Title: Effect of liraglutide on occurrence of total (first and recurrent) major cardiovascular events in the LEADER cardiovascular outcomes trial

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Key points

Question: Is the beneficial effect of liraglutide on the risk of first major adverse cardiovascular events (MACE) maintained when subsequent events are also included?

Findings: In LEADER, a total of 1605 MACE occurred, comprised of 1302 first and 303 recurrent events. Liraglutide was associated with a 16% relative risk reduction for total MACE versus placebo.

Meaning: Considering the overall burden of cardiovascular events, these data reaffirm the efficacy of liraglutide in patients with type 2 diabetes and at high cardiovascular risk.

Structured abstract

Importance: Following non-fatal cardiovascular events, recurrent events are highly likely. Most cardiovascular outcomes trials analyze first events only, but extending analyses to first and recurrent (total) events can provide clinically meaningful information.

Objective: To investigate our hypothesis, formulated after data collection for the LEADER trial, that liraglutide would reduce both first and recurrent major adverse cardiovascular events (MACE) compared with placebo in patients with type 2 diabetes at high cardiovascular risk.

Design: The LEADER trial was a randomized, double-blind, placebo-controlled cardiovascular outcomes trial; this *post hoc* analysis used expanded Cox regression models.

Setting: LEADER was a global, multi-center trial.

Participants: LEADER included patients with type 2 diabetes and with established or high risk for cardiovascular disease.

Interventions: Patients received liraglutide (up to 1.8 mg/day) or placebo (randomization ratio 1:1), both with standard care, for 3.5–5 years.

Main outcomes and measures: Assessed outcomes were MACE (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke), expanded MACE (primary MACE plus coronary revascularization

and hospitalization for heart failure or unstable angina pectoris [UAP]), and the individual endpoints.

Results: The 9340 LEADER participants experienced 1605 total MACE (1302 first and 303 recurrent events, median follow-up = 3.8 years). Patients who experienced any MACE tended to be older and have diabetes for longer than patients without MACE. In the liraglutide group, fewer first and recurrent MACE (608/4668 and 127/4668 events/patients, respectively) versus placebo (694/4672 and 176/4672 events/patients) occurred. Liraglutide, therefore, was associated with a 16% relative risk reduction for total MACE versus placebo (hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.76–0.93) and a 13% reduction for total expanded MACE versus placebo (HR 0.87, 95% CI 0.81–0.93). When individual endpoints were considered (with the exception of UAP), liraglutide was associated with lower risk versus placebo.

Conclusion and relevance: Taken together, these data extend the primary analysis and show that liraglutide reduces recurrent events versus placebo in patients with type 2 diabetes at high cardiovascular risk. This analysis strengthens the absolute benefit of liraglutide with respect to the overall burden of cardiovascular events in this high-risk patient population.

Trial registration: ClinicalTrials.gov number NCT01179048

Introduction

Several recent cardiovascular outcomes trials (CVOTs) with antihyperglycemic therapies demonstrate significant cardiovascular (CV) benefits for patients with type 2 diabetes at high CV risk, including: EMPA-REG,[1] LEADER,[2-4] SUSTAIN 6,[5] CANVAS,[6] and HARMONY Outcomes.[7]

LEADER was a randomized, double-blind, placebo-controlled CVOT of liraglutide (maximum 1.8 mg/day) versus placebo, both added to standard care for 3.5–5 years in patients with type 2 diabetes and high risk for CV disease.[2] The primary analysis demonstrated superiority of liraglutide over placebo for major adverse CV events (MACE) – a composite endpoint of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.78–0.97; p=0.01 for superiority).[2]

The majority of CVOTs on diabetes have used time to first MACE as the primary endpoint.[1,2,5,6] However, following an initial non-fatal event, there is a high likelihood of a recurrent CV event.[8] A total events analysis, capturing both first and recurrent events, can provide important information that may help to guide clinical decision-making from the perspectives of both patient risk and economics.

In this novel, multiple Cox-regression model analysis from the LEADER trial, we sought to evaluate the efficacy of the glucagon-like peptide-1 (GLP-1) analog liraglutide on total (i.e. first and recurrent) occurrences of

any MACE, as well as on expanded MACE (included coronary revascularization and hospitalization for heart failure or unstable angina pectoris [UAP], in addition to primary MACE).

