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# Occurrence of First and Recurrent Major Adverse Cardiovascular Events With Liraglutide Treatment Among Patients With Type 2 Diabetes and High Risk of Cardiovascular Events

## A Post Hoc Analysis of a Randomized Clinical Trial

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**IMPORTANCE** After the occurrence of nonfatal cardiovascular events, recurrent events are highly likely. Most cardiovascular outcomes trials analyze first events only; extending analyses to first and recurrent (total) events can provide clinically meaningful information.

**OBJECTIVE** To investigate whether liraglutide is associated with reduced first and recurrent total major adverse cardiovascular events (MACE) compared with placebo among patients with type 2 diabetes and high risk of cardiovascular events.

**DESIGN, SETTING, AND PARTICIPANTS** This post hoc analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) randomized, double-blind, clinical trial included data from patients with type 2 diabetes who had established or were at high risk for cardiovascular disease at 410 sites in 32 countries from August 2010, to December 2015. Data analysis was performed from August 15, 2016, to July 5, 2019.

**INTERVENTIONS** Patients were randomized 1:1 to receive liraglutide (up to 1.8 mg per day) or placebo, both with standard care, for 3.5 to 5.0 years.

**MAIN OUTCOMES AND MEASURES** Assessed outcomes were MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), expanded MACE (primary MACE plus coronary revascularization and hospitalization for heart failure or unstable angina pectoris), and the individual end points.

**RESULTS** The 9340 LEADER trial participants (6003 [64.3%] male; mean [SD] age, 64.3 [7.2] years) experienced 1605 total MACE (1302 first and 303 recurrent events; median follow-up, 3.8 years [range, 0-5.2 years]). Patients who experienced any MACE were older (1 MACE: mean [SD] age, 65.6 [8.0] years; >1 MACE: 65.7 [7.9] years) and had diabetes for longer duration (1 MACE: mean [SD] duration, 13.4 [8.3] years; >1 MACE: 14.4 [8.7] years) compared with patients without MACE (mean [SD] age, 64.1 [7.1] years; mean [SD] duration, 12.7 [7.9] years). Fewer first and recurrent MACE occurred in the liraglutide group ( $n = 4668$ ; 608 first and 127 recurrent events) than in the placebo group ( $n = 4672$ ; 694 first and 176 recurrent events). Liraglutide was associated with a 15.7% relative risk reduction in total MACE (hazard ratio [HR], 0.84; 95% CI, 0.76-0.93) and a 13.4% reduction in total expanded MACE (HR, 0.87; 95% CI, 0.81-0.93) compared with placebo. For most individual cardiovascular end points, liraglutide was associated with lower risk vs placebo.

**CONCLUSIONS AND RELEVANCE** These results suggest that liraglutide treatment is associated with reduced total MACE compared with placebo among patients with type 2 diabetes and high risk of cardiovascular events. This analysis supports the findings of an absolute benefit of liraglutide treatment with respect to the overall burden of cardiovascular events in this high-risk patient population.

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Several cardiovascular (CV) outcomes trials with antihyperglycemic therapies have shown significant CV benefits for patients with type 2 diabetes at high risk of CV events, including Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME),<sup>1</sup> Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER),<sup>2-4</sup> Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN 6),<sup>5</sup> Canagliflozin Cardiovascular Assessment Study (CANVAS),<sup>6</sup> and Harmony Outcomes.<sup>7</sup>

The LEADER trial was a randomized, double-blind, placebo-controlled CV outcomes trial of the glucagon-like peptide 1 (GLP-1) analog liraglutide (maximum 1.8 mg per day) vs placebo, both added to standard care, for 3.5 to 5.0 years among patients with type 2 diabetes and high risk for CV disease that was conducted at 410 sites in 32 countries from August 2010 to December 2015.<sup>2</sup> The primary analysis showed superiority of liraglutide compared with placebo for major adverse CV events (MACE)—a composite end point of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke (hazard ratio [HR], 0.87; 95% CI, 0.78-0.97;  $P = .01$  for superiority).<sup>2</sup>

Most CV outcomes trials evaluating diabetes therapies used time to first MACE as the primary end point.<sup>1,2,5,6</sup> However, after an initial nonfatal event, there is a high likelihood of a recurrent CV event.<sup>8</sup> A total events analysis capturing both first and recurrent events may provide important information to help guide clinical decision-making from the perspectives of both patient risk and economics.

