Effects of Severe Hypoglycemia on Cardiovascular Outcomes and Death in the Veterans Affairs Diabetes Trial

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OBJECTIVE

To determine the risk factors for severe hypoglycemia and the association between severe hypoglycemia and serious cardiovascular adverse events and cardiovascular and all-cause mortality in the Veterans Affairs Diabetes Trial (VADT).

RESEARCH DESIGN AND METHODS

This post hoc analysis of data from the VADT included 1,791 military veterans (age 60.5 ± 9.0 years) with suboptimally controlled type 2 diabetes (HbA_{1c} 9.4 ± 2.0%) of 11.5 ± 7.5 years disease duration with or without known cardiovascular disease and additional cardiovascular risk factors. Participants were randomized to intensive (HbA_{1c} <7.0%) versus standard (HbA_{1c} <8.5%) glucose control.

RESULTS

The rate of severe hypoglycemia in the intensive treatment group was 10.3 per 100 patient-years compared with 3.7 per 100 patient-years in the standard treatment group ($P < 0.001$). In multivariable analysis, insulin use at baseline ($P = 0.02$), proteinuria ($P = 0.009$), and autonomic neuropathy ($P = 0.01$) were independent risk factors for severe hypoglycemia, and higher BMI was protective ($P = 0.017$). Severe hypoglycemia within the past 3 months was associated with an increased risk of serious cardiovascular events ($P = 0.032$), cardiovascular mortality ($P = 0.012$), and total mortality ($P = 0.024$). However, there was a relatively greater increased risk for total mortality in the standard group compared with the intensive group ($P = 0.019$). The association between severe hypoglycemia and cardiovascular events increased significantly as overall cardiovascular risk increased ($P = 0.012$).

CONCLUSIONS

Severe hypoglycemic episodes within the previous 3 months were associated with increased risk for major cardiovascular events and cardiovascular and all-cause mortality regardless of glycemic treatment group assignment. Standard therapy further increased the risk for all-cause mortality after severe hypoglycemia.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, and Outcome Reduction With Initial Glargine Intervention (ORIGIN Trial), all large randomized controlled studies investigating the effects of improved glycemia control on vascular complications in type 2 diabetes mellitus (T2DM), have found an association between severe hypoglycemia and serious adverse events,

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cardiovascular adverse events, and increased mortality (1–5). In addition, studies investigating the effects of acutely intensifying glucose control in hospital settings have been ended early because of increased deaths (6), and increased hypoglycemia is considered by some as a plausible mechanism for the adverse outcomes. These high-quality trial data are consistent with results from several large longitudinal cohort studies (7). On the other hand, another large randomized trial in T2DM (the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes [BARI 2D] study) did not find an association between severe hypoglycemia and increased cardiovascular morbidity or mortality (8). In addition, risk factors for severe hypoglycemia and the consequences of hypoglycemia in intensive versus standard glucose-lowering treatment also appear to have differed among these studies. Thus, concern as well as uncertainty remain about the level of risk of hypoglycemia on major adverse outcomes in T2DM and in identifying those who are at greatest risk for these events.

The Veterans Affairs Diabetes Trial (VADT) was a randomized controlled multicenter study that investigated the effects of intensive glycemic control on macrovascular and microvascular complications in veterans with T2DM (9). We report on the association between severe hypoglycemia and a major cardiovascular event (a composite of myocardial infarction, stroke, death as a result of cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary artery disease, and amputation for ischemic gangrene), the primary end point in the VADT, and explore whether this effect varied with treatment assignment and the extent of initial cardiovascular disease (CVD) risk.

RESEARCH DESIGN AND METHODS

Design Overview

This study is a post hoc analysis of the VADT, an open-label study of intensive glycemic control in patients with T2DM with moderate to poor glycemic control. The VADT methods and main results were reported previously (9,10). The current analysis uses study data collected during the active phase of the VADT to identify risk factors for hypoglycemia and to examine the association between severe hypoglycemia and major cardiovascular events and mortality.

Settings and Participants

Research settings were diabetes and research clinics of 20 Veterans Administration hospitals across the country. Of the 1,791 participants enrolled in the study, 97% were male. Inclusion and exclusion criteria were described previously (9,10).

