Hypoglycemia, Cardiovascular Outcomes, and Death: The LEADER Experience

Bernard Zinman,[1] Steven P. Marso,[2] Erik Christiansen,[3] Salvatore Calanna,[3] Søren Rasmussen,[3] John B. Buse,[4] and the LEADER Publication Committee on behalf of the LEADER Trial Investigators*

OBJECTIVE

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) cardiovascular (CV) outcomes trial (NCT01179048), liraglutide significantly reduced the risk of CV events (by 13%) and hypoglycemia versus placebo. This post hoc analysis examines the associations between hypoglycemia and CV outcomes and death.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes and high risk for CV disease (n = 9,340) were randomized 1:1 to liraglutide or placebo, both in addition to standard treatment, and followed for 3.5–5 years. The primary end point was time to first major adverse cardiovascular event (MACE) (1,302 first events recorded), and secondary end points included incidence of hypoglycemia. We used Cox regression to analyze time to first MACE, CV death, non-CV death, or all-cause death with hypoglycemia as a factor or time-dependent covariate.

RESULTS

A total of 267 patients experienced severe hypoglycemia (liraglutide n = 114, placebo n = 153; rate ratio 0.69; 95% CI 0.51, 0.93). These patients had longer diabetes duration, higher incidence of heart failure and kidney disease, and used insulin more frequently at baseline than those without severe hypoglycemia. In combined analysis (liraglutide and placebo), patients with severe hypoglycemia were more likely to experience MACE, CV death, and all-cause death, with higher risk shortly after hypoglycemia. The impact of liraglutide on risk of MACE was similar in patients with and without severe hypoglycemia (P-interaction = 0.90).

CONCLUSIONS

Patients experiencing severe hypoglycemia were at greater risk of CV events and death, particularly shortly after the hypoglycemic episode. While causality remains unclear, reducing hypoglycemia remains an important goal in diabetes management.

The clinical management of type 2 diabetes emphasizes the importance of glycemic control to reduce the risk of diabetes-related complications (1). However, hypoglycemia remains a significant barrier to optimizing glucose control with some glucose-lowering medications (1). In the context of macrovascular complications, cardiovascular (CV) events are the leading cause of death among patients with diabetes, and the risk of CV death for patients with diabetes is more than double that for people without diabetes (2).

[1]Lunenfeld–Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada

[2]Research Medical Center, Kansas City, MO

[3]Novo Nordisk A/S, Søborg, Denmark

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

Corresponding author: Bernard Zinman, zinman@lunenfeld.ca.

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) CV outcomes trial, the glucagon-like peptide 1 analog liraglutide was shown to significantly reduce CV events and mortality, compared with placebo, when added to standard of care in patients with type 2 diabetes and high risk for CV events (3). Previous randomized clinical trials of liraglutide have demonstrated clinically significant reductions in hyperglycemia and body weight, with a low incidence of hypoglycemia (4–9). The Effect of Liraglutide Versus Placebo When Added to Basal Insulin Analogues With or Without Metformin in Subjects With Type 2 Diabetes (LIRA-ADD2BASAL) trial showed reductions in HbA_{1c} and body weight with liraglutide added to basal insulin compared with basal insulin alone; however, minor hypoglycemia was more frequent with liraglutide treatment (although no severe hypoglycemia was reported) (10). The authors noted that if the basal insulin dose had been reduced when liraglutide was added, this might have mitigated the effect on minor hypoglycemia. Consistent with this idea, in A Trial Comparing the Efficacy and Safety of Insulin Degludec/Liraglutide and Insulin Degludec in Subjects With Type 2 Diabetes (DUAL II) trial, when added to basal insulin (with a concomitant early decrease in insulin dose), liraglutide reduced HbA_{1c} with no increase in hypoglycemia compared with basal insulin alone (insulin dose was the same in both treatment groups at trial end) (11). The rates of both confirmed and severe hypoglycemia in the LEADER trial were reduced in liraglutide-treated patients, despite lower HbA_{1c} levels, compared with placebo-treated control subjects (3).

Previous studies in people with diabetes have demonstrated an association of hypoglycemia and an increased risk of CV events and mortality (12–14). Mechanistically, this could involve hemodynamic changes and reduced myocardial perfusion, induction of arrhythmias or a prothrombotic state, and release of inflammatory markers, although evidence for a causal effect of hypoglycemia on CV events and mortality is limited (14). In this post hoc analysis, we examine the associations between hypoglycemia and CV outcomes and mortality in patients with type 2 diabetes in the LEADER trial.

RESEARCH DESIGN AND METHODS
Design
LEADER (NCT01179048) was a double-blind, randomized, placebo-controlled, global trial conducted at 410 sites in 32 countries. Patients with type 2 diabetes and high risk for CV events were randomized 1:1 to receive liraglutide or placebo, both in addition to standard-of-care treatment, and followed for 3.5–5 years. Detailed descriptions of the trial design and methods have been published previously (3,15).

End Points and Variables
The primary end point in LEADER was time to the first occurrence of a major adverse cardiovascular event (MACE), a composite outcome consisting of CV death, nonfatal MI, or nonfatal stroke. Secondary end points included each individual component of the primary end point and all-cause death.