We evaluated the association between the liraglutide and total (ie, first and recurrent) occurrences of any MACE and expanded MACE (primary MACE plus coronary revascularization and hospitalization for heart failure or unstable angina pectoris). We hypothesized that liraglutide would be associated with reduced total MACE compared with placebo.

## Methods

In this novel, post hoc analysis of the LEADER randomized clinical trial, we used models generalized from Cox proportional hazards regression models to estimate the association of liraglutide with the risk of total MACE, total expanded MACE, and the individual CV end points in the LEADER trial. The LEADER methods have been reported previously.<sup>2,9</sup> The trial included patients at least 50 years old with type 2 diabetes and either established CV disease or chronic kidney disease, or at least 60 years old with 1 or more CV risk factors. Among the exclusion criteria were type 1 diabetes; the use of GLP-1-receptor agonists, dipeptidyl peptidase-4 inhibitors, pramlintide, or rapid-acting insulin; a familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer; and the occurrence of an acute coronary or cerebrovascular event within 14 days before screening and randomization. The trial was conducted at 410 sites across 32 countries between August 2010, and December 2015. The protocol was approved by the relevant institutional review board or ethics

## Key Points

**Question** Does the association of liraglutide with a lower risk of major adverse cardiovascular events remain when first and subsequent events are included?

**Findings** In this post hoc analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) randomized clinical trial, among 9340 participants with type 2 diabetes and high risk of cardiovascular events, a total of 1605 major adverse cardiovascular events occurred, comprising 1302 first and 303 recurrent events. Liraglutide was associated with a 15.7% relative risk reduction for total major adverse cardiovascular events vs placebo.

**Meaning** These data support the efficacy of liraglutide among patients with type 2 diabetes and high risk of cardiovascular events.

committee at each participating center. Each patient provided written informed consent before participating. Events were adjudicated by an external events adjudication committee, who determined whether multiple events for 1 patient constituted separate events or were all related to the same event.<sup>2,9</sup>

## Statistical Analysis

Post hoc data analysis was performed from August 15, 2016, to July 5, 2019. Baseline characteristics are presented as mean values and SDs for continuous variables, and the number of patients and proportion (%) for categorical variables. Relative risks of CV events in the liraglutide compared with placebo group are presented as HRs and 95% CIs. To analyze data, SAS, version 9.4 Proc Phreg (SAS Institute Inc) was used, applying Andersen-Gill (AG) Proportional Intensity and Prentice-Williams-Petersen (PWP) models.

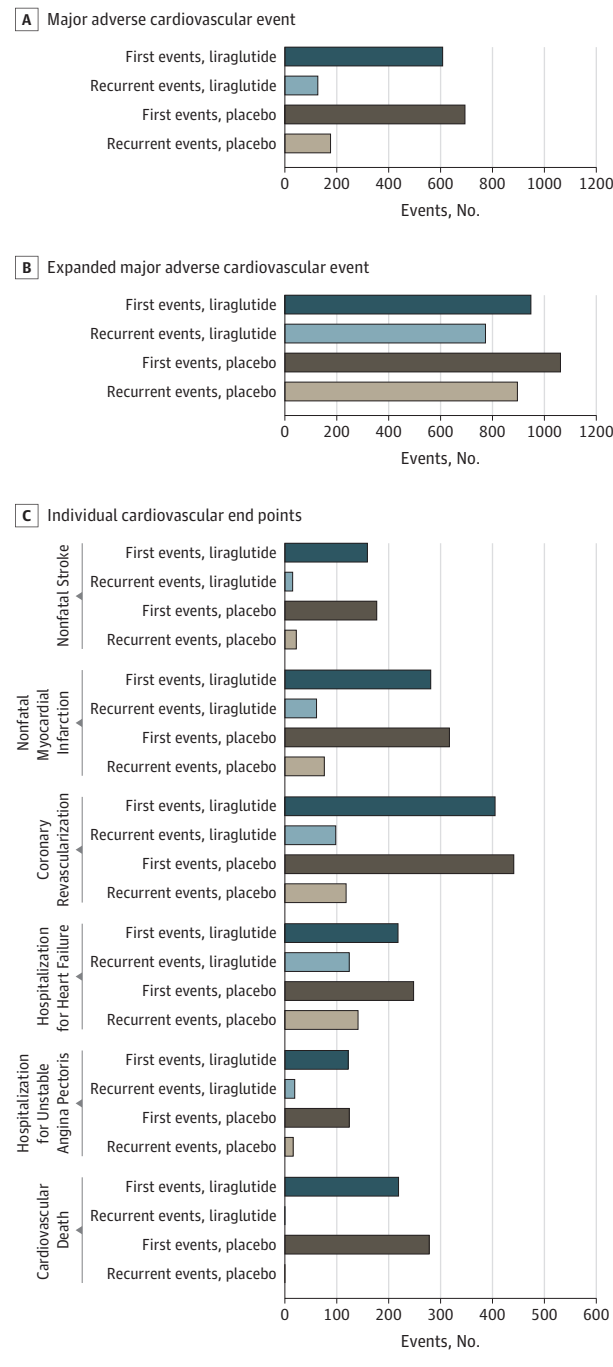
### AG Proportional Intensity Model for Recurrent Events