Methods

We hypothesized that liraglutide would reduce total (both first and recurrent) MACE, when compared with placebo. In this *post hoc* analysis we used expanded Cox regression models (described below) to estimate the effect of liraglutide on risk of total MACE, total expanded MACE (MACE endpoints, coronary revascularization, or hospitalization for heart failure or UAP), and the individual CV endpoints in the LEADER trial. The full LEADER methodology (including its ethical approval and written informed consent details) has been reported previously.[2,9] Events were adjudicated by an external events adjudication committee (EAC), who determined if multiple events within one patient constituted separate events or were all related to the same event.[2,9]

Andersen-Gill proportional intensity (AG) model for recurrent events

The AG model originates from the well-known Cox regression model (proportional hazard model) and assumes that the baseline intensity is the same across time, independent of the number of events.[10,11] Hence, there is no inherited assumption in the model that an event will decrease or increase the likelihood of the next event. EAC-adjudicated separate events within patients are assumed to be independent of each other,

which is considered to be a strong assumption. In the AG model, it is suggested to incorporate usually time-dependent variables that could mitigate the assumption of independence; for example, this could be the number of previous events (or functions thereof) for each patient at the time of a recurrent event.[10,11] We used two AG models. The unadjusted AG model included randomized treatment only, whereas the adjusted AG model included previous events as a time-dependent continuous variable and randomized treatment as a fixed factor. Furthermore, in both AG models, we used the robust (sandwich) estimator of the variance with patient as the cluster to account for dependence between events within patients.[12]

Prentice-Williams-Peterson (PWP) survival model for recurrent events

The PWP model is different from the AG model as the baseline intensity is allowed to vary depending on the number of events, as the model is stratified on this group.[10,11] Hence, the baseline hazard is allowed to be different within the number of events. All patients are at risk for a first event, but a patient could only be at risk for a recurrent event after the first event has occurred. The PWP model can incorporate both common and event-specific effects for each covariate; therefore, unlike the AG model, the effect of covariates may vary from event to event in the PWP model, i.e. the effect of randomized treatment can differ according to event order.[10,11] We used the PWP-total-time model for results pertaining to the PWP model with treatment as a fixed factor. The PWP-total-time

model used the same data structure as the AG model, but with a supplementary stratum variable defined by the number of events within each patient.

Other than the adjustments detailed above, no other adjustments were made for baseline characteristics in these analyses.

Mean cumulative function (MCF) and number needed to treat (NNT)

The MCF was estimated using the Nelson–Aalen non-parametric method. The NNT for event prevention was based on the difference between the MCF for each treatment arm at 3 years.[13] A sensitivity analysis was performed to account for non-CV death as competing risk, which was estimated with the mean cumulative function, as per previously published methods.[14,15]

Results

Baseline characteristics and distribution of MACE, expanded MACE and individual CV endpoints

A total of 1605 MACE occurred during LEADER, of which 1302 were first events and 303 were recurrent events (**Figure 1**). Patients who experienced any MACE tended to be older, with a longer duration of diabetes, higher hemoglobin A_{1C} levels and more frequent prior MI and/or heart failure at baseline than those who did not experience MACE (**Table 1**). As expected, history of prior MI at baseline was more common in

171 those who experienced recurrent MACE, compared with the 'no MACE' and
172 'single MACE' groups (**Table 1**). There was a median follow-up time of 3.8
173 years,[2] allowing robust analyses of data at 3 years.

174 There were 135 fewer total MACE with liraglutide than placebo (**Figure**
175 **1a**). This translated to an NNT of 43 patients to prevent one such event
176 at 3 years (**Figure 2**) and an NNT of 37 patients when accounting for
177 non-CV death as competing risk. The mean cumulative functions taking
178 into account non-CV death tended to be slightly lower for both treatment
179 groups, but slightly more marked for the liraglutide group (**Figure 2**).
180 Recurrent MACE occurred in 97 patients (2.1%) on liraglutide and in 126
181 (2.7%) on placebo, seemingly driven by reductions in the proportions of
182 patients experiencing recurrent non-fatal MI and stroke. Likewise, fewer
183 patients experienced recurrent expanded MACE with liraglutide (n=416,
184 8.9%) versus placebo (n=471, 10.1%), with correspondingly fewer total
185 events (**Figure 1b**). For expanded MACE, the NNT was estimated to be
186 23 patients at 3 years (**Figure 2**), and 21 patients, when non-CV death
187 was included as a competing risk. Overall, few patients experienced
188 recurrent events of individual CV endpoints, and (with the exception of
189 UAP) consistently lower numbers of recurrent events occurred with
190 liraglutide than placebo (**Figure 1c**).