Occurrence of self-reported hypoglycemia was a secondary safety end point in LEADER and was reported using patient diaries and transcribed into the case report form (CRF). Severe hypoglycemia was defined according to American Diabetes Association criteria as hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (16) and was reported as a medical event of special interest in the LEADER trial. Confirmed hypoglycemia was defined as severe hypoglycemia or minor hypoglycemia (defined as plasma glucose <3.1 mmol/L [<56 mg/dL] with or without symptoms). Nocturnal hypoglycemia was defined as episodes occurring between 00:01 and 05:59 h. Patients were instructed to measure blood glucose whenever a hypoglycemic episode was suspected.

Other variables recorded included insulin use, age, duration of diabetes, glucose-lowering medication, HbA_{1c} at baseline, change in HbA_{1c} from baseline, and absolute HbA_{1c} values at the time of a hypoglycemic episode.

Statistical Analysis
We used Cox regression to analyze time to the first MACE, CV death, non-CV death, or all-cause death with either severe hypoglycemia at any time (yes/no) as a factor or with hypoglycemia (severe or confirmed, yes/no) as a time-dependent covariate adjusted for randomized treatment. For each end point, an interaction term between treatment and hypoglycemia was tested and removed if not significant at the 5% significance level. Patients were censored at the time from randomization to the end point of interest, to discontinuation, or to the follow-up visit (scheduled 30 days after treatment end).

For the time-dependent analyses, the patient's status changed from non-exposed to exposed at the time of a hypoglycemic episode. In analyses including fixed periods of follow-up (7–365 days), the patient was considered to be exposed to a hypoglycemic episode at the time of the episode until the end of the fixed period. Time-varying covariates were introduced by dividing the time between randomization and censoring for each patient into distinct periods demarcated by changes of the exposure variables and the time-varying covariate.

Sensitivity analyses were performed with adjustment for the following: 1) baseline covariates (glucose-lowering medication, sex, age, HbA_{1c}, diabetes duration); 2) concomitant insulin use during the trial as a time-dependent covariate; 3) HbA_{1c} during the trial (change from baseline and absolute values at the time of a hypoglycemic episode) as a time-dependent covariate; 4) concomitant sulfonylurea/glinide use during the trial as a time-dependent covariate; and 5) concomitant insulin use, HbA_{1c}, concomitant sulfonylurea/glinide use, estimated glomerular filtration rate (eGFR) (change from baseline and absolute values at the time of a hypoglycemic episode), and event adjudication committee–confirmed hospitalization for heart failure during the trial as time-dependent covariates.

As a supplementary analysis, time to first MACE, CV death, non-CV death, all-cause death and severe hypoglycemia was analyzed using Cox regression with the number of prior confirmed hypoglycemic episodes as a continuous time-dependent covariate and randomized treatment as a factor.

Descriptive statistics were calculated for patient characteristics and the occurrence of hypoglycemia. The number of hypoglycemic episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the observation time (100 years) as offset. Treatment, sex, region, and glucose-lowering medication at baseline were

included as fixed effects, and age at baseline was included as a covariate.

Partial population-attributable risks for exposure to severe hypoglycemia (for MACE, CV death, non-CV death, or all-cause death) were estimated using the approximate method described by Spielgelman et al. (17). We used time at risk for severe hypoglycemia as an estimate for the prevalence, and the hazard ratios (HRs) from the time-varying Cox regression model (with severe hypoglycemia as a time-dependent variable, adjusted for treatment) as plug-ins for the risk ratios.

RESULTS

Patient disposition, demographics, and baseline characteristics have been described previously (3). In summary, 9,340 patients with type 2 diabetes at high risk for CV events were randomized to receive liraglutide ($n = 4,668$) or placebo ($n = 4,672$), both in addition to standard-of-care therapy (3). Median exposure to study drug (liraglutide or placebo) was 3.5 years, and median duration of follow-up was 3.8 years (3). At baseline, patients had a mean age of 64 years, mean BMI of 32.5 kg/m^2, mean HbA$_{1c}$ of 8.7% (72 mmol/mol), and mean diabetes duration of 13 years. Overall, 64% of patients were male (3,15).

The primary outcome (MACE) occurred in 608 of 4,668 patients (13%) in the liraglutide group and in 694 of 4,672 patients (15%) in the placebo treatment group (3).

Hypoglycemia and Patient Characteristics

A total of 267 patients (3%) experienced 433 episodes of severe hypoglycemia during the trial (3). At baseline, these patients were older, had a longer duration of diabetes, tended to have worse renal function (eGFR), had more heart failure (New York Heart Association class II–III), and used insulin more frequently compared with patients without severe hypoglycemia (Table 1). Other baseline characteristics, including HbA$_{1c}$, were similar across the two groups (Table 1).

A total of 4,169 patients (45%) experienced 27,933 episodes of confirmed hypoglycemia during the trial. These patients had a longer duration of diabetes and lower body weight, tended to have worse renal function (eGFR), and more frequently used insulin at baseline than those who did not experience confirmed hypoglycemia (Table 1).

Nocturnal severe hypoglycemia was reported by 59 of 267 patients (22%) who experienced severe hypoglycemia, representing 21% (90/433) of all severe episodes. Nocturnal confirmed hypoglycemia represented 18% (5,150/27,933) of all confirmed episodes.

Treatment Effects on Hypoglycemia

Rates of severe and confirmed hypoglycemia during the trial were higher among patients using insulin at baseline compared with those patients using other or no glucose-lowering medication at baseline and those patients who initiated insulin after baseline (Supplementary Table 1).

