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Paper:
Tack, C., Jacob, S., Desouza, C., Bain, S., Buse, J., Nauck, M., Petrie, J., Poulter, N., Pratley, R., et. al. (2019). Longterm efficacy and safety of combined insulin and GLP1 therapy: evidence from the LEADER trial. *Diabetes, Obesity and Metabolism*
http://dx.doi.org/10.1111/dom.13826

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Received: 4 April 2019 | Revised: 20 June 2019 | Accepted: 1 July 2019

DOI: 10.1111/dom.13826

ORIGINAL PAPER

WILEY

Long-term efficacy and safety of combined insulin and glucagon-like peptide-1 therapy: Evidence from the LEADER trial

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Funding information
The LEADER trial (ClinicalTrials.gov number: NCT01179048) and this post hoc analysis were funded by Novo Nordisk A/S.

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13826.

Abstract

Aim: Glucagon-like peptide-1 receptor agonist (GLP-1RA) and insulin combination therapy is an effective treatment option for type 2 diabetes, but long-term data are lacking. The aim was to assess the long-term efficacy of the GLP-1RA liraglutide in subgroups by insulin use in the LEADER trial.

Materials and Methods: LEADER assessed cardiovascular (CV) safety and efficacy of liraglutide (1.8 mg) versus placebo (plus standard of care therapy) in 9340 patients with type 2 diabetes and high risk of CV disease, for up to 5 years. We analyzed CV events, metabolic parameters and hypoglycaemia post hoc in three subgroups by baseline insulin use (basal-only insulin, other insulin or no insulin). Insulin was a non-random treatment allocation as part of standard of care therapy.

Results: At baseline, 5171 (55%) patients were not receiving insulin, 3159 (34%) were receiving basal-only insulin and 1010 (11%) other insulins. Insulin users had a longer diabetes duration and slightly worse glycaemic control (HbA1c) than the no-insulin

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subgroup. Liraglutide reduced HbA1c and weight versus placebo in all three subgroups ($P < .001$), and severe hypoglycaemia rate in the basal-only insulin subgroup. The need for insulin was less with liraglutide. CV risk reduction with liraglutide was similar to the main trial results in the basal-only and no-insulin subgroups.

Conclusions: In patients on insulin, liraglutide improved glycaemic control, weight and need for insulin versus placebo, for at least 36 months with no increased risk of severe hypoglycaemia, while maintaining CV safety/efficacy, supporting the combination of liraglutide and insulin for management of type 2 diabetes.

KEYWORDS

glucagon-like peptide-1 analogue, insulin analogues, insulin therapy, liraglutide, type 2 diabetes

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recommended for treatment of patients with type 2 diabetes in combination with metformin and other oral glucose-lowering drugs, as monotherapy for patients not suited to metformin or in combination with insulin.[1] Combining GLP-1RAs and insulin has complementary benefits on glycaemic control, while limiting insulin-induced weight gain and reducing hypoglycaemia risk.[2,3] Specifically, the addition of the GLP-1RA liraglutide to basal insulin has been shown to improve glycaemic control and reduce weight.[4] Compared with the addition of bolus insulin, liraglutide reduces weight and rates of hypoglycaemia.[5,6] These findings are reflected in current guidelines supporting the use of GLP-1RAs in combination with basal insulin when glycaemic control is insufficient.[1] However, long-term data for GLP-1RA and insulin combination therapy regarding safety and efficacy are lacking, as relevant clinical trials have generally been limited to a maximum of 52 weeks' duration.[3]

The LEADER (ClinicalTrials.gov, NCT01179048) cardiovascular (CV) outcomes trial compared the CV safety of liraglutide with placebo when added to standard of care (including insulin) over a follow-up period of up to 5 years (median 3.8 years).[7] The main finding from this trial was a reduced risk of major adverse CV events (MACE), along with improvements in glycaemic control, body weight and systolic blood pressure, and reduced rates of hypoglycaemia versus placebo.[7] As a large number of LEADER participants were on insulin, we assessed these outcomes in patients by insulin use (basal-only insulin, other insulin or no insulin) at baseline. In addition, we report changes in low-density lipoprotein cholesterol (LDL-C) and changes in need for insulin (initiation, intensification, dose and discontinuation) during the trial in each treatment group. This post hoc subgroup analysis provides long-term safety and efficacy data for GLP-1RA and insulin combination therapy.

