analyses assessing the impact of liraglutide versus placebo in people with type 2 diabetes and at high risk of cardiovascular (CV) events on the incidence of DFUs and their sequelae.

RESEARCH DESIGN AND METHODS

The LEADER trial (NCT01179048) was a randomized, double-blind, multicenter, CV outcomes trial assessing liraglutide (1.8 mg/day) versus placebo, in addition to standard of care, for up to 5 years. Information on DFUs was collected systematically during the trial, and DFU complications were assessed post hoc through reviewing case narratives.

RESULTS

During a median of 3.8 years' follow-up, similar proportions of patients reported at least one episode of DFU in the liraglutide and placebo groups (3.8% [176/4,668] versus 4.1% [191/4,672], respectively; hazard ratio [HR] 0.92 [95% CI 0.75, 1.13; $P = 0.41$]). Analysis of DFU-related complications demonstrated a significant reduction in amputations with liraglutide versus placebo (HR 0.65 [95% CI 0.45, 0.95; $P = 0.03$]). However, no differences were found for foot infections, involvement of underlying structures, or peripheral revascularization in the main analysis.

CONCLUSIONS

Treatment with liraglutide in patients with type 2 diabetes and at high risk of CV events in the LEADER trial did not increase the risk of DFU events and was associated with a significantly lower risk of DFU-related amputations compared with placebo. This association, possibly due to chance, needs further investigation.

¹Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, U.K.

²Norwich Medical School, University of East Anglia, Norwich, U.K.

³Institute of Life Science, Swansea University Medical School, Swansea, U.K.

⁴University of North Carolina School of Medicine, Chapel Hill, NC

⁵Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia

⁶Nordsjællands Hospital, Hillerød, Denmark

⁷Novo Nordisk A/S, Søborg, Denmark

⁸Translational Research Institute for Metabolism and Diabetes, Florida Hospital, Orlando, FL

Corresponding author: Ketan Dhatariya, ketan.dhatariya@nnuh.nhs.uk.

Received 18 May 2018 and accepted 8 July 2018.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-1094/-/DC1>.

© 2018 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

Diabetes-related foot ulcers (DFUs) are a common complication in people with diabetes, estimated to affect between 9.1 million and 26.1 million people worldwide (1). This equates to a lifetime incidence of 19%–34% in patients with diabetes (1). Long-term outcomes for patients with DFUs are poor (1), particularly reflected in 5-year mortality rates. For example, in patients with DFUs, the 5-year mortality rate is 44% (2) and may be as high as 70% when patients have a related amputation (3), a rate similar to that for patients with colorectal cancer (4). Alongside these high mortality rates, the economic impact of DFU is large (5), with the National Health Service in England spending an estimated £972 million–£1.13 billion in 2014–2015 on treating people with DFUs (6,7), and \$9.1–\$13.2 billion is spent annually in the U.S. (8).

Currently, the standard of care for DFU consists of wound care, pressure off-loading, and, when necessary, antibiotics, vascular reconstruction, or surgical debridement (1). These interventions have some success in healing DFUs in the short term (1,9). In the longer term, however, there is a high risk that DFUs will recur (1). To date, there are few data to suggest that choice of glucose-lowering therapies impacts on the management of DFUs or their sequelae.

It is generally agreed that good glycaemic control reduces the risk of complications in people with diabetes (10,11), but its precise role in decreasing the risk of foot complications remains unclear due to multiple confounding factors in most DFU trials (12). Randomized controlled clinical trials are particularly difficult in this field (9) due to the complexity of foot ulcer pathogenesis and the size of the study population needed to test treatment efficacy (13). These difficulties contribute to the lack of a robust evidence base for adjunctive drug therapies (14) and any benefits they may have for patients. Indeed, a recent cardiovascular outcomes trial (CVOT) program of over 10,000 patients with diabetes at high risk of cardiovascular (CV) events suggested that one glucose-lowering agent, canagliflozin, increases the risk of lower-extremity amputations (15). Little work has been published on the effect of other classes of glucose-lowering drugs, including glucagon-like peptide 1 receptor

agonists (GLP-1RAs), on DFU and its outcomes.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a CVOT that investigated the effect of liraglutide versus placebo, both in addition to standard of care, on CV events and long-term safety in patients with type 2 diabetes and at high CV risk. In the trial, DFU was a prespecified secondary end point (16). Using this existing, extensive data set, we conducted a post hoc analysis to assess the impact of liraglutide, a GLP-1RA, on the incidence of DFUs and their sequelae in people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

In this post hoc analysis of the LEADER data, DFU was defined as an open wound on the foot. Although DFU was a prespecified secondary end point, this was not a primary foot ulcer trial and as such did not include all 21 points recommended for such trials by Jeffcoate et al. (13). For transparency and as good practice, we have included the 21-point checklist in the Supplementary Data online, comparing our methodology against that recommended for good quality DFU publications (Supplementary Table 1).