As previously reported, the rates of severe and confirmed hypoglycemia were significantly lower in the liraglutide-treated versus placebo-treated group (3), and these beneficial effects increased over time (Fig. 1). Furthermore, the rates of severe and confirmed hypoglycemia remained lower among liraglutide-treated versus placebo-treated patients irrespective of baseline glucose-lowering medication (insulin, sulfonylureas, or glinides) (Supplementary Table 2). The rates of nocturnal severe and nocturnal confirmed hypoglycemia were also lower in the liraglutide-treated versus placebo-treated group, but the treatment difference was not statistically significant for nocturnal severe hypoglycemia.

Among patients initiating insulin therapy after baseline, those treated with liraglutide were at lower risk of a severe hypoglycemic episode after insulin initiation compared with those in the placebo-treated group, but this difference was not statistically significant (HR 0.7; 95% CI 0.3, 1.3; $P = 0.24$).

Association of Severe Hypoglycemia With CV Outcomes and Mortality

In total, 66 of 1,302 (5%) first MACE recorded in the trial occurred in patients who experienced severe hypoglycemia (at any time during the trial). Patients who experienced severe hypoglycemia during the trial were more likely than those without severe hypoglycemia to experience MACE, CV death, non-CV death, or all-cause death ($P < 0.001$ for all four outcomes) (Fig. 2). Similar results were observed irrespective of insulin, sulfonylurea, or glinide use, although not all associations were statistically significant (Supplementary Tables 3–5).

Furthermore, a temporal association between severe hypoglycemic episodes and subsequent risk of MACE, CV death, non-CV death, or all-cause death was identified (Fig. 2). This temporal association was strongest shortly after a hypoglycemic episode, with a pattern of increasing risk for MACE, CV death, non-CV death, or all-cause death in the shorter follow-up periods after severe hypoglycemia (Fig. 2). In the 7 days following a severe hypoglycemic episode, patients were at 7- to 15-fold higher risk of MACE, CV death, non-CV death, or all-cause death than those patients without severe hypoglycemia (Fig. 2).

These associations between severe hypoglycemia and MACE, CV death, non-CV death, and all-cause death remained significant when adjusted for relevant covariates including glucose-lowering medication, sex, age, HbA$_{1c}$, and diabetes duration at baseline as well as concomitant insulin and sulfonylurea/glinide use, HbA$_{1c}$, eGFR, and hospitalization for heart failure during the trial (Supplementary Fig. 1).

The estimated risk of MACE, CV death, non-CV death, or all-cause death attributable to severe hypoglycemia was between 1 and 3% (partial population-attributable risks: MACE 1.1% [95% CI 0.4, 1.8], CV death 3.2% [95% CI 1.5, 4.9], non-CV death 2.3% [95% CI 0.4, 4.1], all-cause death 2.8% [95% CI 1.6, 4.1]).

Similar to patients who experienced severe hypoglycemia, those who experienced nocturnal severe episodes during the trial were more likely than patients who did not to experience MACE (HR 2.1; 95% CI 1.3, 3.4; $P = 0.0039$) or CV death (HR 2.7; 95% CI 1.3, 5.4; $P = 0.0058$). There were no significant differences in the risk of non-CV death (HR 0.5; 95% CI 0.1, 3.6; $P = 0.50$) or all-cause death (HR 1.8; 95% CI 0.9, 3.5; $P = 0.07$) between patients who experienced nocturnal severe hypoglycemia and those who did not.

Association of Confirmed Hypoglycemia With CV Outcomes, Mortality, and Severe Hypoglycemia

When analyzed using the Cox regression model with confirmed hypoglycemia (yes, no) as a time-dependent covariate, patients who experienced confirmed hypoglycemia were found to be at higher risk of non-CV death compared with those who did not (HR 1.40; 95% CI

Table 1—Baseline characteristics of patients with and without hypoglycemia during the trial