Randomization and Interventions

Patients were randomly assigned to two groups (intensive or standard therapy) with the use of a permuted block design with a block size of six and stratified per study site, the previous occurrence of a macrovascular event, and current insulin use (10). Patient flow through screening and randomization have been reported previously (9). In both study groups, patients with a BMI $\geq$27 kg/m^2 were started on two oral agents, metformin plus rosiglitazone; those with a BMI $<$27 kg/m^2 were started on glimepiride plus rosiglitazone. Patients in the intensive therapy group were started on maximal doses, and those in the standard therapy group were started on one-half the maximal doses. Before any change in oral medications, insulin was added for patients in the intensive therapy group who did not achieve a glycated hemoglobin (HbA_{1c}) level of $<$6% and for those in the standard therapy group with a level $>$9%. Subsequent changes in medication were determined per protocol guidelines and local assessment. An absolute HbA_{1c} separation of $>$1.5% was to be maintained between the therapy groups.

Other modifiable cardiovascular risk factors were treated identically in the two study groups (11). All patients were prescribed aspirin and an HMG-CoA reductase inhibitor (statin) unless contraindicated.

Protocol and consent forms were approved by the institutional review board at all 20 participating sites. All patients provided written informed consent. An independent data safety monitoring committee whose members were aware of study group assignments monitored safety and efficacy.

Outcomes and Follow-up

The primary outcome was the time to the first occurrence of any one of a composite of cardiovascular events adjudicated by an end point committee that was unaware of study group assignments. The cardiovascular events were documented myocardial infarction; stroke; death as a result of cardiovascular causes; new or worsening congestive heart failure; surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease; inoperable coronary artery disease; and amputation for ischemic gangrene. Total mortality was a prespecified secondary outcome. The patients were followed for a median of 5.6 years (9).

Severe Hypoglycemia

Severe hypoglycemia was defined as a self-reported episode of a low blood glucose value accompanied by confusion requiring assistance from another person or loss of consciousness.

Statistical Analysis

At each 3-month study visit, the number of severe hypoglycemic episodes since the last visit was recorded. Less than 0.5% of the visits had missing hypoglycemia data. As a result of missing data on key covariates, 35 participants were excluded (using listwise deletion) from the analyses (2% of all participants [*N* = 1,791]). Rates of severe hypoglycemia were calculated by dividing the total number of episodes by the total follow-up time for each patient. To evaluate risk factors for severe hypoglycemia, we used a two-level mixed logistic regression model with patients as the cluster variable. In addition, in a multivariable analysis, we evaluated the following potential risk factors for severe hypoglycemia: patient age, baseline BMI, proteinuria (urine albumin/creatinine ratio $>$30 mg/g), autonomic neuropathy, insulin use at baseline, estimated glomerular filtration rate (eGFR), race, duration of diabetes, most recent HbA_{1c} level (as a time-varying covariate), and allocation to the intensive treatment group.

We used Cox proportional hazards regression modeling to evaluate the effect of severe hypoglycemia in the prior 3 months on three outcomes: primary study outcome (major cardiovascular events), cardiovascular death, and all-cause mortality. Because hypoglycemia is a postrandomization intermediate event, controlling for potential confounders is indicated. Therefore, we adjusted for treatment group, overall cardiovascular

risk (as measured by the UK Prospective Diabetes Study [UKPDS] risk score), history of a prior cardiovascular event, insulin use, and eGFR. We used the UKPDS risk engine because it includes important diabetes-specific risk factors, such as duration of diabetes and HbA_{1c} level and because it has well-demonstrated discrimination in various diabetes populations (12). Risk factors that changed over time, including HbA_{1c} and occurrence of severe hypoglycemia in the past 3–6 months, were entered into the modeling as time-varying covariates. If patients missed a visit, that visit was not included in the analysis. Any interaction between severe hypoglycemia and overall cardiovascular risk also was evaluated.

Every significant risk factor met the proportional hazards assumption. Hazard ratios (HRs) and 95% CIs are reported. All analyses were based on intention to treat, and all *P* values are two-sided.

RESULTS

Mean participant characteristics were as follows: age, 60.4 years; duration of diabetes, 11.5 years; BMI, 31.3 kg/m^2; and HbA_{1c}, 9.4%. Seventy-two percent had hypertension, 40% had a previous cardiovascular event, 62% had a microvascular complication, and 52% had baseline insulin use. The standard and intensive treatment groups included 899 and 892 participants, respectively. Baseline clinical parameters for both treatment groups did not differ and are summarized in Table 1.