191

Risk of total MACE, total expanded MACE and individual CV endpoints

The unadjusted AG model with a robust variance estimation showed that liraglutide was associated with a 16% relative risk reduction for total MACE versus placebo: HR 0.84 (95% CI 0.76–0.93). For the adjusted AG (HR 0.86 [95% CI 0.78–0.95]) and PWP model (HR 0.87 [95% CI 0.78–0.95]), risk estimates were slightly higher. In addition, liraglutide was associated with a 13% relative risk reduction for total expanded MACE versus placebo (unadjusted AG model: HR 0.87 [95% CI 0.81–0.93]), and when all individual CV endpoints were considered (with the exception of UAP), liraglutide was associated with lower risk versus placebo (eTable 1).

The *post hoc* inclusion of recurrent events increased the power for showing superiority for time to EAC-confirmed MACE from 72% (primary endpoint of first MACE, Cox regression]) to 82% (post hoc endpoint of recurrent MACE, PWP model using log-HR with corresponding standard errors).

Discussion

We hypothesized that liraglutide, in addition to reducing first MACE in patients with type 2 diabetes at high CV risk, would also reduce recurrent CV events, and therefore total events, when compared with placebo. As we have shown previously, liraglutide reduced the relative risk of first MACE by 13% versus placebo.[2] In this *post hoc* analysis, we show that

the relative risk reduction for total MACE was 16%. For total MACE, this translated into 43 patients needing treatment with liraglutide to prevent one event over 3 years, which is considerably lower than the NNT of 66 calculated based on first MACE alone.[2] Similarly, for expanded total MACE the NNT was 23 versus 49 for expanded first MACE. These are the first such data relating to liraglutide and should help to guide clinical decisions, as the use of liraglutide reduces both first and recurrent MACE in patients at risk of CV disease.

Although it is commonplace in CVOTs to censor primary outcome data after the first event has occurred,[1,2,5-7] many individuals have additional CV events, which are captured and adjudicated, but not used in primary statistical efficacy analyses. The clinical and scientific utility of capturing the total events may increase the power of the study, assuming efficacy is maintained against recurrent events and patients adhere to treatment. It may also allow for a more meaningful assessment of absolute risk reduction/NNT with the pharmacotherapy. Indeed, this concept is gaining support in other CV risk-reduction trials, including those of lipid-lowering[16] and antiplatelet therapy,[17] as well as cost-effectiveness assessments.[18,19]

As with the majority of clinical trials, study treatment (liraglutide or placebo) began at the start of LEADER. However, with the cardioprotective benefit of liraglutide evident in first MACE and total MACE, the question arises as to how the timing and duration of liraglutide treatment before and after a CV event impacts future CV events. This is a

question of clinical importance that has yet to be tested in a randomized clinical trial setting.

Recurrent event analyses have been conducted for different treatments and diseases, and the proportion of recurrent events reported here was within the range of those reported in other trials (18–37%).[16,17,20] In an analysis of ischemic events (CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) in patients with established CV disease or type 1 or 2 diabetes and treated with statins, icosapent ethyl (an anti-lipid therapy) reduced the relative risk of total events by 30% versus placebo over 4.9 years.[20] These previously published data show that recurrent events occur in a substantial proportion of patients and need to be considered when making clinical decisions.

This analysis has limitations. Analyses of recurrent events may overestimate the contribution of patients experiencing MACE early in a trial,[8] cannot differentiate between cardioprotective mechanisms of a drug that may differ between first and subsequent events,[16] and do not account for the decreasing compliance, which is nominally reported as CVOTs progress.[16] While the mean percentage of time on treatment for patients in the liraglutide group was 84% and in the placebo group was 83%,[2] it was uncertain as to the adherence to study drug in the period between first and recurrent MACE. This lack of data is a potential limitation; however, it should be balanced with 96.8% of patients