2 | MATERIALS AND METHODS

2.1 | Design

Detailed descriptions of the LEADER trial have been published previously.[7,8] In brief, LEADER was a multinational (32 countries), double-blind, randomized, placebo-controlled trial designed to assess the CV safety and efficacy of liraglutide.[7]

Patients with type 2 diabetes were eligible for inclusion if they had HbA1c > 7% (>53 mmol/mol), were at high risk of CV disease (aged ≥50 years with established CV disease [CVD] or chronic kidney disease, or aged ≥60 years with ≥1 risk factor for CVD) and were treated with oral glucose-lowering drugs, insulin (human neutral protamine Hagedorn, long-acting analog or premix insulin), a combination of these, or were treatment-naïve at baseline.[7] The use of GLP-1RAs, dipeptidyl peptidase-4 inhibitors (DPP-4is), pramlintide or rapid-acting insulin was an exclusion criterion.[7]

Patients were randomized 1:1 to liraglutide (up to 1.8 mg, as tolerated) or placebo, in addition to standard of care treatment, and followed for a minimum of 3.5 years, and up to 5 years.[7] Standard of care treatment guidelines were followed that encouraged investigators to intensify treatment for patients who did not achieve HbA1c ≤7.0% (53 mmol/mol), or their individualized glycaemic targets. The addition of any glucose-lowering therapy (including insulin) was permitted, except for GLP-1RAs, DPP-4is or pramlintide.[7]

2.2 | Endpoints

The primary endpoint was the time to first occurrence of a composite CV outcome comprising CV death, non-fatal myocardial infarction or non-fatal stroke (MACE).[7] Other endpoints assessed included metabolic parameters such as HbA1c, body weight, systolic blood pressure and LDL-C, and the occurrence of severe hypoglycaemia (hypoglycaemia requiring the assistance of another person to administer carbohydrate, glucagon or other resuscitative actions).[7,9]

2.3 | Statistical analysis

In this paper, we present the results from post hoc subgroup analyses by insulin use at baseline. The primary analysis was performed for MACE, HbA1c, body weight, systolic blood pressure, LDL-C, severe hypoglycaemia and changes in insulin use (insulin initiation, basal insulin intensification, insulin discontinuation and insulin dose), based on three categories of insulin use at baseline: (a) basal-only insulin

(intermediate or long-acting insulin only, ATC codes A10AE or A10AC), (b) other insulin, basal insulin in combination with other insulin or other insulin regimens (ATC codes A10AD [premixed preparations], A10AB [short-acting insulin] or codes starting A10A not categorized elsewhere), and (c) no insulin.

Changes in HbA1c, insulin dose, body weight, systolic blood pressure and LDL-C from baseline to 36 months were estimated using a mixed model for repeated measurements with a compound symmetry variance, with treatment, sex, region and insulin subgroup as fixed effects, including the treatment and insulin subgroup interaction, and with the baseline value of the variable being estimated (e.g. baseline HbA1c for changes in HbA1c) and age as covariates, all nested within the visit. Analyses of insulin dose were restricted to patients for whom insulin dose data were available and reported in international units (IU). The 36-month time point was used because it represents the last scheduled clinic visit for the whole trial population at which all of the parameters of interest were measured.

Rates of severe hypoglycaemia were compared using a negative binomial regression model with treatment, sex, region and insulin subgroup as fixed effects, treatment and insulin subgroup interaction and age as covariates, and a log link and logarithm of the observation time as offset.

A Cox proportional-hazards model with treatment group (liraglutide or placebo) as a fixed factor was used to analyze time to insulin initiation in patients not using insulin at baseline, and time to intensification of basal insulin (addition of fast-acting insulin or change to mixed insulin) in patients using basal insulin only at baseline. The same model, but with addition of the insulin subgroup and the interaction between randomized treatment group and insulin subgroup as fixed factors, was used to analyze time to permanent discontinuation of insulin during the trial in patients using insulin at baseline. The numbers needed to treat (NNT) were calculated for avoiding insulin initiation and obtaining permanent discontinuation of insulin during the trial, respectively, according to the methods described by Altman and Andersen.[10]

A Cox proportional-hazards model with treatment, subgroup, and the interaction between treatment and subgroup as covariates was used to analyze time to first MACE with liraglutide versus placebo in the aforementioned three categories of baseline insulin use. The following analyses were also performed for MACE: (a) according to two categories of insulin use at baseline (no insulin or any insulin), (b) by three groups of total daily insulin dose at baseline (<30; ≥30 to <50; and ≥ 50 IU), and (c) in patients not using insulin at baseline or during the trial (i.e. censoring those who initiated insulin before first MACE, at the time of insulin initiation).

3 | RESULTS

In the LEADER trial, 9340 patients with type 2 diabetes at high risk of CV events were randomized to liraglutide (n = 4668) or placebo (n = 4672), both in addition to standard of care therapy.[7] Median exposure to study drug (liraglutide or placebo) was 3.5 years, and the median follow-up was 3.8 years.[7]

At baseline, 4169 (45%) patients were on insulin therapy. Of these patients, 3159 (76%) were receiving basal only and 1010 (24%) were treated with other insulin regimens, mostly premixed preparations (908 patients).

Insulin users (basal-only and other insulin subgroups) in both randomized treatment groups had a longer duration of diabetes, slightly worse glycaemic control (HbA1c) and more frequently had established heart disease and chronic kidney disease than patients not using insulin at baseline (Table 1). Baseline characteristics and demographics were balanced between randomized treatment groups (liraglutide and placebo) in the three subgroups by insulin use (data not shown).