	Severe hypoglycemia		Confirmed hypoglycemia	
	Yes (n = 267)	No (n = 9,073)	Yes (n = 4,169)	No (n = 5,171)
Male	166 (62.2)	5,837 (64.3)	2,631 (63.1)	3,372 (65.2)
Age, years	66.4 ± 7.7	64.2 ± 7.2	64.6 ± 7.2	64.0 ± 7.3
Diabetes duration, years	16.0 ± 8.3	12.7 ± 8.0	14.6 ± 8.4	11.4 ± 7.4
Insulin use	180 (67.4)	3,989 (44.0)	2,321 (55.7)	1,848 (35.7)
Geographic region				
Europe	83 (31.1)	3,213 (35.4)	1,300 (31.2)	1,996 (38.6)
North America	96 (36.0)	2,751 (30.3)	1,329 (31.9)	1,518 (29.4)
Asia	17 (6.4)	694 (7.6)	319 (7.7)	392 (7.6)
Rest of the world	71 (26.6)	2,415 (26.6)	1,221 (29.3)	1,265 (24.5)
HbA$_{1c}$, %	8.8 ± 1.7	8.7 ± 1.5	8.7 ± 1.5	8.7 ± 1.6
HbA$_{1c}$, mmol/mol	72.9 ± 18.9	71.5 ± 16.6	71.4 ± 16.3	71.6 ± 17.0
BMI, kg/m^2	32.3 ± 6.4	32.5 ± 6.3	32.0 ± 6.2	32.9 ± 6.3
Body weight, kg	90.4 ± 22.5	91.8 ± 20.9	89.7 ± 20.6	93.4 ± 21.2
Systolic blood pressure, mmHg	137.8 ± 20.7	135.8 ± 17.6	135.3 ± 18.2	136.4 ± 17.4
Diastolic blood pressure, mmHg	75.5 ± 10.1	77.1 ± 10.2	76.1 ± 10.3	77.9 ± 10.1
Heart rate, bpm	73.4 ± 12.0	72.6 ± 11.4	72.3 ± 11.5	72.9 ± 11.2
CV medication				
Antihypertensive therapy	255 (95.5)	8,376 (92.3)	3,914 (93.9)	4,717 (91.2)
β-Blockers	146 (54.7)	5,035 (55.5)	2,389 (57.3)	2,792 (54.0)
Diuretics	151 (56.6)	3,755 (41.4)	1,857 (44.5)	2,049 (39.6)
Statins	196 (73.4)	6,545 (72.1)	3,177 (76.2)	3,564 (68.9)
Platelet aggregation inhibitors	174 (65.2)	6,152 (67.8)	2,976 (71.4)	3,350 (64.8)
Established CVD (age ≥50 years)	229 (85.8)	7,369 (81.2)	3,456 (82.9)	4,142 (80.1)
Prior myocardial infarction	89 (33.3)	2,775 (30.6)	1,347 (32.3)	1,517 (29.3)
Prior stroke or transient ischemic attack	51 (19.1)	1,456 (16.0)	686 (16.5)	821 (15.9)
Prior revascularization	108 (40.4)	3,530 (38.9)	1,730 (41.5)	1,908 (36.9)
>50% stenosis of coronary, carotid, or lower-extremity arteries	60 (22.5)	2,319 (25.6)	1,115 (26.7)	1,264 (24.4)
Documented symptomatic CHD*	16 (6.0)	802 (8.8)	349 (8.4)	469 (9.1)
Documented asymptomatic cardiac ischemia†	60 (22.5)	2,412 (26.6)	1,093 (26.2)	1,379 (26.7)
Heart failure NYHA II–III	56 (21.0)	1,249 (13.8)	559 (13.4)	746 (14.4)
Chronic kidney disease‡	119 (44.6)	2,188 (24.1)	1,245 (29.9)	1,062 (20.5)
CVD risk factors (age ≥60 years)	38 (14.2)	1,704 (18.8)	713 (17.1)	1,029 (19.9)
Microalbuminuria or proteinuria	26 (9.7)	1,033 (11.4)	459 (11.0)	600 (11.6)
Hypertension and left ventricular hypertrophy	8 (3.0)	491 (5.4)	193 (4.6)	306 (5.9)
Left ventricular systolic or diastolic dysfunction	6 (2.2)	388 (4.3)	160 (3.8)	234 (4.5)
Ankle-brachial index <0.9	10 (3.7)	216 (2.4)	88 (2.1)	138 (2.7)
Renal function, eGFR mL/min/1.73 m^2				
Normal (≥90)	67 (25.1)	3,208 (35.4)	1,228 (29.5)	2,047 (39.6)
Mild impairment (60–89)	82 (30.7)	3,825 (42.2)	1,767 (42.4)	2,140 (41.4)
Moderate impairment (30–59)	96 (36.0)	1,838 (20.3)	1,036 (24.9)	898 (17.4)
Severe impairment (<30)	22 (8.2)	202 (2.2)	138 (3.3)	86 (1.7)
Creatinine, μmol/L	108.4 ± 63.2	86.8 ± 38.3	92.3 ± 42.4	83.5 ± 36.4
Albumin/creatinine ratio, mg/g	536.9 ± 1,482.8	180.1 ± 874.3	217.6 ± 730.8	168.2 ± 1,014.3
Alanine aminotransferase, units/L	23.8 ± 14.1	26.8 ± 16.2	25.8 ± 15.7	27.6 ± 16.4
Bilirubin, μmol/L	7.3 ± 4.2	7.8 ± 4.2	7.5 ± 3.9	8.1 ± 4.4
Sodium, mmol/L	140.1 ± 2.8	140.0 ± 2.7	140.1 ± 2.7	139.9 ± 2.7
Potassium, mmol/L	4.6 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5

Values are mean ± SD or number of patients (proportion of patients with or without severe or confirmed hypoglycemia [%]). CHD, coronary heart disease; CVD, cardiovascular disease; NYHA, New York Heart Association. *Positive exercise stress test or any cardiac imaging or unstable angina with electrocardiogram changes. †Positive nuclear imaging test, exercise test, or dobutamine stress echo. ‡eGFR <60 mL/min/1.73 m^2 per MDRD formula or Cockcroft-Gault formula.

1.12, 1.74), but there was no significant difference in the risk for MACE (HR 1.07; 95% CI 0.95, 1.20), CV death (HR 0.98; 95% CI 0.82, 1.18), or all-cause death (HR 1.13; 95% CI 0.98, 1.31).