Table 1—Baseline characteristics by treatment group

	Baseline	
	Standard	Intensive
Age (years)	60.3	60.5
Sex		
Male	873	866
Female	26	26
Duration of T2DM (years)	11.5	11.5
Previous major cardiovascular event	368	355
Hypertension	650	642
Race/ethnicity		
Non-Hispanic white	572	539
Hispanic white	136	155
Black	147	152
Other	44	46
HbA_{1c} (%)	9.4	9.4
Weight (pounds)	214	214
BMI (kg/m^2)	31.2	31.3
Blood pressure (mmHg)		
Systolic	132	131
Diastolic	76	76
Lipids (mg/dL)		
Total cholesterol	185	182
LDL	108	107
HDL	36	36
Triglycerides (mg/dL)	223	201
Creatinine (mg/dL)	1.0	1.0
Smoking status		
Current	145	154
Past	505	494
Never	247	244

Data are mean or *n*. Data were published in part previously (9).

During the study, the standard treatment group averaged 3.7 severe hypoglycemic events per 100 patient-years versus 10.3 events per 100 patient-years in the intensive treatment group ($P < 0.001$). Overall, the combined rate of severe hypoglycemia during follow-up in the VADT from both study arms was 7.0 per 100 patient-years.

Univariate and Multivariate Predictors of Severe Hypoglycemia

Baseline univariate parameters of participants with severe hypoglycemia are shown in Table 2. Assignment to intensive treatment, presence of proteinuria, autonomic neuropathy, and insulin use at baseline were independent multivariable predictors of an increased risk for severe hypoglycemia. Baseline BMI was inversely predictive of future severe hypoglycemia (i.e., lower BMI had an increased risk of hypoglycemia).

Severe Hypoglycemia and Cardiovascular Events and Mortality

Severe hypoglycemia within the prior 3 months was associated with an increased risk for composite cardiovascular outcome (HR 1.9 [95% CI 1.1, 3.5]; $P = 0.03$), cardiovascular mortality (3.7 [1.3, 10.4]; $P = 0.01$), and all-cause mortality (2.4 [1.1, 5.1]; $P = 0.02$) (Table 2). More distant hypoglycemia (4–6 months prior) had no independently associated increased risk with adverse events or death. The association of severe hypoglycemia with cardiovascular events or cardiovascular mortality were not significantly different between the intensive and standard treatment groups (Table 3). In contrast, the association of severe hypoglycemia with all-cause mortality was significantly greater in the standard versus the intensive treatment group (6.7 [2.7, 16.6] vs. 0.92 [0.2, 3.8], respectively; $P = 0.019$ for interaction). Because of the relative paucity of repeated severe hypoglycemic events in either study group, there was insufficient power to determine whether more than one episode of severe hypoglycemia increased the risk of subsequent outcomes.

Effect of Overall Cardiovascular Risk on Consequences of Severe Hypoglycemia

Patients at higher baseline cardiovascular risk as assessed by the UKPDS risk engine had a significantly greater relative risk for a subsequent cardiovascular event after severe hypoglycemia than those at lower cardiovascular risk ($P = 0.012$ for interaction) (Table 3). Although recent severe hypoglycemia increased the risk of major cardiovascular events for those with a 10-year cardiovascular risk score of 35% (HR 2.88 [95% CI 1.57, 5.29]; absolute risk increase per 10 episodes = 0.252; number needed to harm = 4), hypoglycemia was not significantly associated with increased major

Table 2—Baseline parameters predictive of severe hypoglycemia (*N* = 1,791)

	Univariate predictors of severe hypoglycemia		
Variable	No severe hypoglycemic events (*n* = 1,523)	At least one severe hypoglycemic event (*n* = 268)	*P* value
Treatment group			<0.001
Standard (*n* = 899)	810 (53.2)	89 (33.2)	
Intensive (*n* = 892)	713 (46.8)	179 (66.8)	
Age (years)	60.2 ± 8.6	61.8 ± 8.8	0.005
Baseline insulin	752 (49.4)	186 (69.4)	<0.001
History of hypoglycemia	245 (16.1)	59 (22.1)	0.017
Neuropathy	619 (40.7)	142 (53.2)	<0.001
Sex			0.931
Male	1,479 (97.1)	260 (97.0)	
Female	44 (2.9)	8 (3.0)	
Time since diagnosis of T2DM (years)	11.2 ± 7.4	13.0 ± 7.6	<0.001
Previous CVD event	599 (39.3)	124 (46.3)	0.033
Race/ethnicity			0.849
Non-Hispanic white	939 (61.6)	172 (64.2)	
Hispanic white	250 (16.4)	41 (15.3)	
Black	258 (16.9)	41 (15.3)	
Other	76 (5.0)	14 (5.2)	
HDL (mg/dL)	35.7 ± 9.9	37.2 ± 11.4	0.044
Creatinine (mg/dL)	1.00 ± 0.21	1.05 ± 0.23	<0.001
eGFR (mL/min/1.73 m^2)	83.1 ± 22.2	77.4 ± 20.0	<0.001
UKPDS risk score	0.36 ± 0.20	0.39 ± 0.21	0.010