In patients on insulin, the HbA1c reductions in response to liraglutide during the trial were similar to those not on insulin (Figure 1, Table 2). Compared with the placebo-treatment group, greater proportions of patients in the liraglutide-treatment group achieved HbA1c <7.0% (<53 mmol/mol), <7.5% (<58 mmol/mol) or <8.0% (<64 mmol/mol), as well as clinically relevant reductions in HbA1c (>0.5% [>5 mmol/mol]) without weight gain at 36 months, in all three subgroups by insulin use at baseline (Figures S1 and S2).

In the basal-only insulin subgroup, the rate of severe hypoglycaemia in patients treated with liraglutide (1.2 episodes per 100 patient-years of observation [PYO]) was substantially lower than in those who received placebo (2.6 episodes per 100 PYO, rate ratio: 0.44, 95% confidence interval [CI]: 0.28; 0.70) (Figure S3) despite better glycaemic control. No significant differences were detected in the rates of severe hypoglycaemia in the other insulin subgroup (rate ratio: 1.54, 95% CI: 0.74; 3.20) and the no-insulin subgroup (rate ratio: 0.76, 95% CI: 0.47;1.21) (Figure S3). Two patients (one patient in the basal-only insulin subgroup, randomized to placebo, and one patient in the other insulin subgroup, randomized to liraglutide) experienced a total of 66 severe hypoglycaemic episodes during the trial.[7] A sensitivity analysis excluding patients with >10 severe hypoglycaemic episodes (therefore, with just these two patients removed) confirmed a significant reduction in the rate of severe hypoglycaemia in patients treated with liraglutide in the basal-only subgroup (rate ratio: 0.62, 95% CI: 0.41; 0.94), and indicated comparable rates of severe hypoglycaemia in patients treated with liraglutide and placebo in the other insulin subgroup (rate ratio: 1.12, 95% CI: 0.56; 2.21).

At baseline, the mean ± standard deviation (SD) total daily dose of insulin in the basal-only subgroup was 43.7 ± 35.6 IU, and in the other insulin group was 77.1 ± 55.5 IU (Table S1). Insulin requirements during the trial were lower in the liraglutide-treatment group than in the placebo-treatment group. Among patients not treated with insulin at baseline, initiation of insulin during the trial was less frequent in those randomized to liraglutide than in those randomized to placebo (800/2630 [30%] vs. 1198/2541 [47%] patients, hazard ratio: 0.55, 95% CI: 0.50; 0.60) (Figure S4). Among patients treated with insulin at baseline, those in the liraglutide group discontinued insulin during the trial more frequently than those in the placebo group (206/2038 [10%] vs. 122/2131 [6%] patients, hazard ratio: 1.62, 95% CI: 1.16; 2.27) (Figure S5). The number of patients needed to be treated with liraglutide to prevent insulin

TABLE 1 Baseline characteristics of patients according to baseline insulin use

Characteristic	All patients (n = 9340)	Insulin use at baseline		
		Basal-only insulin (n = 3159)	Other insulin (n = 1010)	No insulin (n = 5171)
Male sex	6003 (64.3)	1953 (61.8)	623 (61.7)	3427 (66.3)
Age, y	64.3 ± 7.2	64.4 ± 7.2	64.8 ± 7.1	64.1 ± 7.3
Diabetes duration, y	12.8 ± 8.0	14.9 ± 7.8	16.9 ± 8.1	10.8 ± 7.4
HbA1c, %	8.7 ± 1.5	8.9 ± 1.6	8.8 ± 1.5	8.5 ± 1.5
HbA1c, mmol/mol	71.5 ± 16.7	73.8 ± 17.2	72.9 ± 16.7	69.9 ± 16.2
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.2	34.2 ± 6.6	32.2 ± 6.2
Body weight, kg	91.7 ± 21.0	91.2 ± 20.6	96.7 ± 21.3	91.1 ± 21.0
Systolic blood pressure, mm Hg	135.9 ± 17.7	136.2 ± 18.4	136.1 ± 18.1	135.7 ± 17.3
Diastolic blood pressure, mm Hg	77.1 ± 10.2	76.5 ± 10.3	74.7 ± 10.3	77.9 ± 10.1
LDL-C, mmol/L	2.3 ± 0.9	2.3 ± 0.9	2.3 ± 0.9	2.4 ± 1.0
HDL-C, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
Heart failure[a]	1305 (14.0)	431 (13.6)	153 (15.1)	721 (13.9)
Established CVD (age ≥50 y)	7598 (81.3)	2613 (82.7)	866 (85.7)	4119 (79.7)
CVD risk factors (age ≥60 y)	1742 (18.7)	546 (17.3)	144 (14.3)	1052 (20.3)
Renal function				
Normal (eGFR ≥90)	3275 (35.1)	1055 (33.4)	285 (28.2)	1935 (37.4)
Mild impairment (eGFR 60-89)	3907 (41.8)	1278 (40.5)	398 (39.4)	2231 (43.1)
Moderate impairment (eGFR 30-59)	1934 (20.7)	726 (23.0)	292 (28.9)	916 (17.7)
Severe impairment (eGFR <30)	224 (2.4)	100 (3.2)	35 (3.5)	89 (1.7)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association. Data are mean ± standard deviation or number of patients (proportion, %).