However, when analyzed according to the number of prior confirmed hypoglycemic episodes, each confirmed episode significantly increased the subsequent risk of all-cause death (HR 1.01; 95% CI 1.00, 1.02) and severe hypoglycemia (HR 1.03; 95% CI 1.02, 1.03). Numerically increased risks for MACE (HR 1.01; 95% CI 1.00, 1.01), CV death (HR 1.01; 95% CI 1.00, 1.02), and non-CV
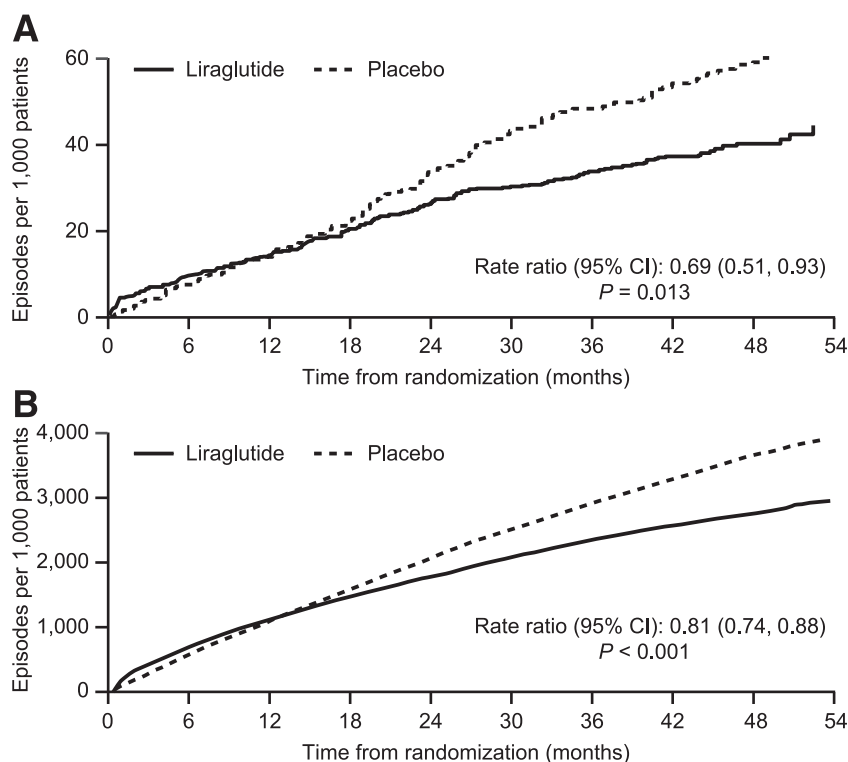
Figure 1—Severe (*A*) and confirmed (*B*) hypoglycemia over time among patients treated with liraglutide or placebo. Severe hypoglycemia was defined according to American Diabetes Association criteria as hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (16). Confirmed hypoglycemia was defined as severe hypoglycemia or minor hypoglycemia (defined as plasma glucose <3.1 mmol/L [<56 mg/dL] with or without symptoms). The number of episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the observation time (100 years) as offset.

death (HR 1.01; 95% CI 1.00, 1.02) were also observed but were not statistically significant.

Protective Interaction Between Liraglutide Treatment and Severe Hypoglycemia

The protective effect of liraglutide on risk of first MACE in LEADER reported previously (3) was similar in patients with or without severe hypoglycemia (*P*-interaction = 0.90) (Table 2). Similar results were observed for CV death and all-cause death.

The association between severe hypoglycemia and MACE, CV death, non-CV death, or all-cause death was unaffected by treatment with liraglutide or placebo: no interaction was identified between randomized treatment and severe hypoglycemia (*P*-interaction = nonsignificant for all four outcomes). There was also no interaction identified after adjustment for covariates including glucose-lowering medication, sex, age, HbA$_{1c}$, and diabetes duration at baseline as well as

concomitant insulin use and HbA$_{1c}$ as time-dependent covariates during the trial.

CONCLUSIONS

This post hoc analysis has demonstrated an association between the occurrence of severe hypoglycemia and an increased risk of CV events and mortality in the overall LEADER trial population (irrespective of randomized treatment). The association was maintained after correction for important variables at baseline and during the study. We have also shown a temporal relationship between the risk of CV events and death after a severe hypoglycemic episode, with event rates being higher closer to the episode. These findings further support the associations between severe hypoglycemia and the risk of CV events and mortality described in recent literature (12–14,18–21), with this association becoming more robust and with a stronger temporal relationship, albeit with a small attributable risk. These

results demonstrate the potentially serious implications of severe hypoglycemia on CV events and naturally raise questions as to how clinical practice can lower this burden and manage patients effectively after severe hypoglycemic episodes in the short- and longterm. There is currently no clear guidance for managing such patients.