The AG model originates from the Cox proportional hazards regression model and assumes that the baseline intensity is the same across time independent of the number of events.<sup>10,11</sup> Thus, there is no inherited assumption in the model that an event will decrease or increase the likelihood of the next event. Adjudicated separate events within patients were assumed to be independent of each other, which is considered to be a strong assumption. For the AG model, time-dependent variables could be incorporated to 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.<sup>10,11</sup> We used 2 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. 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.<sup>12</sup>

### PWP Survival Model for Recurrent Events

The PWP model is different from the AG model because the baseline intensity is allowed to vary depending on the number of events, as the model is stratified on this group.<sup>10,11</sup> Thus,

**Figure 1. Total First and Recurrent Cardiovascular Events During the LEADER Trial**



Analysis included the total number of randomized patients in the liraglutide group (n = 4668) and in the placebo group (n = 4672). Hazard ratios (HRs) (95% CIs) for recurrent events were calculated using the pooled treatment effects across event numbers of 2 or more from the Prentice-Williams-Peterson model. A, The 3-point composite end point included time to cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. First events: HR, 0.87 (95% CI, 0.78-0.97); recurrent events: HR, 0.85 (95% CI, 0.67-1.07). B, The 6-point composite end point included the 3-point major adverse cardiovascular event end points plus coronary revascularization and hospitalization for heart failure or unstable angina pectoris. First events: HR, 0.88 (95% CI, 0.81-0.96); recurrent events: HR, 0.97 (95% CI, 0.87-1.07).

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 (ie, the effect of randomized treatment can differ according to event order).<sup>10,11</sup> 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 and Number Needed to Treat**

The mean cumulative function was estimated using the Nelson-Aalen nonparametric method. The number needed to treat (NNT) for event prevention was based on the difference between the mean cumulative function for each treatment arm at 3 years.<sup>13</sup> 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.<sup>14,15</sup>

**Results**

**Baseline Characteristics and Distribution of MACE, Expanded MACE, and Individual CV End Points**

A total of 1605 MACE occurred among 9340 LEADER trial participants (6003 [64.3%] male; mean [SD] age, 64.3 [7.2] years); 1302 were first events, and 303 were recurrent events (Figure 1). On average, patients who experienced any MACE were older (1 MACE: mean [SD] age, 65.6 [8.0] years; >1 MACE: 65.7 [7.9] years) and had a longer duration of diabetes (1 MACE: mean [SD] duration, 13.4 [8.3] years; >1 MACE: 14.4 [8.7] years) compared with patients without MACE (mean [SD] age, 64.1 [7.1] years; mean [SD] diabetes duration, 12.7 [7.9] years). Patients who experienced any MACE had higher hemoglobin A<sub>1c</sub> levels, and more frequent prior MI and/or heart failure at baseline compared with those who did not experience a MACE (Table). A history of MI at baseline was more common among those who experienced recurrent MACE compared with the none and single groups (Table). There was a median (range) follow-up of 3.8 (0-5.2) years,<sup>2</sup> allowing robust analyses of data at 3 years.