[a]Chronic heart failure, NYHA class II-III.

initiation during the trial in one patient was six. The number of patients needed to be treated with liraglutide to subsequently discontinue insulin treatment during the trial (patients treated with insulin at baseline) in one patient was 27. In patients treated with basal insulin, intensification (addition of fast-acting insulin or change to premixed insulin) was less frequently required during the trial in the liraglutide-treatment group than in the placebo group (Figure S6).

Compared with patients who received placebo, change in mean insulin dose from baseline to month 36 (total dose for all types of insulin, including prandial insulin added in the basal-only subgroup) was significantly lower in liraglutide-treated patients in both the basal-only insulin (estimated liraglutide vs. placebo difference: −12.1 IU, 95% CI: −14.3; −9.9) and other insulin (estimated difference: −9.5 IU, 95% CI: −13.4;−5.6) subgroups (Table S1). A similar result was observed with weight-corrected insulin dose (Table S1).

In addition to improvements in glycaemic control and decreased insulin requirements, there were also significant reductions in body weight in patients on insulin treated with liraglutide compared with placebo, which was greater than in patients not treated with insulin at baseline (*P*-interaction < .001) (Table 2).

In the main trial population, treatment with liraglutide was associated with improvements in systolic blood pressure[7] and LDL-C compared with placebo (Table 2). Similar results were observed for systolic blood pressure in the three subgroups by insulin use (Table 2). There was also a trend for improvement in LDL-C in the three subgroups (Table 2).

There was a higher incidence of MACE in the subgroup of patients treated with insulin at baseline (15%-16% of patients) than in patients in the no-insulin subgroup (13% of patients) (Figure 2).

CV risk reductions with liraglutide compared with placebo were shown in the main trial population, and hazard ratios were of similar magnitude in the basal-only, any-insulin (pooled subgroup of insulin users) and no-insulin subgroups (Figure 2). In a sensitivity analysis for the subgroup using no insulin at baseline, liraglutide was shown to reduce the risk of first MACE compared with placebo in patients who were not treated with insulin at baseline and who were censored if initiating insulin before MACE (Figure 2). The risk of MACE with liraglutide versus placebo appeared to be unaffected by baseline insulin dose (<30, 30 to <50, ≥50 IU): no interactions between randomized treatment and these subgroups were identified (Figure 2).

4 | DISCUSSION

In this post hoc analysis of the LEADER trial, we present long-term safety and efficacy data for GLP-1RA and insulin combination