Study Design and Oversight

The trial design (NCT01179048) and methods have been published previously (16). The trial protocol, available with the full article text, was approved by an institutional review board or ethics committee as required by each participating center, and all patients provided written informed consent. Briefly, the LEADER trial was of double-blind, placebo-controlled design, during which patients with type 2 diabetes and at high risk of 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 (16). Information on diabetes complications and risk factors for DFU was collected at baseline. A total of 9,340 patients were randomized (full-analysis set), 4,668 to receive liraglutide and 4,672 to placebo, with a median follow-up of 3.8 years. The mean percentage of time that patients took their assigned trial treatment was 84% in the liraglutide group and 83% in the placebo group.

Collection of DFU Data

A selective and targeted approach to safety data collection was applied (17), and reporting was required only for events meeting the definition of a serious adverse event or prespecified medical event of special interest (MESI). In the trial, DFU was prespecified as a MESI. As with other prespecified MESIs, information related to DFU events (including complications of such events) was collected on a designated form.

Patients were classified as “with DFU event” if they reported an incident DFU or worsening of an existing DFU (i.e., one that was present at study entry) during the trial. Patients “without DFU events” did not experience a DFU as an adverse event during the trial; however, they may have had a DFU at baseline that continued throughout the trial without worsening. Such preexisting, nonworsening DFUs were not included in this analysis.

The development of a DFU and worsening of an existing DFU were captured as adverse events and identified posttrial based on a prespecified search using terms from the Medical Dictionary for Regulatory Activities on all adverse events reported in the trial (Supplementary Table 2). In addition, a blinded review conducted before database lock of the case narratives of the events identified by this search was used to establish the nature of the DFU event and any associated complications (i.e., amputations, infections, involvement of underlying structures, or peripheral revascularizations). Any events judged by medical evaluation not to be DFUs or that were reported as a complication of a DFU event previously captured (i.e., reported as two separate events, but during case narrative review realized to be an event plus its complication) were excluded from the analyses.

Unless otherwise specified, the term “amputation” refers to all amputations identified in this analysis. Amputations were also further categorized (after database lock and per International Working Group on the Diabetic Foot guidelines [18]) as minor, which included midtarsal or distal amputations; major, which included any resection proximal to midtarsal level; or unknown, which were those that could not be classified as major or minor based on the case narratives.

Statistical Methods

Summary statistics were calculated for baseline data. The hazard ratio (HR) for time to first DFU event and each of the four complications (i.e., amputation [overall, major, and minor], infection, involvement of underlying structures, or peripheral revascularization) was estimated using a Cox regression model with treatment as a fixed factor. The cumulative incidence was estimated using the Aalen-Johansen method, with death as a competing risk factor. The HR for time to all DFU events was estimated using the Andersen-Gill method for the Cox regression model on recurrent events with treatment as a fixed factor.

In a separate analysis, DFU events that occurred within 1 year of enrollment into the study were excluded. This was to allow for a latency effect because it was considered that any potential protective effect of liraglutide would not be present within the first year of treatment. Thus, time to first DFU event and DFU-related complications that occurred 1 year or more after randomization were investigated. The HR for the time to these events was also estimated using the Cox regression model.

No corrections for multiple testing were performed because all these analyses were post hoc and exploratory in nature.

RESULTS

For this post hoc analysis of the published LEADER trial (16), 260 DFU events in 176 patients treated with liraglutide and 291 DFU events in 191 patients treated with placebo were identified (Supplementary Fig. 1 and Supplementary Data).

Baseline Characteristics, Including Risk Factors for DFU

Of the patients experiencing DFU events, proportionally more were male, had longer diabetes duration and poorer glycemic control, and were administering insulin at baseline versus those without DFU events (Supplementary Table 3). Although patients who experienced DFU events during the trial appeared to have a higher mean body weight than those without DFU events, the mean BMI of both groups was similar. In addition, other risk factors for DFU (history of DFU, neuropathy, nephropathy, retinopathy,

peripheral arterial disease, and smoking) were present at greater proportions in patients who experienced a DFU event during the trial compared with those who did not. For patients who reported DFU events during the trial, 40.3% in the liraglutide group and 36.1% in the placebo group had a history of DFU at baseline, consistent with previous data on the recurrent nature of DFU. This compared with 3.0% and 2.8% in the liraglutide and placebo groups, respectively, for those who did not develop a DFU event during the trial. The corresponding numbers for patients with ongoing DFU at baseline were 16.5% and 13.6%, respectively, for patients who reported a DFU event during the trial compared with 0.9% and 0.7%, respectively, for patients without DFU events (Supplementary Table 3).