	Multivariate predictors of severe hypoglycemia	
Predictor	Odds ratio (95% CI)	*P* value
Intensive treatment arm	2.20 (1.46, 3.29)	<0.001
Baseline BMI (per unit)	0.95 (0.91, 0.99)	0.017
Proteinuria	1.42 (1.09, 1.85)	0.009
Autonomic neuropathy	1.75 (1.14, 2.69)	0.010
Insulin use at baseline	1.68 (1.09, 2.60)	0.020

Data are mean ± SD or *n* (%), unless otherwise indicated. Baseline values were measured upon entry into the original VADT.

cardiovascular events for those with a risk score of ≤7.5%. The absolute associated risk of major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality increased with higher CVD risk for all three outcomes (Table 4). We were not able to identify, however, any group of patients in either treatment arm in which severe hypoglycemia did not increase the risk of CVD events and mortality at least to some degree.

CONCLUSIONS

The VADT was a large randomized controlled trial aimed at determining the effects of intensive treatment of T2DM in U.S. veterans (9). In the current study, we examine predictors and consequences of severe hypoglycemia within the VADT and report several key findings. First, we identified risk factors for severe hypoglycemia that included intensive therapy, insulin use, proteinuria, and autonomic neuropathy. Consistent with prior reports in glucose-lowering studies, severe hypoglycemia occurred at a threefold significantly greater rate in those assigned to intensive glucose lowering. Second, severe hypoglycemia was associated with an increased risk of cardiovascular events, cardiovascular mortality, and all-cause mortality in both the standard and the intensive treatment groups. Of importance, however, severe hypoglycemia was associated with an even greater risk of all-cause mortality in the standard compared with the intensive treatment group. Third, the association between severe hypoglycemia and serious cardiovascular events was greater in individuals with an elevated risk for CVD at baseline.

Our finding of an association between severe hypoglycemia with vascular events and mortality has been previously reported (4–5,13,14). Whether, hypoglycemia was directly responsible for the increased mortality cannot be determined from the current data. Hypoglycemia is associated with several electrocardiogram changes, including ST-segment depression consistent with ischemia, heart rate variability, and QT prolongation that can be associated with arrhythmias and increased mortality (15). In addition, hypoglycemia has been noted to result in increased blood viscosity, enhanced platelet aggregation, increased plasminogen activator inhibitor-1, thromboglobulin, coagulation factor VIII, Von Willebrand factor, and thrombin generation. All these create a hypercoagulable and atherothrombotic state that increases cardiovascular risk (16).

In this study, we report that the association of severe hypoglycemia with the risk of all-cause mortality was significantly increased in the standard glycemic treatment group compared with

Table 3—Increased risk of cardiovascular events and mortality associated with severe hypoglycemia within the prior 3 months

	All participants*		Standard treatment group only	Intensive treatment group only	*P* value for interaction effect by treatment group
	HR (95% CI)	*P* value	HR (95% CI)	HR (95% CI)	
Cardiovascular event	1.9 (1.06, 3.52)	0.032	2.50 (1.0, 6.1)	1.7 (0.75, 3.83)	>0.2
Cardiovascular mortality	3.7 (1.3, 10.4)	0.012	8.6 (1.9, 37.7)	2.1 (0.51, 8.9)	0.184
All-cause mortality	2.4 (1.1, 5.1)	0.024	6.7 (2.7, 16.6)	0.92 (0.23, 3.8)	0.019

*Adjusted for treatment group, cardiovascular risk (as estimated by UKPDS score), history of cardiovascular event, insulin at baseline, and eGFR.

the intensive treatment group. This finding appears in concert with data from the ACCORD and ADVANCE studies and the ORIGIN Trial (1,2,4,5). In ACCORD and the ORIGIN Trial, participants in the standard arm who had experienced severe hypoglycemia had a significantly higher relative risk of death (4,5). In ADVANCE, there was a trend for a higher annual death rate in participants with severe hypoglycemia in the standard glycemic therapy group (5.1%) than for those in the intensive therapy group (3.6%) (17). Thus, severe hypoglycemia appears to carry an additional risk in individuals with higher HbA_{1c} values and who may be attempting intensification of glucose-lowering therapy, at least in older participants with more advanced diabetes.