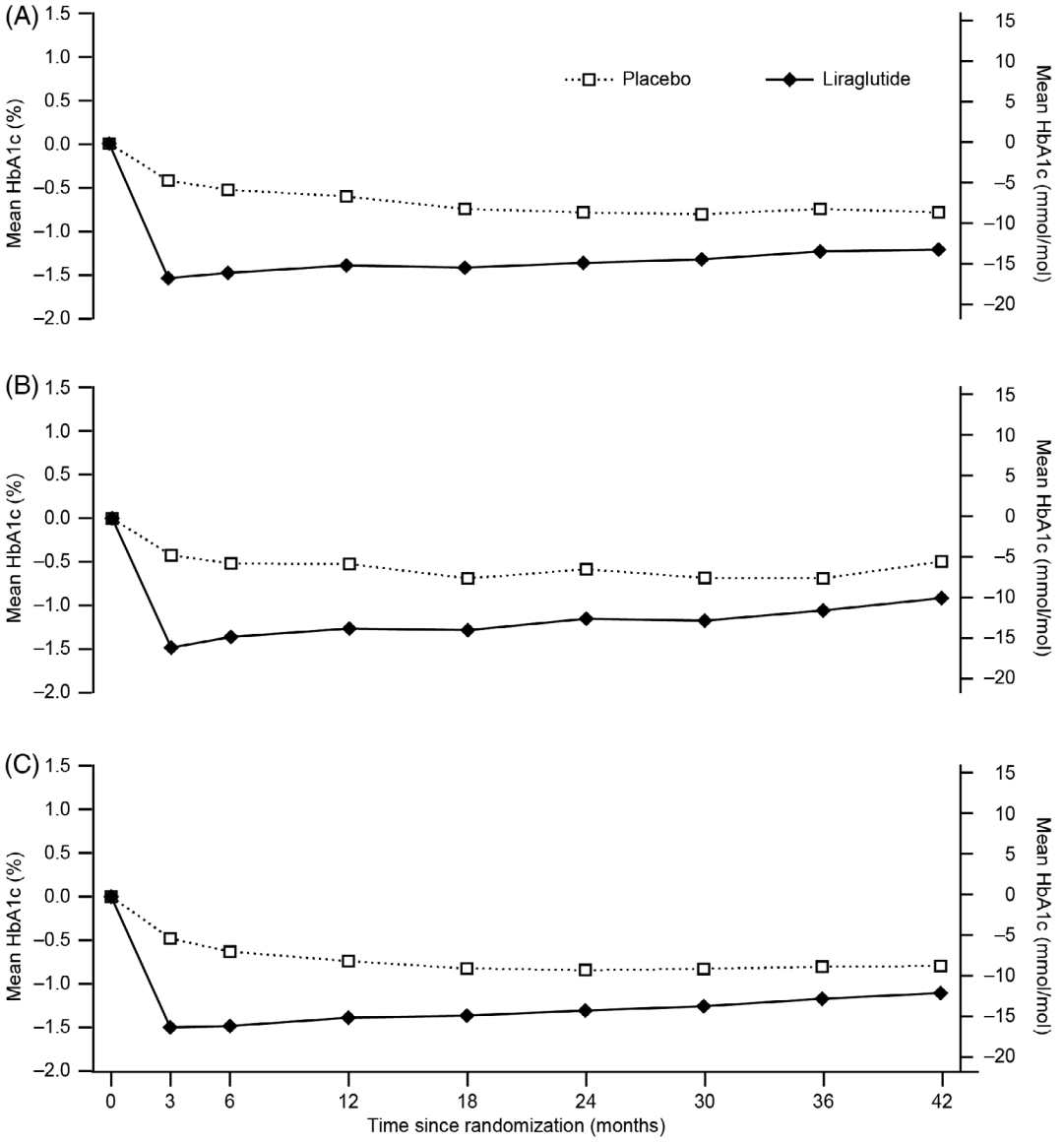

FIGURE 1 Change in HbA1c from baseline in liraglutide and placebo-treatment groups, according to baseline insulin use: A, basal-only insulin, B, other insulin and C, no insulin

therapy. We have shown that addition of liraglutide to insulin treatment in patients with type 2 diabetes at high CV risk improves glycaemic control, and reduces body weight and insulin need for at least 36 months with no increased risk of severe hypoglycaemia. We have also shown that the CV safety of liraglutide is maintained, irrespective of insulin use or dose at baseline. Together, these results support the safety and efficacy of combined liraglutide and insulin treatment.

In the largest subgroup of patients who were treated with basal-only insulin at baseline, liraglutide compared with placebo improved glycaemic control, reduced body weight and insulin requirement, and halved the risk of severe hypoglycaemia, with hazard ratios for MACE that were similar to patients not on insulin at baseline. These results over 3 years are in agreement with and extend the findings from previous clinical trials of 6-12 months' duration with liraglutide added to insulin.[4-6,11,12] In the LIRA ADD2BASAL trial, adding liraglutide to basal insulin for 26 weeks improved glycaemic control, body weight, systolic blood pressure and LDL-C, and reduced insulin requirements compared with placebo.[4] In contrast to the present analysis, a higher rate of confirmed hypoglycaemia was reported when adding liraglutide compared with placebo to basal insulin in that trial, but the authors suggested that this may have resulted from a lack of insulin dose adjustment at the time of liraglutide initiation.[4] A recent subgroup analysis of the DEVOTE trial showed a reduced risk of MACE in patients using liraglutide in combination with basal insulin compared with patients using basal insulin without liraglutide, over a median follow-up of 2 years.[13] Adding further support to our results, this analysis also showed a non-significant trend for a reduced risk of severe hypoglycaemia, and slightly lower mean bolus insulin dose in patients with concomitant liraglutide use.[13]

TABLE 2 Liraglutide effects on metabolic parameters according to baseline insulin use

	Estimated treatment group difference (liraglutide vs. placebo) at 36 months (95% CI), *P*-value			Estimated treatment group ratio (liraglutide vs. placebo) at 36 months, (95% CI), *P*-value
Insulin use at baseline	**HbA1c, %**	**Body weight, kg**	**Systolic blood pressure, mm Hg**	**LDL-C, mmol/L**
All patients (n = 9340)	−0.40 (−0.45; −0.34), *P* < .001	−2.3 (−2.5; −2.0), *P* < .001	−1.2 (−1.9; −0.5), *P* = .001	0.98 (0.96; 0.99), *P* = .003
Basal-only insulin (n = 3159)	−0.48 (−0.57; −0.39), *P* < .001	−2.5 (−2.9; −2.1), *P* < .001	−1.2 (−2.4; 0.0), *P* = .055	0.98 (0.95; 1.01), *P* = .118
Other insulin (n = 1010)	−0.37 (−0.54; −0.21), *P* < .001	−3.5 (−4.2; −2.8), *P* < .001	−1.8 (−4.0; 0.4), *P* = .106	0.97 (0.92; 1.01), *P* = .166
No insulin (n = 5171)	−0.36 (−0.43; −0.29), *P* < .001	−1.9 (−2.3; −1.6), *P* < .001	−1.1 (−2.1; −0.2), *P* = .018	0.98 (0.96; 1.00), *P* = .029

Abbreviation: LDL-C, low-density lipoprotein cholesterol. Estimated mean differences using a mixed model for repeated measurements with a compound symmetry variance, with treatment, sex and region as fixed effects and with age as a covariate.