completing a final study visit, who died or had a primary outcome,[2] demonstrating the overall robustness of the data. There was also a lack of data about CV medication use between first and recurrent MACE, which potentially biased the results. Also, although inclusion of recurrent events increased the *post hoc* power, LEADER was not designed to test for treatment differences in recurrent events. Although such analyses of recurrent events may amplify any positive result for primary events (as counting each recurrent event individually may augment the effect size), in CVOTs this has to be considered in parallel with any differences in CV versus non-CV death. In the analyses of recurrent events for the composite endpoint MACE and expanded MACE, non-CV death was a competing event. As only a marginal non-significant treatment difference was observed for non-CV death in LEADER (HR 0.95, 95% CI 0.76–1.18),[2] it was likely that this competing risk would only have a marginal impact on the results. This was supported by the sensitivity analyses of the mean cumulative function for both endpoints. For the analyses of the individual components, CV death and non-CV death were competing events. A treatment effect in favor of liraglutide was observed for all-cause death in LEADER with a HR of 0.85 (95% CI 0.74–0.92).[2] Hence, the results for the recurrent models applied for the individual components in (expanded) MACE could potentially be biased towards neutrality of the treatment effects.

A final potential limitation was related to the statistical approaches used. In a randomized clinical trial setting, the PWP model has been criticized as

its use of the event history may reduce the estimated treatment effect[10] and, furthermore, there could be a selection bias as randomization is not preserved after the first event. However, in a recent paper by Ozga and colleagues,[11] the PWP model seemed to be advantageous (followed by the AG model) in estimating treatment effects. It met most data scenarios for clinical trials with composite endpoints including fatal events, as compared with marginal recurrent models such as the Wei-Lin-Weissfeld model.[11]

Altogether, these data extend the primary analysis, and reaffirm the efficacy of liraglutide in reducing recurrent MACE in patients with type 2 diabetes at high CV risk. This strengthens the absolute benefit of liraglutide with respect to the overall burden of CV events in this high-risk patient population.

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Prior presentation of these data

Parts of this analysis were presented at the European Association for the Study of Diabetes 2018 congress (Berlin, October 1–5). Data supporting this *post hoc* analysis are available from the corresponding author on reasonable request.

Author contributions

SV had full access to all the data in the post hoc analysis reported in this manuscript and takes responsibility for the integrity of the data and accuracy of the data analysis.

Analysis concept and design: SV, DDØ and SR.

Acquisition, analysis, or interpretation of data: all authors.

Drafting of the manuscript: SV and SR.

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Statistical analysis: SR.

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Figure legends

Figure 1. Number of total (first and recurrent) CV events during the LEADER trial

A) Number of MACE, B) Number of expanded MACE and C) Number of individual CV endpoints.

Total number of patients in the liraglutide group = 4668. Total number of patients in the placebo group = 4672. [a]3-point composite endpoint: time to CV death, non-fatal MI, or non-fatal stroke. [b]6-point composite endpoint: included MACE endpoints, plus coronary revascularization and hospitalization for heart failure or UAP. HRs (95% CI) for recurrent events were calculated using the pooled treatment effects across event numbers ≥2 from the PWP model.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; n, total number of events; PWP, Prentice–Williams–Peterson; UAP, unstable angina pectoris.

Figure 2. Mean total MACE per patient over the trial period

[a]3-point composite endpoint: time to CV death, non-fatal MI, or non-fatal stroke.
[b]6-point composite endpoint: included MACE endpoints, plus coronary revascularization and hospitalization for heart failure or unstable angina pectoris.