Although the explanation for the relatively greater risk of serious adverse events after severe hypoglycemia in the standard treatment group is unknown, we agree with previous reports that milder episodes of hypoglycemia, which are more frequent in the intensive treatment group, may quantitatively blunt the release of neuroendocrine and autonomic nervous system responses and their resultant metabolic and cardiovascular responses to hypoglycemia, thereby lessening the impact of subsequent severe hypoglycemic episodes (18,19). Episodes of prior hypoglycemia have rapid and significant effects on reducing (i.e., blunting) subsequent counterregulatory responses to a falling plasma glucose level (20,21). Thus, if one of the homeostatic counterregulatory responses (e.g., epinephrine) also can initiate unwanted intravascular atherothrombotic

Table 4—Association of severe hypoglycemia with cardiovascular events and cardiovascular mortality by baseline cardiovascular risk

	For cardiovascular risk		
Hypoglycemic episode	Ten-year cardiovascular risk score, %	HR (95% CI)*	Absolute risk increase over a 3-month period† (per 10 severe hypoglycemic episodes) (95% CI)
Cardiovascular risk			
Any severe hypoglycemic episode in past 3 months	7.5	1.24 (0.49, 3.14)	0.023 (0.009, 0.059)
	15	1.56 (0.71, 3.42)	0.059 (0.027, 0.128)
	25	2.12 (1.11, 4.04)	0.133 (0.069, 0.253)
	35	2.88 (1.57, 5.29)	0.252 (0.137, 0.463)
P value for interaction		0.012	
CV mortality			
Any severe hypoglycemic episode in past 3 months	7.5	3.05 (0.56, 16.74)	0.019 (0.004, 0.107)
	15	3.48 (0.83, 14.69)	0.025 (0.006, 0.106)
	25	4.15 (1.30, 13.30)	0.062 (0.020, 0.200)
	35	4.95 (1.76, 13.96)	0.105 (0.037, 0.295)
P value for interaction		0.2	
All-cause mortality			
Any severe hypoglycemic episode in past 3 months	7.5	3.90 (1.41, 10.81)	0.077 (0.028, 0.212)
	15	3.41 (1.49, 7.84)	0.080 (0.035, 0.183)
	25	2.86 (1.33, 6.16)	0.101 (0.047, 0.217)
	35	2.39 (0.93, 6.19)	0.137 (0.053, 0.356)
P value for interaction		0.2	

*A statistically significant increase in the relative association (HR) of severe hypoglycemia with CVD risk (as measured by the UKPDS risk engine) was found for major CVD events. †The absolute risk of adverse events increased greatly with higher CVD risk for all three outcomes. Models include treatment group, severe hypoglycemia in prior 3 months, UKPDS risk, and the UKPDS × severe hypoglycemia interaction. Estimated using UKPDS risk engine.

consequences, it may follow that severe hypoglycemia in a more intensively treated and metabolically well-controlled individual would provoke a reduced counterregulatory response. Although hypoglycemia frequency may be increased in these individuals, this may also lower unwanted and deleterious effects on the vasculature from counterregulatory responses. On the other hand, an isolated severe hypoglycemic event in a less well-controlled individual could provoke a relatively greater counterregulatory response with a proportionally attendant elevated risk for adverse vascular effects (22). In support of this, we previously reported in a subset of VADT participants that despite more frequent serious hypoglycemia in the intensive therapy group, progression of coronary artery calcium scores after severe hypoglycemia only occurred in the standard treatment group (23).