DFU Events Over Time

A slight separation of the curves for time to first DFU event in favor of liraglutide appeared from month 18 and onward; however, the HR for time to first DFU event was 0.92 (95% CI 0.75, 1.13; *P* = 0.41) (Fig. 1 and Table 1), showing no significant difference, which was the same for time to first DFU event reported from 1 year after randomization (i.e., excluding events occurring within the first year of trial participation [Table 1]).

The mean number of DFU events per 100 patients was also numerically less with liraglutide compared with placebo from month 18 onward (Supplementary

Fig. 2). However, a HR of 0.97 (95% CI 0.82, 1.16; *P* = 0.76) (Table 1) for analysis of all DFU events, including recurrent events, indicated no significant difference between treatment arms.

Similar results were seen for the time to first DFU event in patients with or without a history of DFU and in patients at high risk of DFU (i.e., no active foot ulcer at baseline but with peripheral neuropathy or presence of peripheral artery disease or history of DFU) (Table 1).

DFU-Related Amputations

Treatment with liraglutide resulted in a lower proportion (25.0%; 44/176) of patients with DFU events leading to amputations compared with placebo (35.1%; 67/191) (Table 2). The Cox regression analysis of time to first amputation with a HR of 0.65 (95% CI 0.45, 0.95; *P* = 0.028) (Fig. 2A) demonstrated a risk reduction in amputations with liraglutide.

The treatment difference seen in amputations seemed driven mostly by major amputations (liraglutide 6.3% [11/176]; placebo 11.5% [22/191]; *P* = 0.06) rather than minor amputations (liraglutide 19.3% [34/176]; placebo 24.1% [46/191]; *P* = 0.17) (Table 2). However, analysis of time to first (overall) amputations that occurred after 1 year from randomization (i.e., excluding amputations within the first year of trial participation) decreased the risk further in favor of liraglutide (HR 0.55, 95% CI 0.36, 0.84; *P* = 0.006) (Table 2).

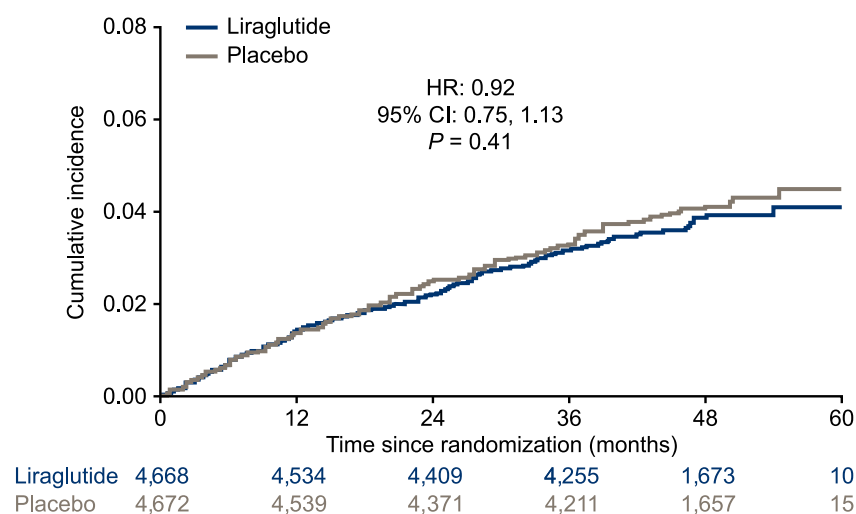


Figure 1—Cumulative incidence plot of time to first DFU event among all patients in the LEADER trial. Aalen-Johansen plot, with death as a competing risk factor. This figure includes data from the first DFU events in 176 liraglutide-treated and 191 placebo-treated patients.

Table 1—HRs associated with DFU events in the LEADER trial

| | Liraglutide | Placebo | HR (95% CI) | P value |
|---|-------------------------|-------------------------|-------------------|---------|
| DFU events | | | | |
| Time to first DFU event, <i>n</i> (%) [*] | 176 (3.8) [FAS = 4,668] | 191 (4.1) [FAS = 4,672] | 0.92 (0.75, 1.13) | 0.41 |
| Time to first DFU event after 1 year, <i>n</i> (%) [†] | 127 (2.8) [FAS = 4,599] | 149 (3.2) [FAS = 4,601] | 0.85 (0.67, 1.07) | 0.16 |
| Time to all DFU events (including recurrent events), <i>n</i> of events | 260 | 291 | 0.97 (0.82, 1.16) | 0.76 |
| By background characteristics, <i>n</i> (%) | | | | |
| Time to first DFU event in patients with history of DFU | 71 (34.1) [FAS = 208] | 69 (35.2) [FAS = 196] | 0.97 (0.69, 1.35) | 0.84 |
| Time to first DFU event in patients with no history of DFU | 105 (2.4) [FAS = 4,460] | 122 (2.7) [FAS = 4,476] | 0.86 (0.66, 1.11) | 0.25 |
| Time to first DFU event in patients at high risk of DFU | 101 (5.8) [FAS = 1,747] | 110 (6.2) [FAS = 1,787] | 0.93 (0.71, 1.22) | 0.60 |