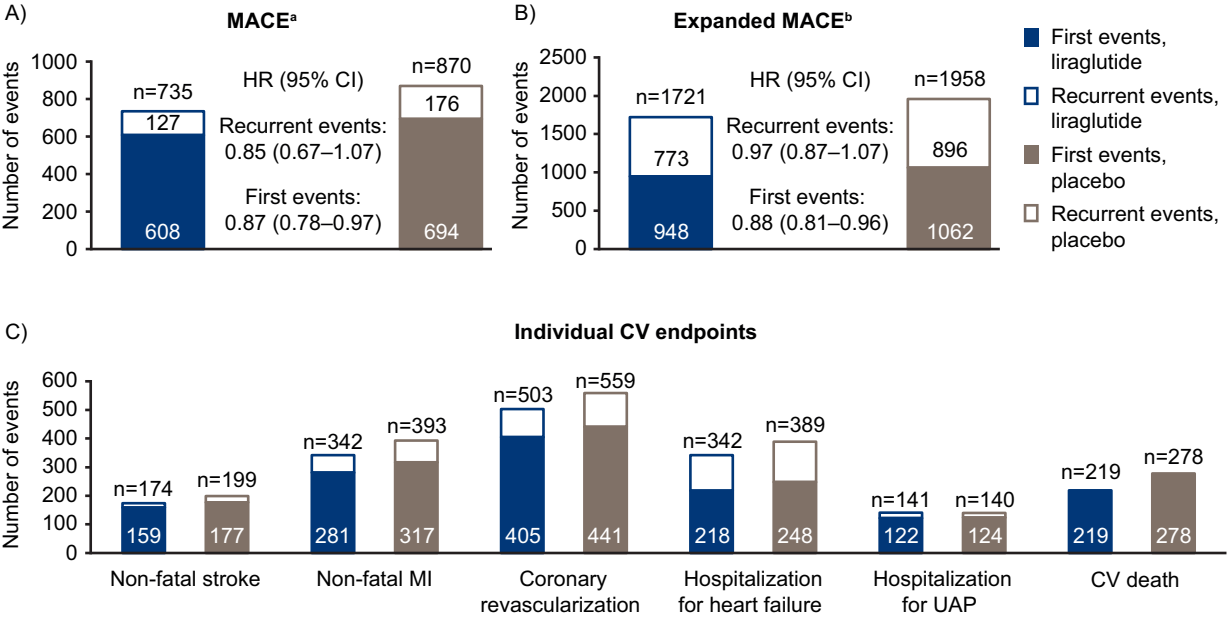
449 MCF estimated using the Nelson-Aalen non-parametric method; NNT based on
450 the MCF at 3 years without taking into account competing risk.

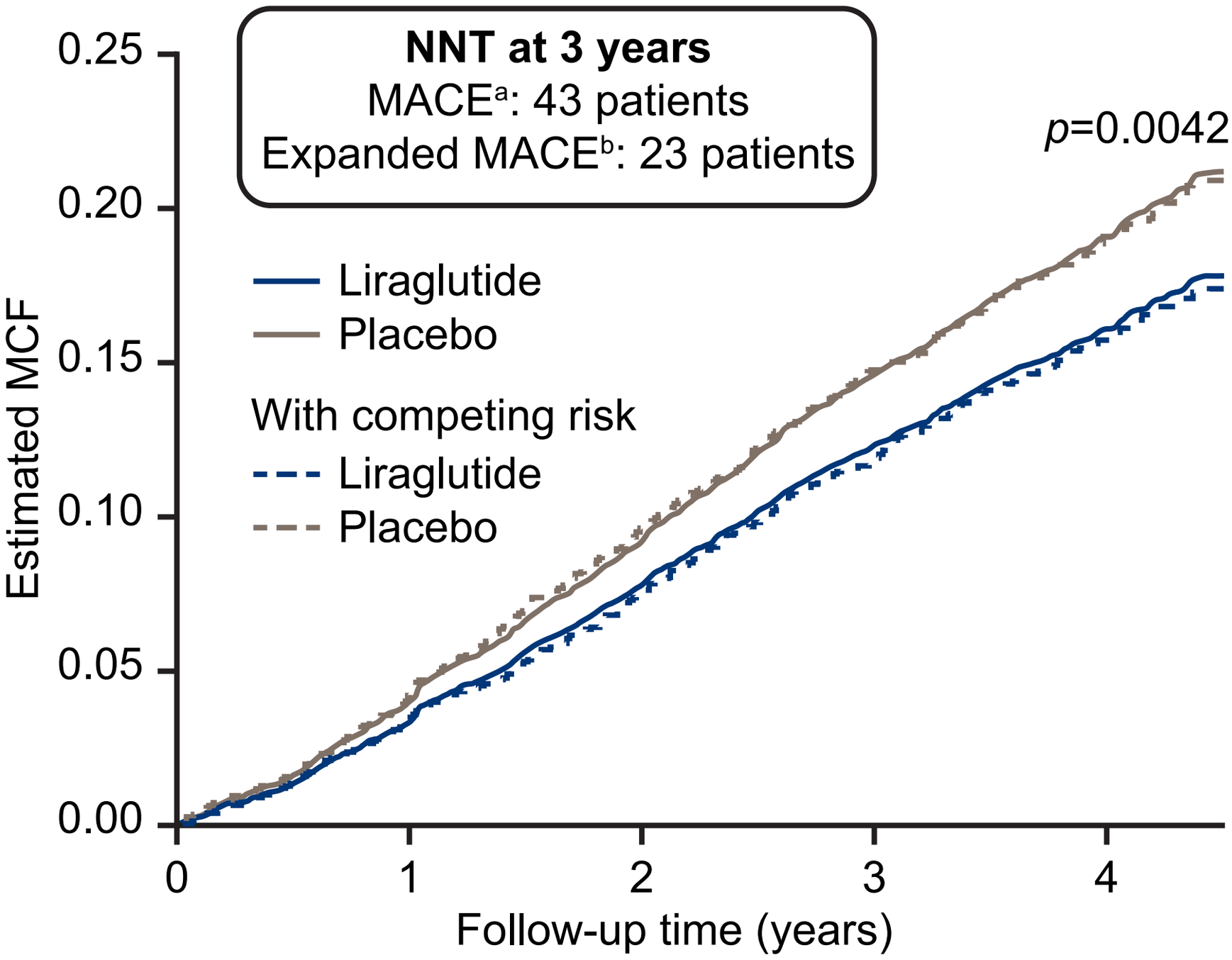
451 CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial
452 infarction; MCF, mean cumulative function; NNT, number needed to treat to
453 avoid one event.