Our analysis advances the literature by showing the temporal association between severe hypoglycemia and CV outcomes and mortality in type 2 diabetes: the risk of these outcomes increased with shorter follow-up periods after a severe hypoglycemic episode. There was a plateau effect in the trend for increasing risk closer to the hypoglycemic episode observed with fewer than 30 days of follow-up. This could arise from an incubation period after the episode, before the effect manifests, but we believe that it is more likely to result from a low number of events and consequential lack of precision in the HRs (large CIs) after 7 and 15 days of follow-up. A subanalysis of the smaller Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) CV outcomes trial (*n* = 5,380) identified an association between hypoglycemia and risk of MACE, but the association was no longer significant when considering a temporal association (MACE after hypoglycemic episodes) (18). Similarly, analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (*n* = 11,140) showed strong associations between severe hypoglycemia and a range of clinical outcomes including CV events and death, but no temporal association was identified (19). Analyses from the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial (*n* = 12,537) also showed increased risks of CV events and death in patients who experienced severe hypoglycemia (20). These associations remained significant after adjusting for a severe hypoglycemia propensity score and for outcomes that occurred within 1 or 7 days following a severe hypoglycemic episode (20). Results from the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) (*n* = 14,671) have confirmed the association between severe hypoglycemia and subsequent CV events (21). Recent analysis of the Trial Comparing Cardiovascular Safety of Insulin Degludec
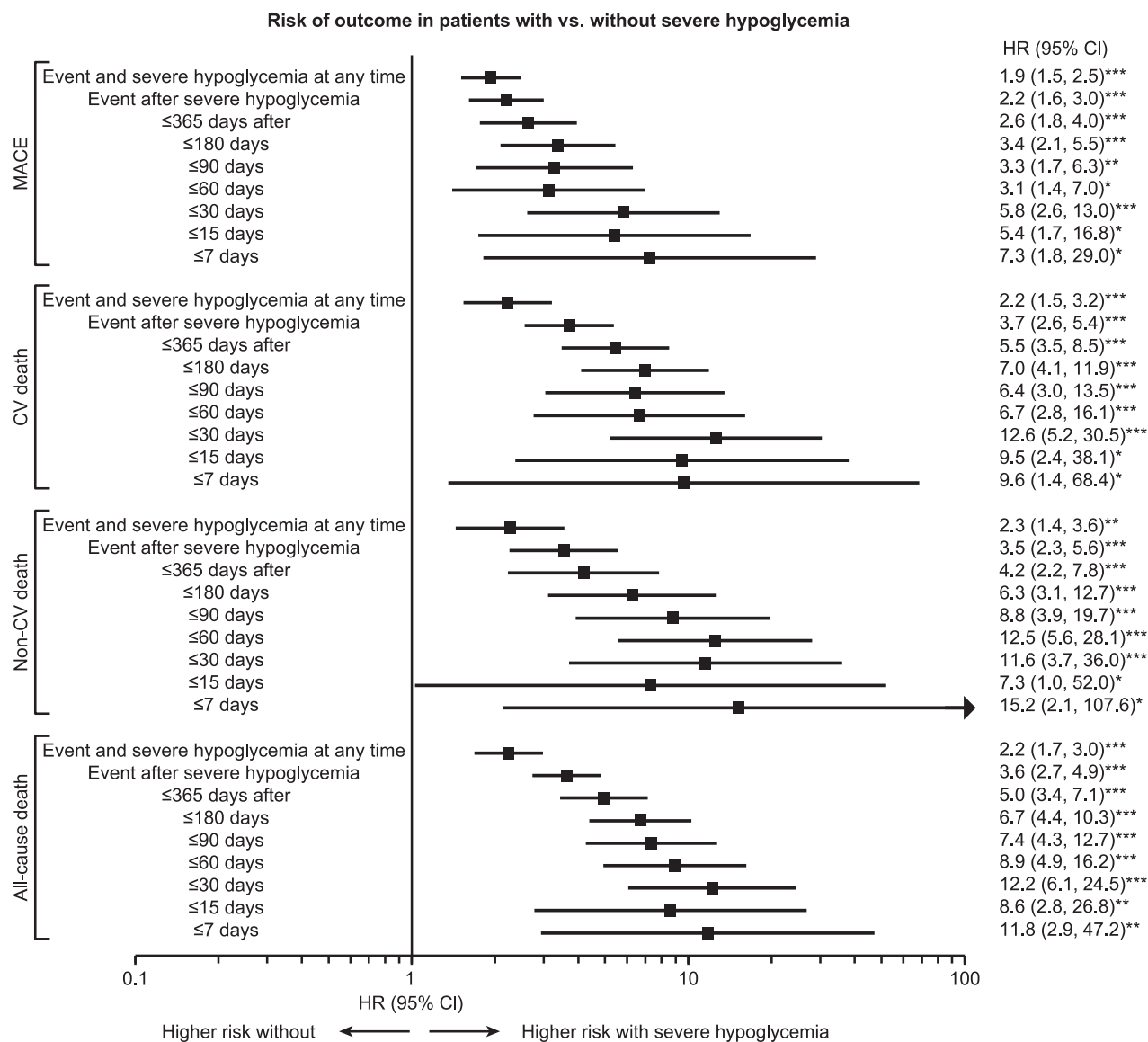
Risk of outcome in patients with vs. without severe hypoglycemia

Figure 2—Association between severe hypoglycemia and CV events and death. Risk of outcome with event and severe hypoglycemia at any time is based on analysis of time to first MACE, CV death, non-CV death, or all-cause death, using Cox regression with severe hypoglycemia (yes/no) at any time as a factor. Risk of outcome with events after severe hypoglycemia is based on severe hypoglycemic episodes prior to MACE, CV death, non-CV death, or all-cause death, using a time-dependent covariate Cox regression: all events (follow-up until last contact date), follow-up within 7, 15, 30, 60, 90, 180, and 365 days. *$P < 0.05$; **$P < 0.001$; ***$P < 0.0001$.

Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) trial ($n = 7,637$) is largely in agreement with our analysis, showing a higher risk of all-cause mortality in patients experiencing severe hypoglycemia when examining temporal associations, although no association was found between severe hypoglycemia and CV events (22).