DFU event is defined as reporting of an incident DFU or worsening of an existing DFU. Cox regression model with treatment as a fixed factor. High risk of DFU is defined as a patient with type 2 diabetes who at baseline did not have an active foot ulcer but had peripheral neuropathy or presence of peripheral artery disease or history of DFU. FAS, full-analysis set. ^{*}*n*, number of patients with a first DFU between randomization and follow-up dates. [†]*n*, number of patients with first foot ulcer after 1 year from randomization date and before follow-up date (i.e., excludes event occurring within the first year of trial participation).

Other DFU-Related Complications

For DFU-related infection and DFU involving underlying structures, the cumulative incidence plots appeared to separate over time (at months 18 and 24, respectively) in favor of liraglutide, but the HRs of time to these events were not significant (Fig. 2B and C). In addition,

there was no difference between treatments in DFU requiring peripheral revascularization (Fig. 2D).

The HR for time to first DFU-related infection that occurred after 1 year from randomization was 0.74 (95% CI 0.55, 0.99; *P* = 0.044) in favor of liraglutide (Table 2).

CONCLUSIONS

This post hoc analysis of data from the LEADER trial showed that the use of liraglutide in patients with type 2 diabetes at high risk of CV events did not increase the risk of a DFU event compared with placebo. Although there were numerically fewer DFU events with

Table 2—Complications associated with DFU events

| | Liraglutide (N = 4,668) (PYO = 17,822) | | | | | Placebo (N = 4,672) (PYO = 17,741) | | | | | HR (95% CI) | P value |
|--|---|--------|-----------------------|--------|-------------------|---------------------------------------|---------|-----------------------|-----|------|-------------------|---------|
| | <i>n</i> | % of N | Patients with DFU (%) | E | R | <i>n</i> | % of N | Patients with DFU (%) | E | R | | |
| DFU events or related complications | | | | | | | | | | | | |
| Patients with DFU event(s) | 176 | 3.8 | 100.0 | 260 | 1.46 | 191 | 4.1 | 100.0 | 291 | 1.64 | 0.92 (0.75, 1.13) | 0.41 |
| Patients with DFU event(s) + complication of | | | | | | | | | | | | |
| Amputation | 44 | 0.9 | 25.0 | 60 | 0.34 | 67 | 1.4 | 35.1 | 78 | 0.44 | 0.65 (0.45, 0.95) | 0.03 |
| Minor | 34 | 0.7 | 19.3 | 45 | 0.25 | 46 | 1.0 | 24.1 | 50 | 0.28 | 0.74 (0.47, 1.15) | 0.17 |
| Major | 11 | 0.2 | 6.3 | 13 | 0.07 | 22 | 0.5 | 11.5 | 24 | 0.14 | 0.50 (0.24, 1.02) | 0.06 |
| Unknown | 1 | 0.0 | 0.6 | 2 | 0.01 | 4 | 0.1 | 2.1 | 4 | 0.02 | — | — |
| Infection | 107 | 2.3 | 60.8 | 146 | 0.82 | 131 | 2.8 | 68.6 | 162 | 0.91 | 0.81 (0.63, 1.05) | 0.11 |
| Involvement of underlying structures | 64 | 1.4 | 36.4 | 86 | 0.48 | 80 | 1.7 | 41.9 | 98 | 0.55 | 0.80 (0.57, 1.11) | 0.17 |
| Peripheral revascularization | 20 | 0.4 | 11.4 | 24 | 0.13 | 23 | 0.5 | 12.0 | 26 | 0.15 | 0.87 (0.48, 1.58) | 0.64 |
| | Liraglutide (N = 4,599) | | Placebo (N = 4,601) | | HR (95% CI) | | P value | | | | | |
| | <i>n</i> | % of N | <i>n</i> | % of N | | | | | | | | |
| Analysis of first DFU-related complications that occurred after 1 year from randomization[*] | | | | | | | | | | | | |
| Amputation | 32 | 0.70 | 58 | 1.26 | 0.55 (0.36, 0.84) | | 0.006 | | | | | |
| Infection | 75 | 1.63 | 101 | 2.20 | 0.74 (0.55, 0.99) | | 0.044 | | | | | |
| Involvement of underlying structures | 47 | 1.02 | 67 | 1.46 | 0.70 (0.48, 1.01) | | 0.06 | | | | | |
| Peripheral revascularization | 11 | 0.24 | 20 | 0.43 | 0.55 (0.26, 1.14) | | 0.11 | | | | | |