Fewer first and recurrent MACE occurred in the liraglutide group (n = 4668 randomized participants; 608 first events and 127 recurrent events) compared with the placebo group (n = 4672 randomized participants; 694 first events and 176 recurrent events) (Figure 1A). Overall, there were 135 fewer total MACE with liraglutide compared with placebo (735 vs 870 events) (Figure 1A). This translated to an NNT of 43 patients to prevent 1 event at 3 years (Figure 2) and an NNT of 37 patients when accounting for non-CV death as competing risk. The mean cumulative functions taking into account non-CV

**Table. Baseline Patient Characteristics in the LEADER Trial by Number of MACE**

Characteristic	MACE, No.								
	None			Single			>1		
	Liraglutide (n = 4060)	Placebo (n = 3978)	Total (n = 8038)	Liraglutide (n = 511)	Placebo (n = 568)	Total (n = 1079)	Liraglutide (n = 97)	Placebo (n = 126)	Total (n = 223)
Age, mean (SD), y	64.0 (7.2)	64.1 (7.0)	64.1 (7.1)	65.5 (7.7)	65.8 (8.2)	65.6 (8.0)	65.0 (7.4)	66.2 (8.3)	65.7 (7.9)
Male, No. (%)	2586 (63.7)	2507 (63.0)	5093 (63.4)	361 (70.6)	402 (70.8)	763 (70.7)	64 (66.0)	83 (65.9)	147 (65.9)
Diabetes duration, mean (SD), y	12.7 (7.9)	12.7 (8.0)	12.7 (7.9)	13.3 (8.1)	13.4 (8.5)	13.4 (8.3)	15.1 (8.7)	13.8 (8.7)	14.4 (8.7)
Hemoglobin A <sub>1c</sub> , mean (SD), %	8.7 (1.5)	8.6 (1.5)	8.7 (1.5)	8.9 (1.7)	8.8 (1.6)	8.9 (1.6)	9.0 (1.7)	9.0 (1.7)	9.0 (1.7)
Previous myocardial infarction, No. (%)	1182 (29.1)	1077 (27.1)	2259 (28.1)	202 (39.5)	245 (43.1)	447 (41.4)	50 (51.5)	51 (40.5)	101 (45.3)
Previous chronic heart failure, No. (%) <sup>a</sup>	541 (13.3)	533 (13.4)	1074 (13.4)	94 (18.4)	99 (17.4)	193 (17.9)	18 (18.6)	20 (15.9)	38 (17.0)
Body weight, mean (SD), kg	91.7 (21.1)	91.4 (20.7)	91.6 (20.9)	93.1 (22.0)	92.6 (21.5)	92.8 (21.7)	93.0 (20.1)	92.2 (20.6)	92.6 (20.3)
Body mass index, mean (SD) <sup>b</sup>	32.6 (6.3)	32.5 (6.3)	32.5 (6.3)	32.3 (6.4)	32.4 (6.4)	32.4 (6.4)	32.9 (6.5)	32.8 (6.2)	32.8 (6.3)

Abbreviations: LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE, major adverse cardiovascular events (3-point composite end point of time to cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke).

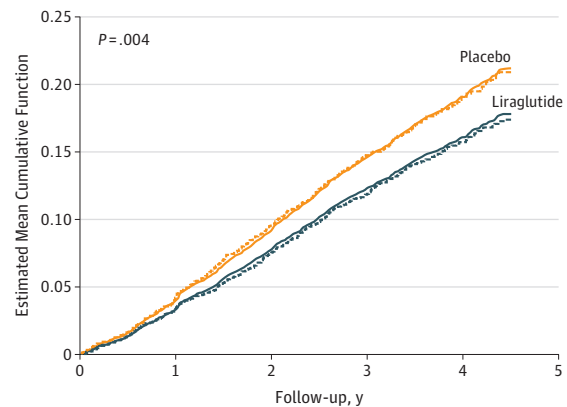
<sup>a</sup> New York Heart Association class II or III.