The associations we have shown between severe hypoglycemia and CV outcomes and mortality were robust and were maintained after correction for important variables that could confound the results, including insulin use and change in HbA_{1c}. After analyzing the association of hypoglycemia and CV and mortality outcomes in the ADVANCE trial, it was noted that the associations were markedly attenuated after adjustment for potential confounders, and the

Table 2—MACE according to severe hypoglycemia and treatment group

Patient population	Liraglutide		Placebo			
	n	MACE*	n	MACE*	HR (95% CI)	*P*-interaction
All	4,668	608	4,672	694	0.87 (0.78, 0.97)	
With severe hypoglycemia	114	26	153	40	0.85 (0.52, 1.39)	0.90
Without severe hypoglycemia	4,554	582	4,519	654	0.88 (0.78, 0.98)	

HRs were estimated with the use of a Cox proportional hazards model with treatment as a covariate. *First MACE (CV death, nonfatal myocardial infarction, or nonfatal stroke).

authors suggested that along with the absence of a temporal relationship, this indicated that severe hypoglycemia was unlikely to have a direct causal role in CV events and mortality (19). Similarly, the associations between severe hypoglycemia and subsequent CV events in TECOS were not apparent in fully adjusted models (21). In combination with a converse relationship between CV events and subsequent severe hypoglycemia (maintained in fully adjusted models), this led the authors to conclude that severe hypoglycemia and CV events are common markers of at-risk, frail patients (21). Compared with the results from ADVANCE, ORIGIN, TECOS, and DEVOTE, we have shown more distinct temporal relationships between severe hypoglycemia and CV and mortality outcomes that are maintained after adjusting for confounders (19–22). However, while our findings differ from those of the ADVANCE and TECOS analyses, it is unclear whether our results represent a direct effect of severe hypoglycemia; hence, we cannot rule out the possibility that severe hypoglycemia is a marker of frail and vulnerable patients (14,19,21).

Beyond randomized clinical trial data, there is recent epidemiological evidence for the association of severe hypoglycemia and CV disease and mortality from the Atherosclerosis Risk in Communities (ARIC) study (23). This study also found that the association between severe hypoglycemia and CV events was stronger in the first year for those events with an atherosclerotic pathophysiology (23). This supports atherosclerosis as a possible mechanism, which could be induced by an increase in platelet aggregation and the release of inflammatory cytokines as a direct causal effect of severe hypoglycemia on the risk of CV events (23,24).

In contrast to the clear association between severe hypoglycemia and CV outcomes and mortality, the relationship between confirmed hypoglycemia (severe or minor hypoglycemia) and these outcomes is less straightforward. While the occurrence of severe hypoglycemia increased the risk of CV outcomes and mortality, the occurrence of confirmed hypoglycemia appeared to have a neutral effect on CV mortality and MACE. This is in line with other studies reporting a clear association with severe hypoglycemia but without a significant effect of

nonsevere hypoglycemia on CV or all-cause mortality (14).

A linear relationship was observed between the number of confirmed hypoglycemic episodes and the risk of all-cause death, with each confirmed episode increasing the risk of death. The effect of a single confirmed hypoglycemic episode on the risk of all-cause death was modest, but the increased risk corresponded to ~9% for a patient experiencing 10 confirmed hypoglycemic episodes. Similar associations were also observed for MACE, CV death, and non-CV death, but the increased risks were not statistically significant. Furthermore, there was also an increased risk of severe hypoglycemia associated with an increasing burden of confirmed hypoglycemia, in line with the hypothesis that episodes of severe hypoglycemia act as a marker or manifestation of frequent, recurrent, but less severe hypoglycemic episodes that may lead to death (25). Overall, the results of our analyses show that episodes of severe and confirmed hypoglycemia are associated with increased risks for adverse CV and mortality outcomes, albeit with stronger associations for severe hypoglycemia.

Patients experiencing hypoglycemia in the LEADER trial had worse renal function and more frequently used insulin at baseline than those patients who did not experience hypoglycemia. Higher age, longer duration of diabetes, and greater frequency of heart failure at baseline also highlighted the patients who experienced severe versus confirmed hypoglycemia, supporting the notion that these populations represent different patients or at least that those experiencing severe hypoglycemia are a distinct subgroup.

Treatment with liraglutide reduced hypoglycemia in the LEADER trial compared with placebo (3). This is in agreement with previous results showing a protective effect of liraglutide on insulin-induced hypoglycemia (11). Approximately one-fifth of hypoglycemic episodes (severe and confirmed) in the LEADER trial were classified as nocturnal, and we have shown that these were also reduced with liraglutide treatment (albeit the reduction was not statistically significant for nocturnal severe hypoglycemia). This finding may be particularly pertinent due to the clinical

impact these episodes can have on hypoglycemia unawareness, counterregulatory responses and glycemic control, daily well-being, and sleep (26–29). The beneficial effects on hypoglycemia in liraglutide-treated patients increased over time, and given that hypoglycemia increases with duration of insulin use (30), this may reflect the reduced requirement for insulin in liraglutide-treated patients during the trial compared with placebo-treated patients (3).

The mechanisms underlying the cardioprotective effects of liraglutide in the LEADER trial are unknown, but the association between severe hypoglycemia and CV and mortality outcomes, along with the reduction in severe hypoglycemia observed with liraglutide, could be contributing factors. However, even if severe hypoglycemia has a causal effect on CV events and mortality, attributable risk calculations suggested that preventing severe hypoglycemia could have only modestly reduced the incidence of CV and mortality outcomes (reductions of 8–23 events for the CV and mortality end points analyzed). Thus, while reducing severe hypoglycemia may contribute to the cardioprotective effects of liraglutide, it could not alone represent the key mechanism. Furthermore, there was no treatment interaction with severe hypoglycemia for the CV and mortality end points analyzed.

In addition to the LEADER trial, three other CV outcomes trials, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, and Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) (post hoc analysis), have recently reported beneficial effects on CV outcomes with the sodium–glucose cotransporter 2 inhibitors empagliflozin and canagliflozin as well as the glucagon-like peptide 1 analog semaglutide, respectively (relative to placebo, in addition to standard care) (31–33). No differences in the occurrence of hypoglycemia between active treatment and placebo were found in these trials, suggesting that other mechanisms were responsible for the reduction in CV risk (31–33). Nevertheless, the importance of reduced severe hypoglycemia, as observed with

liraglutide, remains high due to the association with major CV events and death as well as more direct consequences such as compromised physical, mental, and social functioning and reduced quality of life (34).