Analyses based on review of case narratives. *P* values were based on an analysis of time to first event using a Cox regression model with treatment as fixed factor. Infection is defined as presence of clinical signs of infection, including redness, warmth, pain, purulence, or discharge. Involvement of underlying structures is defined as tendon, joint capsule, or bone. Minor amputations are defined as midtarsal or distal amputation and major amputations as any resection proximal to midtarsal level (18). Unknown amputations are defined as those that could not be classified as major or minor based on the case narratives. E, number of events; N, number of patients in the treatment group; *n*, number of patients with an event or complication; PYO, patient-years of observation; R, event rate per 100 PYO. ^{*}Percentages of patients are of the full-analysis set (liraglutide, N = 4,599; placebo, N = 4,601). This analysis excluded complications occurring within the first year of trial participation.

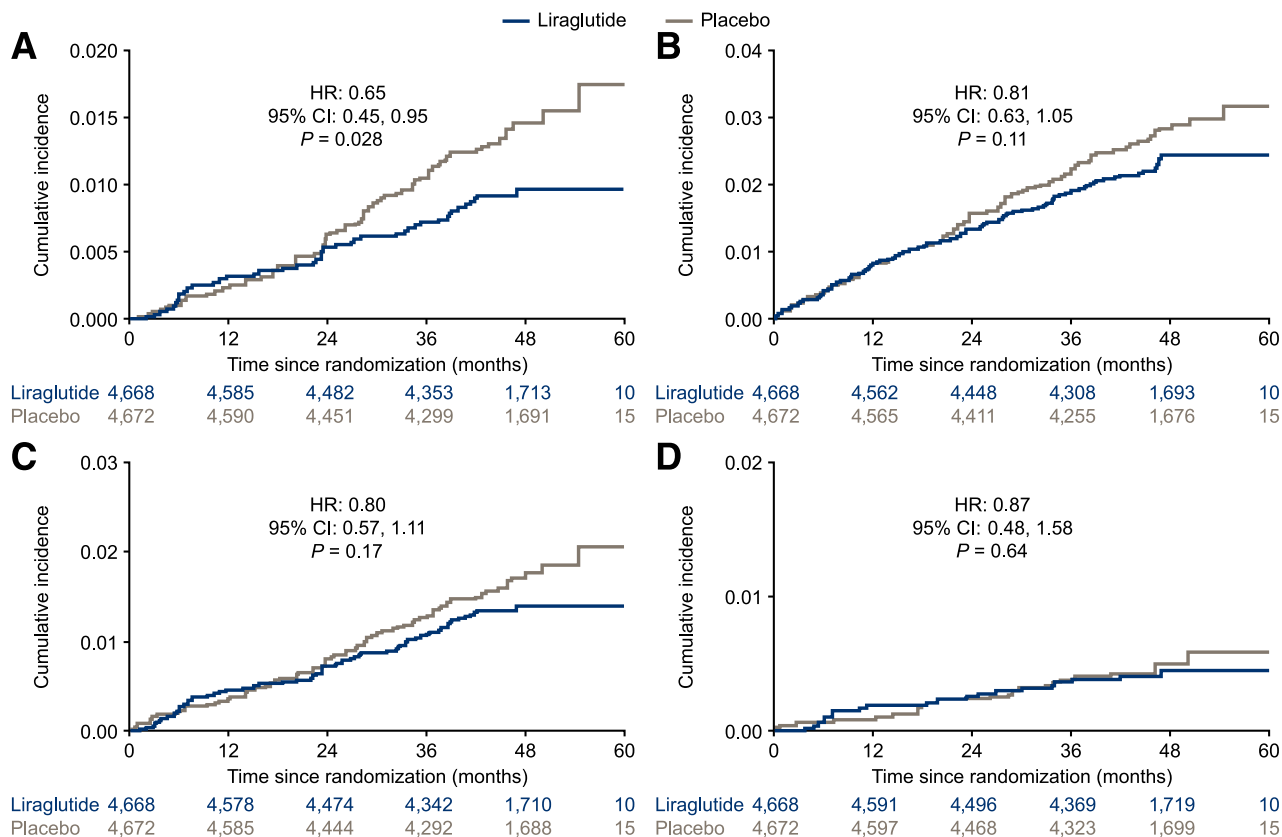


Figure 2—Cumulative incidence plot of time to first DFU-related complication among patients treated with liraglutide vs. placebo in the LEADER trial. **A:** Amputation (44 first DFU events in the liraglutide group and 67 first DFU events in the placebo group). **B:** Infection (107 and 131 first DFU events in liraglutide and placebo groups, respectively). **C:** Involvement of underlying structures (64 and 80 first DFU events in liraglutide and placebo groups, respectively). **D:** Peripheral revascularization (20 and 23 first DFU events in liraglutide and placebo groups, respectively).

liraglutide compared with placebo, the difference was not significantly different. However, the HRs for time to DFUs requiring lower-extremity amputation were significantly lower in the liraglutide arm than for those given placebo. Treatment with liraglutide also resulted in a risk reduction in DFU-related amputations compared with placebo when excluding amputations that occurred within the first year of enrollment into the trial.