In the current study, we demonstrate that the association of severe hypoglycemia with subsequent serious adverse cardiovascular events and death occurred within the preceding 3 months but not beyond. The temporal relationship and proximity of severe hypoglycemia to a subsequent serious cardiovascular event and/or death has been investigated in a number of recent clinical trials in T2DM (2–5,13,14). All these trials consistently reported an association between severe hypoglycemic and subsequent serious adverse events. However, the proximity of severe hypoglycemic events to subsequent adverse events and death varies. In ADVANCE, a severe hypoglycemic episode increased the risk of major cardiovascular events for both the next 3 months and the following 6 months. In A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) and the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, there was an increased risk of either serious cardiovascular events or all-cause mortality starting 15 days and extending (albeit with decreasing risk) up to 1 year after severe hypoglycemia (13,14). Superficially, the current findings seem to differ from those in ADVANCE, DEVOTE, and LEADER because we could not determine after weighting the risk for serious adverse cardiovascular and death in the first 3 months after a hypoglycemic event whether more-distant hypoglycemic events also were independently associated with serious adverse events.

In addition, we cannot definitively state that a single severe hypoglycemic event was the only cause for subsequent mortality. Also possible is that a patient may become more unwell with another serious underlying condition (apart from T2DM), which increases the frequency of hypoglycemia as an individual moves toward an agonal event.

The serious consequences of these hypoglycemia-associated outcomes (cardiovascular events and mortality) emphasize the importance of careful selection of patients and medications when initiating intensification of therapy and close monitoring of patients for evidence of these events. We have identified several clinical characteristics that increased the risk of severe hypoglycemia in the VADT. These included insulin use, proteinuria (a marker of reduced renal function and, therefore, reduced insulin clearance), and autonomic neuropathy. Several of these have been identified before (3,17) and confirm the importance of factoring in these clinical characteristics when selecting glucose targets and therapy approaches. Of note, greater BMI provided a protective effect against severe hypoglycemia perhaps because of the associated insulin resistance providing some protection against the glucose-lowering effects of insulin or insulin secretagogues. Although baseline HbA_{1c} levels were not a significant multivariable predictor of severe hypoglycemia in the whole group, there was a significant association in the standard group and a strong trend in the intensive group for greater frequency of episodes in participants with higher initial values. This seems paradoxical, but it may be that higher HbA_{1c} levels also identify patients with more variation in glucose levels who are, therefore, more likely to become hypoglycemic with any attempt at intensification of glycemic control. Of note, this includes individuals striving to improve glycemic control but who have HbA_{1c} values of 9–10% and are proving resistant to change. These individuals, whether in intensive or standard treatment groups, have an increased risk of serious adverse events after severe hypoglycemia and were the group most at risk for mortality after severe hypoglycemia in the ACCORD study (3,4). The observation that individuals with T2DM and HbA_{1c} values of ~9% can experience severe hypoglycemia complements the findings from The Diabetes Control and Complications Trial (DCCT) in younger individuals with type 1 diabetes (24).

We also sought to determine whether the level of underlying cardiovascular risk could help to identify those at greatest risk from hypoglycemia. Therefore, we stratified participants by baseline cardiovascular risk using the UKPDS risk engine (12). Those with the greatest UKPDS risk score were at greatest relative and absolute risk for future primary cardiovascular events after severe hypoglycemia. In contrast, those with the lowest risk score demonstrated no increased association after severe hypoglycemia. This may help to explain the importance of the proximity of severe hypoglycemia to the outcome because a recent episode may provide an acute stress event that is most harmful to those already predisposed to a cardiovascular event.

The current study has some limitations. We only report severe hypoglycemia that was defined as a low blood glucose event associated with confusion requiring assistance by another person or loss of consciousness. Thus, although we are confident that episodes of severe hypoglycemia (those requiring assistance) were accurately captured and reported, it is likely that other incidents of clinically relevant, but less severe hypoglycemia have not been included in the analysis. Moreover, we do not have glucose values immediately preceding the cardiovascular event, so we cannot address the acute association between hypoglycemia and outcomes. Furthermore, 97% of study participants were male, which prevents generalization to females. Finally, we studied a cohort with advanced T2DM and with or at high risk for CVD. Thus, our participants may have been more vulnerable to the deleterious effects of severe hypoglycemia, a possibility consistent with our finding of a stronger relative and absolute effect in those with higher cardiovascular risk.

In summary, severe hypoglycemia occurred at a peak rate of 10.3 and 3.7 per 100 patient-years in the intensive and standard treatment groups, respectively. Severe hypoglycemia within the prior

3 months in these groups was associated with increased risk for primary cardiovascular outcomes, cardiovascular death, and all-cause mortality. However, the association of severe hypoglycemia with all-cause mortality was significantly greater in the standard treatment arm.

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