In addition to confirming the efficacy of liraglutide in combination with insulin for glycaemic control and CV safety, we have shown that liraglutide reduced the need for insulin initiation. NNTs with liraglutide to prevent insulin initiation and to discontinue insulin during the trial were low. When insulin was required in combination with liraglutide, a lower mean dose was used, and for patients on a basal-insulin regimen at baseline, intensification was less frequent and delayed. These results corroborate previous studies indicating improved or equivalent glycaemic control, and reduced weight and rates of hypoglycaemia when liraglutide is added to basal insulin, compared with more complex basal–bolus insulin regimens.[5,6]

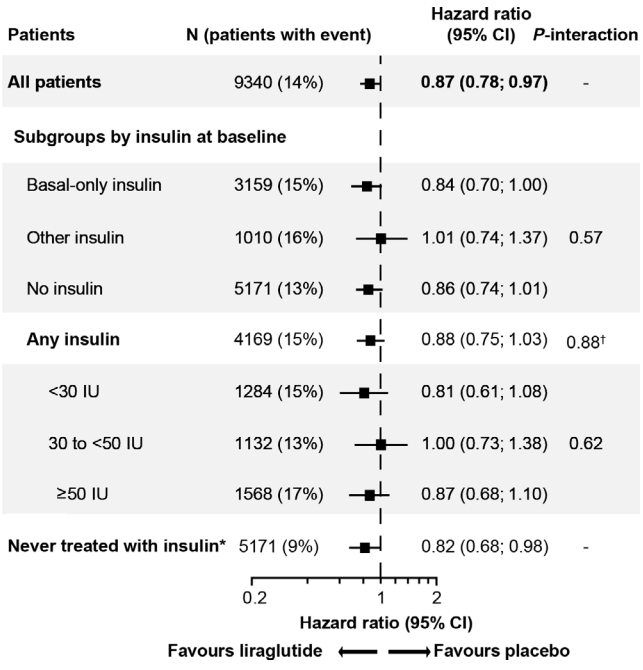

FIGURE 2 Risk of first major adverse cardiovascular event with liraglutide versus placebo, according to subgroups by insulin use. IU, international unit; MACE, major adverse cardiovascular events; N, number of patients analyzed. *Patients not treated with insulin at baseline, censored if initiating insulin before MACE. †*P*-value for interaction between randomized treatment and any insulin/no-insulin subgroups. Time to first MACE with liraglutide versus placebo analyzed using a Cox proportional-hazards model with treatment as a covariate

While different study designs and patient populations limit direct comparisons, the overall consistency of results between our analysis and previous studies suggests that the established efficacy and safety profile of liraglutide added to basal insulin is maintained in the long term. Our results are also largely consistent with those derived from shorter studies of other GLP-1RAs.[3]

Other than a neutral hazard ratio for MACE, and a non-significant increase in the rate of severe hypoglycaemia compared with placebo, similar results for liraglutide treatment were detected in the other insulin subgroup to those observed in the basal-only insulin subgroup. The hypoglycaemia result is probably related in part to the heterogeneous nature of the 'other insulin' group, but also to an 'outlier' patient with numerous severe hypoglycaemic episodes (when this patient was excluded, there was no difference between the treatment groups).

Weight reduction was greater with liraglutide compared with placebo in patients treated with insulin at baseline than in those not requiring insulin at baseline. This is in keeping with previous studies that have reported greater weight loss with liraglutide in insulin-treated patients, possibly because of reversal of insulin-induced weight gain associated with insulin dose reduction.[14,15]

At baseline, compared with patients not receiving insulin, insulin-treated patients had a longer duration of diagnosed type 2 diabetes, slightly worse glycaemic control, and higher frequency of CV disease and renal impairment. These characteristics are consistent with a more advanced disease state and contraindications for oral agents, as expected for patients requiring insulin. It might be expected that beta cell loss associated with longer diabetes duration would dictate that insulin becomes the optimal therapy. However, we have shown that, independent of insulin treatment and diabetes duration, liraglutide improved glycaemic control in a similar way. Negative results of some earlier CV outcome trials conducted before the GLP-1RA/sodium-

glucose co-transporter-2 inhibitor (SGLT-2i) era (e.g. VADT) have been attributed to recruitment of a population sample with CV disease too advanced to benefit.[16,17] The present analysis of LEADER shows that the efficacy and safety profile of liraglutide is maintained even in a type 2 diabetes population with advanced disease and at high risk of CV events. The CV safety of liraglutide versus placebo was confirmed for all subgroups of insulin use and dose analyzed. This pattern of results was consistent with the prespecified subgroup analyses published previously (i.e. point estimates for hazard ratios indicating reductions in MACE for the majority of subgroups).[7] We have extended the prespecified subgroup analysis for MACE by insulin use at baseline (yes/no) with additional endpoints and more detailed subgroups.