<sup>b</sup> Calculated as weight in kilograms divided by height in meters squared.

death was lower in both treatment groups but more marked in the liraglutide group (Figure 2). Recurrent MACE occurred in 97 of 4668 patients (2.1%) receiving liraglutide and in 126 of 4672 (2.7%) receiving placebo; this finding was associated with reductions in the proportions of patients experiencing recurrent nonfatal MI and stroke. Fewer patients experienced recurrent expanded MACE with liraglutide (416 of 4668 [8.9%]) compared with placebo (471 of 4672 [10.1%]), with correspondingly fewer total events (Figure 1B). For expanded MACE, the NNT was estimated to be 23 patients at 3 years (Figure 2), and 21 patients when non-CV death was included as a competing risk. Overall, few patients experienced recurrent events of individual CV end points, and (with the exception of unstable angina pectoris) consistently lower numbers of recurrent events occurred with liraglutide compared with placebo (Figure 1C). The most prevalent recurrent expanded MACE (n = 1669 events) were coronary revascularization (710 [42.5%]) and hospitalization for heart failure (385 [23.1%]), followed by nonfatal MI (240 [14.4%]), CV death (172 [10.3%]), nonfatal stroke 81 [4.9%]), and hospitalization for unstable angina pectoris (81 [4.9%]). This was different compared with the distribution of first expanded MACE (n = 2010 events) of which nonfatal MI (495 [24.6%]) was the most prevalent, followed by coronary revascularization (352 [17.5%]), hospitalization for heart failure (346 [17.2%]), and CV death (325 [16.2%]) (eFigure in the Supplement).

### Risk of Total MACE, Total Expanded MACE, and Individual CV End Points

The unadjusted AG model with a robust variance estimation showed that liraglutide was associated with a 15.7% relative risk reduction for total MACE vs placebo (HR, 0.84; 95% CI, 0.76-0.93). In 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

**Figure 2. Mean Total Major Adverse Cardiovascular Events per Patient During the Trial Period**

Mean cumulative function estimated using the Nelson-Aalen nonparametric method. The number needed to treat to avoid 1 event was based on the mean cumulative function at 3 years without accounting for competing risk. Dashed lines indicate liraglutide or placebo with competing risk. The P value was calculated for no treatment difference in the mean cumulative function with competing risk. The 3-point composite end point included time to cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (number needed to treat at 3 years: 43 patients). The 6-point composite end points included the 3-point MACE end points plus coronary revascularization and hospitalization for heart failure or unstable angina pectoris (number needed to treat at 3 years: 23 patients).

were slightly higher. In addition, liraglutide was associated with a 13.4% relative risk reduction for total expanded MACE vs placebo (unadjusted AG model: HR, 0.87; 95% CI, 0.81-0.93), and when all individual CV end points were considered (with the exception of unstable angina pectoris), liraglutide was associated with lower risk vs placebo (eTable in the Supplement).



The post hoc inclusion of recurrent events increased the power for showing superiority for time to events adjudication committee–confirmed MACE from 72.2% (primary end point of first MACE, Cox proportional hazards regression model) to 82.4% (post hoc end point of recurrent MACE, PWP model using log-HR with corresponding SEs).

## Discussion

We hypothesized that liraglutide, in addition to reducing first MACE in patients with type 2 diabetes and high risk of CV events, would also be associated with a reduction in recurrent CV events and therefore total events compared with placebo. It has been previously reported<sup>2</sup> that, in LEADER, liraglutide was associated with a reduced relative risk of first MACE by 13% compared with placebo. In this post hoc analysis, the relative risk reduction for total MACE was 15.7%. For total MACE, this translated into 43 patients needing treatment with liraglutide to prevent 1 event within 3 years, which was notably lower compared with the NNT of 66 calculated based on first MACE alone.<sup>2</sup> Similarly, for expanded total MACE, the NNT was 23 vs 49 for expanded first MACE. To our knowledge, these are the first such data relating to liraglutide and may help guide clinical decisions because the use of liraglutide was associated with reduced first and recurrent MACE among patients at risk for CV disease.

Although it is common in CV outcomes trials to censor primary outcome data after the first event has occurred,<sup>1,2,5-7</sup> many individuals have additional CV events that 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 that efficacy is maintained against recurrent events and patients adhere to treatment. It may also allow for a more meaningful assessment of absolute risk reduction and NNT with the pharmacotherapy. This concept is gaining support in other CV risk-reduction trials, including those of lipid-lowering<sup>16</sup> and antiplatelet therapy,<sup>17</sup> as well as cost-effectiveness assessments.<sup>18,19</sup>

As with most clinical trials, study treatment (liraglutide or placebo) began at the start of the LEADER trial. 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 is associated with future CV events. This is a question of clinical importance that has yet to be tested in a randomized clinical trial.