There is a need for DFU therapies with proven benefit with the large disease burden; social, personal, and economic impact of DFUs (1,5,6); current limited treatment options available (1,19); and the high risk of DFU recurrence (1). To date, very limited data have been published on the effect of glucose-lowering drugs on DFUs and associated complications. Intensive glucose control had no impact on the risk of amputation or development of peripheral vascular disease compared with conventional therapy in the UK Prospective Diabetes Study (UKPDS) and Action in Diabetes

and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) studies, but DFU was not a specified end point in these trials (11,20,21). In the Veterans Affairs Diabetes Trial (VADT), amputation due to ischemic gangrene was included within the composite primary end point, but data related to amputation or foot ulcers only do not appear to have been published (22,23). For the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, data relating to some types of microvascular foot complications have been published but not amputation or foot ulcers (24). More recently, results from Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R) (studies in which amputation data were systematically collected and reported) have indicated that the risk for both leg and foot amputations in canagliflozin-treated patients is approximately double that for placebo-treated patients (15). At this point in time, this does not seem to

be a class effect of the sodium–glucose cotransporter 2 inhibitors as a post hoc analysis of the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial did not show an increase in major or minor amputation risk in those with preexisting peripheral arterial disease, a group known to be at high risk of DFU events (25). More data regarding amputation on another sodium–glucose cotransporter 2 inhibitor (dapagliflozin) will be available when the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) CVOT is published later this year. To date, other than antibiotics used to treat infected wounds, only one other drug, fenofibrate, has been suggested to reduce the risk of amputation in patients with type 2 diabetes (26).

Examining the DFU data from the LEADER trial in detail, it was apparent that these were similar to data from other DFU studies. Within the LEADER trial population, the proportion of

patients who had a medical history of DFU but did not report another (i.e., recurrent) DFU during the trial was very low (placebo 2.8%, liraglutide 3.0%). When compared with those who reported a DFU event during the trial, the proportion with a medical history of DFU was much higher (placebo 36.1%, liraglutide 40.3%), indicating the recurrent nature of DFU. These numbers agree with those published by Armstrong et al. (1), which showed that the recurrence rate within 1 year of healing was 40%, increasing to 65% within 5 years.

The important findings for DFU-related amputations lead to the question as to the possible mechanisms. Well-known risk factors for DFU include poor glycemic control, history of DFU, smoking, and long diabetes duration (19,27). Analysis of the baseline characteristics of patients who experienced a DFU event during the trial reflected these risk factors. Any differences reported here are likely to be directly a result of the assigned study treatment because the risk factors for DFU were balanced at baseline between the two treatment groups. Within the trial, there was modest improvement in some of these risk factors, such as glycemic control and weight loss, in the liraglutide group compared with placebo (16). It is unknown if the improvements in these effects contributed to the reduced incidence of DFU-related amputations in the liraglutide group.

Other possible links between DFU pathology and GLP-1RA receptor agonism could be reduced inflammation and increased angiogenesis. These have been demonstrated in rodents with diabetes treated intraperitoneally with exendin-4 (28). Also, liraglutide increased atherosclerotic plaque stability in rodents, which could reduce vascular disease (29). It is possible that similar mechanisms could be induced by liraglutide in humans and are relevant here, as inflammation is linked to DFU pathology (27). This effect may not be unique to the GLP-1RA class because other incretin-based therapies may also impact DFU healing, as shown recently by a preclinical and clinical study with saxagliptin, a dipeptidyl peptidase 4 inhibitor (30).

Limitations and Strengths

Although we evaluated a previously unexplored question, this was a post hoc

analysis of the LEADER trial, which was designed to assess CV safety and not the risk of DFU in great detail. This analysis was exploratory in nature and did not correct for multiple testing; therefore, caution is needed when interpreting the data. Also, the inclusion/exclusion criteria did not mention DFU; however, the target population was those at high risk for CV events, which would inherently have included patients at risk for DFU events. DFU was a prespecified MESI, which resulted in the systematic collection of events and associated complications. However, information on the location of the DFU and management of DFU (e.g., care afforded to individual patients and duration of event) was not systematically collected, which would have allowed events to be investigated in greater detail.