The interpretation of results from the analyses we present is constrained by limitations inherent to post hoc analyses, as well as the limitations that apply to the primary analysis of the LEADER trial, including recruitment of a patient population with type 2 diabetes at high risk of CV events, limiting extrapolation of the results to patients with less advanced type 2 diabetes.[7] Nevertheless, the double-blind nature of the trial and high patient retention rates with little missing data increase the validity of our results. A specific limitation is the use of subgroup analyses based on insulin treatment at baseline. Insulin treatment was initiated, adjusted and discontinued during the trial for some patients – according to the study design to achieve so-called glycaemic equipoise – such that comparator treatment groups are not equivalent to previous smaller studies specifically designed to assess the effect of GLP-1RAs in combination with insulin. Based on the differences in HbA1c between treatment groups in LEADER, it could be argued that the differences in insulin use during the trial should have been even greater. We cannot rule out the confounding effects of these changes on our results, but defining subgroups based on insulin use at baseline did avoid the post-randomization confounding that could have occurred by comparing patients in the placebo and liraglutide groups who initiated insulin during the trial (with the latter more likely having more advanced disease). Furthermore, it is reassuring that, compared with placebo, the effect of liraglutide on MACE was similar in the subgroup using no insulin at baseline and in a sensitivity analysis of patients not treated with insulin either at baseline or during the trial. Our decision to base analyses primarily on three subgroups by insulin use means that the no-insulin and other insulin subgroups in particular probably represent heterogeneous cohorts of patients receiving a range of different glucose-lowering therapies. However, we reasoned that clear differences would probably be apparent between patients using insulin and those using other therapies, and between patients using basal-only insulin and those using other insulin regimens. While we cannot infer any results for patients using specific therapies within the three subgroups, more detailed subgroups would have further reduced patient numbers and hindered interpretation. It must also be considered that, while patients enrolled in the trial had poor glycaemic control, intensification of therapy with GLP-1RAs and DPP-4is in the placebo group was prohibited, and SGLT-2is were largely unavailable during the trial. It could therefore be argued that, for many patients in the placebo group, insulin was the only treatment option, and that greater insulin use in this group was a function of the trial design. Finally, our analyses based on insulin dose are somewhat limited by a lack of available dose data for a small proportion of patients (185 patients [4% of insulin users] at baseline).

In summary, addition of liraglutide to insulin treatment for patients with type 2 diabetes at high CV risk improved glycaemic control, reduced body weight and insulin need for at least 36 months with no increased risk of severe hypoglycaemia, and maintained CV safety. These results support the use of combined liraglutide and insulin treatment.

ACKNOWLEDGMENTS

The authors thank all trial personnel and participants, Steven Marso, MD, of HCA Midwest Health Heart & Vascular Institute, Kansas City, Missouri, for feedback on the draft manuscript, and Charlie Hunt, PhD, Izabel James, MBBS, and Helen Marshall, BA, of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc (funded by Novo Nordisk A/S), for medical writing and editorial assistance.

The subject-level analysis datasets for the research presented in the publication are available from the corresponding author on reasonable request.

Results from this manuscript have been partly published in abstract form and were presented at the 78th Scientific Sessions of the American Diabetes Association, 22-26 June 2018, Orlando, Florida, as a poster presentation.

The LEADER trial (ClinicalTrials.gov number: NCT01179048) and this post hoc analysis were funded by Novo Nordisk A/S.

CONFLICT OF INTEREST

C.J.T. has served on advisory panels for MSD and Novo Nordisk; and speaker's bureau for Novo Nordisk. He has received research support from AstraZeneca. S.J. has served on advisory panels for AstraZeneca, Boehringer Ingelheim, MSD, and Novo Nordisk; and on speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly, Menarini Group, MSD, Novo Nordisk (and Foundation), and Roche. C.D. has served on an advisory panel for Medscape, and has acted as a consultant for Novo Nordisk. He has received research support from Merck & Co. S.C.B. has received research grants (includes principal investigator, collaborator or consultant and pending grants as well as grants already received) from Healthcare and Research Wales (Welsh Government) and Novo Nordisk. He has received other research support from Healthcare and Research Wales (Welsh Government) and honoraria from Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, and Merck. He has an ownership interest in Gycosmedia (diabetes online news service). J.B.B. has been an advisor, with all fees paid to the University of North Carolina, for Adocia, AstraZeneca, Dance Biopharm, Eli Lilly, MannKind, NovaTarg, Novo Nordisk, Senseonics, and vTv