Limitations
When interpreting the results of this analysis, it is important to remember that it was conducted post hoc without adjustment for multiple comparisons and that it is based on self-reporting of hypoglycemia using patient diaries with details transcribed into CRFs. This process could lead to underreporting of hypoglycemia, particularly in the period between the last CRF update and a death. With a further requirement for reporting of severe hypoglycemia as a medical event of special interest, we suggest that severe episodes are less susceptible to this issue than confirmed hypoglycemic episodes. Other studies have adjudicated hypoglycemic episodes or reported severe episodes leading to hospitalization (25,35). Studies using continuous glucose monitoring suggest that self-reporting of hypoglycemia underestimates the true incidence of hypoglycemia, particularly during the nocturnal period (36). Although the associations between severe hypoglycemia and CV events and mortality appear robust, the risk of these events attributable to severe hypoglycemia was small. It should also be noted that the analyses indicating that liraglutide has the same effect on CV outcomes and mortality in patients both with and without severe hypoglycemia are limited by the inclusion of postrandomization covariates. Furthermore, it has been proposed that hypoglycemia may trigger CV events in patients already at risk (14), and the high–CV risk patient population from the LEADER trial may limit the application of these results to other patients with diabetes.

Summary
In summary, patients experiencing severe hypoglycemia in LEADER were at greater risk of MACE, CV death, non-CV death, and all-cause death than patients who did not experience severe hypoglycemia. This may warrant specific clinical attention and treatment, particularly in the time shortly after a hypoglycemic episode, to reduce the risk of these serious events. Although the precise

impact of different treatments is unclear, with the cardioprotective effects of liraglutide appearing largely independent of reductions in hypoglycemia, minimizing the risk of hypoglycemia is clearly an important goal in diabetes management.

References
1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58:429–442
2. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841
3. 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
4. Buse JB, Rosenstock J, Sesti G, et al.; LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; 374:39–47
5. Garber A, Henry R, Ratner R, et al.; LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373: 473–481
6. Marre M, Shaw J, Brändle M, et al.; LEAD-1 SU study group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). Diabet Med 2009; 26:268–278
7. Nauck M, Frid A, Hermansen K, et al.; LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 study. Diabetes Care 2009;32:84–90
8. Russell-Jones D, Vaag A, Schmitz O, et al.; Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia 2009;52:2046–2055
9. Zinman B, Gerich J, Buse JB, et al.; LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care 2009;32:1224–1230
10. Ahmann A, Rodbard HW, Rosenstock J, et al.; 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
11. Buse JB, Vilsbøll T, Thurman J, et al.; NN9068-3912 (DUAL-II) Trial Investigators. Contribution of liraglutide in the fixed-ratio combination of

insulin degludec and liraglutide (IDegLira). Diabetes Care 2014;37:2926–2933

12. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ 2013;347:f4533

13. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. Diabetes Care 2015;38:316–322

14. Hanefeld M, Frier BM, Pistrosch F. Hypoglycemia and cardiovascular risk: is there a major link? Diabetes Care 2016;39(Suppl. 2):S205–S209

15. 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.e5

16. 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

17. Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. Cancer Causes Control 2007;18:571–579

18. Heller SR, Bergenstal RM, White WB, et al.; EXAMINE Investigators. Relationship of glycated haemoglobin and reported hypoglycaemia to cardiovascular outcomes in patients with type 2 diabetes and recent acute coronary syndrome events: the EXAMINE trial. Diabetes Obes Metab 2017;19:664–671

19. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycaemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418

20. Mellbin LG, Rydén L, Riddle MC, et al.; ORIGIN Trial Investigators. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J 2013;34:3137–3144

21. Standl E, Stevens SR, Armstrong PW, et al.; TECOS Study Group. Increased risk of severe hypoglycemic events before and after cardiovascular outcomes in TECOS suggests an at-risk type 2 diabetes frail patient phenotype. Diabetes Care 2018;41:596–603

22. Pieber TR, Marso SP, McGuire DK, et al.; DEVOTE Study Group. DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality. Diabetologia 2018;61:58–65

23. Lee AK, Warren B, Lee CJ, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. Diabetes Care 2018;41:104–111

24. Jialal I, Dhindsa S. Hypoglycemia and the predisposition to cardiovascular disease: is the pro-inflammatory-pro-coagulant diathesis a plausible explanation? Atherosclerosis 2016;251:504–506

25. Rutter MK. Devoting attention to glucose variability and hypoglycaemia in type 2 diabetes. Diabetologia 2018;61:43–47

26. Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health 2011;14:665–671

27. Davis S, Alonso MD. Hypoglycemia as a barrier to glycemic control. J Diabetes Complications 2004;18:60–68

28. Frier BM. How hypoglycaemia can affect the life of a person with diabetes. Diabetes Metab Res Rev 2008;24:87–92

29. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J. Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. Diabetes 1993;42:1233–1237

30. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140–1147

31. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

32. 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

33. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844

34. Fidler C, Elmelund Christensen T, Gillard S. Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. J Med Econ 2011;14:646–655

35. Marso SP, McGuire DK, Zinman B, et al.; DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med 2017;377:723–732

36. Chico A, Vidal-Ríos P, Subirà M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care 2003;26:1153–1157