Due to the protocol and method of safety data collection, it was not possible to analyze all amputations that occurred during the trial, but only those related to DFU events. This is because the underlying cause for any procedure or surgery was reported as the adverse event and not the procedure itself (unless the underlying cause was unknown). However, as 85% of lower-extremity amputations are preceded by a DFU (18), it is likely that the number of amputations not included in this analysis was relatively small.

The checklist to assess the quality of study reports about DFU (13) was completed for this post hoc analysis (Supplementary Table 1). Although the trial prespecified DFU as secondary end point, it was not powered for the analyses applied here. The low number of events and the relatively short follow-up (median follow-up 3.8 years) may have affected the potential to find further differences between the liraglutide and placebo arms. For example, the cumulative plots for DFU events overall, DFU events with infection, and DFU events with involvement of underlying structures separated in favor of liraglutide after between 18 and 24 months, but did not reach statistical significance. However, given that this trial recruited those at high CV risk with baseline glycosylated hemoglobin concentrations $>7.0\%$ (53 mmol/mol)—and thus at high risk of DFU—and had large sample size, it is unlikely that a similar trial will be done to examine foot outcomes specifically.

Although the overall risk of DFU events was similar between liraglutide and placebo, the reduced risk for DFU-associated amputations suggests the value from such a post hoc analysis. Furthermore, the prespecified data collection increased the robustness of these analyses; other strengths include that DFU incidence was monitored in a large population at risk for DFU within a randomized clinical trial population.

Summary

This post hoc analysis of data from the LEADER trial suggests that treatment with liraglutide in patients with type 2 diabetes and at high risk of CV events did not increase the risk of DFU events and was associated with a significantly lower risk of DFU-related amputations compared with placebo. The association between the use of liraglutide and reduction in amputation in those at high CV risk could be due to chance but merits further investigation.

Acknowledgments. Helen Vanya Biering Kjær Stegmann completed the statistical analyses and together with Bernt Johan von Scholten reviewed the manuscript, contributing to its development (both from Novo Nordisk).

Funding and Duality of Interest. The trial and analysis were sponsored by Novo Nordisk. The study sponsor completed the analyses and contributed to data interpretation with the authors (three of the authors are employees of the sponsor). The corresponding author had full access to the data and the final responsibility for the decision to submit for publication. Medical writing and editorial support were provided by Gillian Groeger and Izabel James, both from Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc, funded by Novo Nordisk. K.D. has received honoraria and/or travel support from Novo Nordisk, Sanofi Diabetes, Eli Lilly, Lexicon Pharmaceuticals, Genentech, and Uro Laboratories. S.C.B. has received research grants (including principal investigator, collaborator/consultant, and pending grants) from Health and Care Research Wales (Welsh Government) and Novo Nordisk, other research support from Health and Care Research Wales (Welsh Government) infrastructure support, and honoraria from Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, and Merck. He has ownership interest in Glycosmedia (diabetes online news service). J.B.B. has received consulting fees paid to his institution and travel support from Adocia, AstraZeneca, Dexcom, Elcelyx Therapeutics, Eli Lilly, Intarcia Therapeutics, Lexicon, MannKind, Metavention, NovaTarg, Novo Nordisk, Sanofi, Senseonics, and vTv Therapeutics and grant support from AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Lexicon, Novo Nordisk, Sanofi, Theracos, and vTv Therapeutics. He holds stock options from Mellitus

Health, PhaseBio, and Stability Health. He is a consultant to Neurimmune AG and is supported by a grant from the National Institutes of Health (UL1TR002489). R.S. has received research grants from Novo Nordisk and Merck; travel support and/or honoraria from Merck, Eli Lilly, Novo Nordisk, GlaxoSmithKline, AstraZeneca, and Sanofi; and consulting fees from Novo Nordisk and Sanofi. L.T. has received research grants, travel support, and honoraria from Novo Nordisk and holds shares in Novo Nordisk. M.S.K., M.S., and K.T. are employees of Novo Nordisk A/S, and all hold stocks/shares in Novo Nordisk. R.E.P. has received research grants (to his institution) from Novo Nordisk; speaker and consultancy fees (paid to his institution) from AstraZeneca and Takeda; consultancy fees (paid to his institution) from Boehringer Ingelheim, GlaxoSmithKline, Hanmi Pharmaceutical Co., Ltd., Janssen Scientific Affairs, LLC, Ligand Pharmaceuticals, Inc., Eli Lilly, Merck, Novo Nordisk, Pfizer, and Eisai, Inc.; research grants from Gilead Sciences, Lexicon Pharmaceuticals, Ligand Pharmaceuticals, Inc., Eli Lilly, Merck, Novo Nordisk, Sanofi, and Takeda. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. K.D. as lead author was responsible for the development of the first draft. K.D., S.C.B., J.B.B., R.S., L.T., M.S.K., M.S., K.T., and R.E.P. conceived this analysis of the LEADER data, advised on analysis and interpretation of the data, and drafted and revised the manuscript. K.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability. The data and details of analytic methods that support the findings of this study are available from the corresponding author upon request.