Therapeutics. He has received grant support from Novo Nordisk, Sanofi, and vTv Therapeutics. He is a consultant to Cirius Therapeutics Inc., CSL Behring, and Neurimmune AG. He holds stock options in Mellitus Health, PhaseBio, and Stability Health. He is supported by a grant from the National Institutes of Health (UL1TR002489). M.A.N. has served on advisory boards or consulted for AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Fractyl, GlaxoSmithKline, Intarcia, Menarini/Berlin Chemie, Merck, Sharp & Dohme, and Novo Nordisk. His institution has received grant support from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Intarcia, Menarini/Berlin-Chemie, Merck, Sharp & Dohme, Novartis Pharma, and Novo Nordisk A/S. He has served on speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Menarini/Berlin Chemie, Merck, Sharp & Dohme, Novo Nordisk A/S, and Sun Pharma. J.R.P. is Chair of Clinical Studies Group 6 for Diabetes UK. He has served on advisory boards for AstraZeneca and Novo Nordisk, and has acted as a consultant for Novo Nordisk, and as a speaker for Pfizer. He has received research support from Merck, Itamar Medical, and Janssen Pharmaceuticals. He has served as a member of endpoint committees for Boehringer Ingelheim, Applied Clinical Intelligence, Bayer, and Quintiles. N.R.P. has received personal speaker fees from Servier, Takeda, and Novo Nordisk; and has served on advisory boards for AstraZeneca and Novo Nordisk (in relation to type 2 diabetes). He has received research grants for his research group relating to type 2 diabetes from Diabetes UK, NIHR EME, Julius Clinical, and the British Heart Foundation, with a pending grant from Novo Nordisk. R.E.P. has received research grants from Gilead Sciences, Lexicon Pharmaceuticals, Ligand Pharmaceuticals Inc., Lilly, Merck, Novo Nordisk, Sanofi-Aventis US LLC, and Takeda; has acted as a speaker for AstraZeneca, Novo Nordisk, and Takeda; and as a consultant for AstraZeneca, Boehringer Ingelheim, Eisai, Inc., GlaxoSmithKline, Janssen Scientific Affairs LLC, Ligand Pharmaceuticals Inc., Lilly, Merck, Novo Nordisk, Pfizer, and Takeda. All payments are made directly to his employer (AdventHealth). H.V.B.K.S., H.B.-T. and E.S. are full-time employees of Novo Nordisk. H.V.B.K.S. and H.B.-T. also hold stocks in Novo Nordisk. B.Z. has received consulting fees from Merck, Novo Nordisk, Sanofi-Aventis, Eli Lilly, AstraZeneca, Janssen, and Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

J.B.B., M.A.N., N.R.P. and B.Z. were members of the LEADER trial steering committee and contributed significantly to the design and conduct of the study and acquisition of clinical data. C.J.T., S.J., S.C.B., J.R.P. and R.E.P. were trial investigators, members of the LEADER global expert panel, and contributed to conduct of the study and acquisition of clinical data. H.V.B.K.S. performed the statistical analyses. All authors reviewed and interpreted the data, and were involved in drafting and critically revising the manuscript. All authors approved the final version of the manuscript and take full responsibility for the content.

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REFERENCES

1. Davies MJ, D'Alessio DA, Fradkin J, et al; Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2018;41:2669-2701.
2. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014;384:2228-2234.
3. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care*. 2017;40:614-624.
4. Ahmann A, Rodbard HW, Rosenstock J, et al; on behalf of the NN2211-3917 Study Group. Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2015;17:1056-1064.
5. Mathieu C, Rodbard HW, Cariou B, et al; on behalf of the BEGIN: VICTOZA ADD-ON (NN1250-3948) study group. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes Metab*. 2014;16:636-644.
6. Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin; DUAL VII randomized clinical trial. *Diabetes Care*. 2018;41:1009-1016.
7. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322.
8. Marso SP, Poulter NR, Nissen SE, et al. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. *Am Heart J*. 2013;166:823-830.
9. American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association workgroup on Hypoglycemia. *Diabetes Care*. 2005;28:1245-1249.
10. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ*. 1999;319:1492-1495.
11. Rosenstock J, Rodbard HW, Bain SC. et al; Liraglutide-Detemir Study Group. One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA1c target. *J Diabetes Complications*. 2013;27:492-500.
12. Seino Y, Kaneko S, Fukuda S, et al. Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: a 36-week, randomized, double-blind, parallel-group trial. *J Diabetes Investig*. 2016;7:565-573.
13. Brown-Frandsen K, Emerson SS, McGuire DK, et al. Lower rates of cardiovascular events and mortality associated with liraglutide use in patients treated with basal insulin: a DEVOTE subanalysis (DEVOTE 10). *Diabetes Obes Metab*. 2019;21:1437-1444.
14. de Wit HM, Vervoort GM, Jansen HJ, de Galan BE, Tack CJ. Durable efficacy of liraglutide in patients with type 2 diabetes and

pronounced insulin-associated weight gain: 52-week results from the effect of Liraglutide on insulin-associated wEight GAiN in patients with type 2 diabetes' (ELEGANT) randomized controlled trial. *J Intern Med*. 2016;279:283-292.
15. de Wit HM, Vervoort GM, Jansen HJ, de Grauw WJ, de Galan BE, Tack CJ. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: a 26 week, randomised clinical trial (ELEGANT). *Diabetologia*. 2014;57:1812-1819.
16. 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.
17. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559.

SUPPORTING INFORMATION

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

How to cite this article: Tack CJ, Jacob S, Desouza C, et al. Long-term efficacy and safety of combined insulin and glucagon-like peptide-1 therapy: Evidence from the LEADER trial. *Diabetes Obes Metab*. 2019;1–9. https://doi.org/10.1111/dom.13826