Recurrent event analyses have been conducted for different treatments and diseases.<sup>16,17,20</sup> These trials investigated patients with different underlying conditions<sup>16,17,20</sup> than those in the LEADER trial,<sup>2</sup> making direct comparisons between the size of treatment effects on recurrent events difficult. Although the proportion of recurrent events reported in the LEADER trial was within the range of those reported in other trials (18%-37%),<sup>16,17,20</sup> the benefit associated with liraglutide treatment for risk of first and recurrent events was a 15.7% reduction. Although this reduction was an improvement from

the 13% lower risk with liraglutide observed when primary events only were analyzed,<sup>2</sup> it may seem modest compared with other trials. For example, in an analysis of ischemic events (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina) among patients with established CV disease or type 1 or type 2 diabetes who were treated with statins, icosapent ethyl (an antilipid therapy) reduced the relative risk of total events by 30% compared with placebo during 4.9 years.<sup>20</sup> Although effect sizes for recurrent events will inevitably vary between treatments and in different patient populations, these previously published data<sup>16,20</sup> suggest that recurrent events occur in a substantial proportion of patients and should be considered when making clinical decisions. Coronary revascularization was the most prevalent recurrent (expanded MACE) event in the LEADER trial, highlighting the importance of such events within the context of population health. Effectively treating patients to reduce recurrent events could reduce time spent in the hospital, and it is for such reasons that recurrent events have been included in some recent cost-effectiveness studies.<sup>18,19</sup>

## Limitations

This analysis has limitations. Analyses of recurrent events may overestimate the contribution of patients experiencing MACE early in a trial,<sup>8</sup> cannot differentiate between cardioprotective mechanisms of a drug that may differ between first and subsequent events<sup>16</sup> and do not account for the decreasing compliance that is nominally reported as CV outcomes trials progress.<sup>16</sup> Although the mean percentage of time that patients received trial treatment was 84% in the liraglutide group and 83% in the placebo group,<sup>2</sup> adherence to study drug during the period between first and recurrent MACE was uncertain. This lack of data is a potential limitation; however, it should be balanced by the 96.8% of patients who completed a final study visit, died, or had a primary outcome<sup>2</sup> showing 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, the LEADER trial 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 (because counting each recurrent event individually may augment the effect size), in CV outcomes trials, this has to be considered in parallel with any differences in CV vs non-CV death. For example, in these analyses of recurrent events for the composite end point MACE and expanded MACE, non-CV death was a competing event. Because only a marginal nonsignificant treatment difference was observed for non-CV death in the LEADER trial (HR, 0.95; 95% CI, 0.76-1.18),<sup>2</sup> it was likely that this competing risk would only have a marginal effect on the results. This was supported by the sensitivity analyses of the mean cumulative function for both end points. 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 the

LEADER trial with an HR of 0.85 (95% CI, 0.74-0.92).<sup>2</sup> Thus, the results for the recurrent models applied for the individual components in expanded MACE could potentially be biased toward neutrality of the treatment effects.

Another potential limitation was related to the statistical approaches used. In a randomized clinical trial setting, the PWP model has been criticized because its use of the event history may reduce the estimated treatment effect,<sup>10</sup> and, furthermore, there could be a selection bias because randomization is not preserved after the first event. However, in a recent study by Ozga and colleagues,<sup>11</sup> 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 compos-

ite end points including fatal events compared with marginal recurrent models such as the Wei-Lin-Weissfeld model.<sup>11</sup>

## Conclusions

These results suggest that liraglutide treatment is associated with a reduction in risk of total (first and recurrent) MACE compared with placebo among patients with type 2 diabetes and high risk of cardiovascular events. This analysis supports the findings of an absolute benefit of liraglutide treatment with respect to the overall burden of CV events in this high-risk patient population.

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**Concept and design:** Verma, Buse, Idorn, Rasmussen, Ørsted, Nauck.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Verma, Ørsted.

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