Prior Presentation. Parts of this analysis were presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes, 11–15 September 2017, Lisbon, Portugal, and at the International Diabetes Federation Congress 2017, 4–8 December 2017, Abu Dhabi, United Arab Emirates, and was endorsed at some local congresses.

References

1. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med* 2017;376:2367–2375
2. Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care* 2003;26:491–494
3. Lavery LA, Hunt NA, Ndip A, Lavery DC, Van Houtum W, Boulton AJ. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. *Diabetes Care* 2010;33:2365–2369
4. Office for National Statistics. U.K. Cancer survival in England: patients diagnosed between 2010 and 2014 and followed up to 2015 [Internet], 2016. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinenglandadultsdiagnosed/2010and2014andfollowedupto2015>. Accessed 20 November 2017
5. Petrakis I, Kyriopoulos IJ, Ginis A, Athanasakis K. Losing a foot versus losing a dollar; a systematic review of cost studies in diabetic foot complications. *Expert Rev Pharmacoecon Outcomes Res* 2017;17:165–180
6. Kerr M. Diabetic foot care in England: an economic study [Internet], 2017. Available from [https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/Diabetic%2520footcare%2520in%2520England%2C%2520An%2520economic%2520case%2520study%2520\(January%25202017\).pdf](https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/Diabetic%2520footcare%2520in%2520England%2C%2520An%2520economic%2520case%2520study%2520(January%25202017).pdf). Accessed 2 October 2017
7. NHS Digital. National Diabetes Footcare Audit Hospital Admissions Report 2014–2016 [Internet], 2017. Available from <http://www.digital.nhs.uk/catalogue/PUB30107>. Accessed 25 July 2017
8. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. *Diabetes Care* 2014;37:651–658
9. Jeffcoate WJ, Price PE, Phillips CJ, et al. Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. *Health Technol Assess* 2009;13:1–86, iii–iv
10. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg* 2016;63(Suppl.):35–215
11. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
12. Hasan R, Firwana B, Elraiyah T, et al. A systematic review and meta-analysis of glycemic control for the prevention of diabetic foot syndrome. *J Vasc Surg* 2016;63(2 Suppl.):225–285. e1–2
13. Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC; International Working Group on the Diabetic Foot and the European Wound Management Association. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. *Lancet Diabetes Endocrinol* 2016;4:781–788
14. Elraiyah T, Tsapas A, Prutsky G, et al. A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. *J Vasc Surg* 2016;63(2 Suppl.):465–585. e1–2
15. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–657
16. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–322
17. U.S. Food and Drug Administration. *Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations* [Internet], 2016. Available from <https://www.fda.gov/downloads/drugs/guidances/ucm291158.pdf>. Accessed 5 September 2017
18. International Working Group on the Diabetic Foot. Amputations in people with diabetes [Internet], 2007. Available from <http://iwgdf.org/consensus/amputations-in-people-with-diabetes>. Accessed 13 June 2017
19. American Diabetes Association. Microvascular complications and foot care. Sec. 10. In *Standards of Medical Care in Diabetes—2017*. *Diabetes Care* 2017;40(Suppl. 1):S88–S98
20. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589
21. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
22. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139
23. Hayward RA, Reaven PD, Wiitala WL, et al.; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;372:2197–2206
24. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD Trial Group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
25. Verma S, Mazer CD, Al-Omran M, et al. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. *Circulation* 2018;137:405–407
26. Rajamani K, Colman PG, Li LP, et al.; FIELD Study Investigators. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomized controlled trial. *Lancet* 2009;373:1780–1788
27. Volmer-Thole M, Lobmann R. Neuropathy and diabetic foot syndrome. *Int J Mol Sci* 2016;17:917
28. Roan JN, Cheng HN, Young CC, et al. Exendin-4, a glucagon-like peptide-1 analogue, accelerates diabetic wound healing. *J Surg Res* 2017;208:93–103
29. Gaspari T, Welungoda I, Widdop RE, Simpson RW, Dear AE. The GLP-1 receptor agonist liraglutide inhibits progression of vascular disease via effects on atherogenesis, plaque stability and endothelial function in an ApoE(-/-) mouse model. *Diab Vasc Dis Res* 2013;10:353–360
30. Long M, Cai L, Li W, et al. DPP-4 inhibitors improve diabetic wound healing via direct and indirect promotion of epithelial-mesenchymal transition and reduction of scarring. *Diabetes* 2018;67:518–531