Table 1. Baseline characteristics of patients in LEADER by number of MACE experienced

Number of MACE experienced	No MACE		A single MACE		>1 MACE	
Treatment group	Liraglutide (n=4060)	Placebo (n=3978)	Liraglutide (n=511)	Placebo (n=568)	Liraglutide (n=97)	Placebo (n=126)
Age, years	64.0 (7.2)	64.1 (7.0)	65.5 (7.7)	65.8 (8.2)	65.0 (7.4)	66.2 (8.3)
Male, n (%)	2586 (63.7)	2507 (63.0)	361 (70.6)	402 (70.8)	64 (66.0)	83 (65.9)
Diabetes duration, years	12.7 (7.9)	12.7 (8.0)	13.3 (8.1)	13.4 (8.5)	15.1 (8.7)	13.8 (8.7)
Hemoglobin A_{1C}, %	8.7 (1.5)	8.6 (1.5)	8.9 (1.7)	8.8 (1.6)	9.0 (1.7)	9.0 (1.7)
Prior MI, n (%)	1182 (29.1)	1077 (27.1)	202 (39.5)	245 (43.1)	50 (51.5)	51 (40.5)
Prior HF[a], n (%)	541 (13.3)	533 (13.4)	94 (18.4)	99 (17.4)	18 (18.6)	20 (15.9)
Body weight, kg	91.7 (21.1)	91.4 (20.7)	93.1 (22.0)	92.6 (21.5)	93.0 (20.1)	92.2 (20.6)
BMI, kg/m^2	32.6 (6.3)	32.5 (6.3)	32.3 (6.4)	32.4 (6.4)	32.9 (6.5)	32.8 (6.2)

Data are mean (SD) unless otherwise stated. MACE: 3-point composite endpoint of time to CV death, non-fatal MI, or non-fatal stroke. [a]Prior chronic HF (New York Heart Association class II or III). BMI, body mass index; CV, cardiovascular; hemoglobin A_{1C}, glycated hemoglobin; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; n, number of patients; SD, standard deviation.


A)
MACE[a]
Number of events
1000
800
600
400
200
0
n=735
127
608
HR (95% CI)
Recurrent events:
0.85 (0.67–1.07)
First events:
0.87 (0.78–0.97)
n=870
176
694
B)
Expanded MACE[b]
Number of events
2500
2000
1500
1000
500
0
n=1721
773
948
HR (95% CI)
Recurrent events:
0.97 (0.87–1.07)
First events:
0.88 (0.81–0.96)
n=1958
896
1062
First events, liraglutide
Recurrent events, liraglutide
First events, placebo
Recurrent events, placebo
C)
Individual CV endpoints
Number of events
600
500
400
300
200
100
0
n=174
159
n=199
177
n=342
281
n=393
317
n=503
405
n=559
441
n=342
218
n=389
248
n=141
122
n=140
124
n=219
219
n=278
278
Non-fatal stroke
Non-fatal MI
Coronary revascularization
Hospitalization for heart failure
Hospitalization for UAP
CV death


NNT at 3 years
MACE[a]: 43 patients
Expanded MACE[b]: 23 patients
p=0.0042
Liraglutide
Placebo
With competing risk
Liraglutide
Placebo
Estimated MCF
0.25
0.20
0.15
0.10
0.05
0.00
0
1
2
3
4
Follow-up time (years)