Confirming the Bidirectional Nature of the Association Between Severe Hypoglycemic and Cardiovascular Events in Type 2 Diabetes: Insights From EXSCEL

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OBJECTIVE

We sought to confirm a bidirectional association between severe hypoglycemic events (SHEs) and cardiovascular (CV) event risk and to characterize individuals at dual risk.

RESEARCH DESIGN AND METHODS

In a post hoc analysis of 14,752 Exenatide Study of Cardiovascular Event Lowering (EXSCEL) participants, we examined time-dependent associations between SHEs and subsequent major adverse cardiac events (CV death, nonfatal myocardial infarction [MI] or stroke), fatal/nonfatal MI, fatal/nonfatal stroke, hospitalization for acute coronary syndrome (hACS), hospitalization for heart failure (hHF), and all-cause mortality (ACM), as well as time-dependent associations between nonfatal CV events and subsequent SHEs.

RESULTS

SHEs were uncommon and not associated with once-weekly exenatide therapy (hazard ratio 1.13 [95% CI 0.94–1.36], $P = 0.179$). In fully adjusted models, SHEs were associated with an increased risk of subsequent ACM (1.83 [1.38–2.42], $P < 0.001$), CV death (1.60 [1.11–2.30], $P = 0.012$), and hHF (2.09 [1.37–3.17], $P = 0.001$), while nonfatal MI (2.02 [1.35–3.01], $P = 0.001$), nonfatal stroke (2.30 [1.25–4.23], $P = 0.007$), hACS (2.00 [1.39–2.90], $P < 0.001$), and hHF (3.24 [1.98–5.30], $P < 0.001$) were all associated with a subsequent increased risk of SHEs. The elevated bidirectional time-dependent hazards linking SHEs and a composite of all CV events were approximately constant over time, with those individuals at dual risk showing higher comorbidity scores compared with those without.

CONCLUSIONS

These findings, showing greater risk of SHEs after CV events as well as greater risk of CV events after SHEs, validate a bidirectional relationship between CV events and SHEs in patients with high comorbidity scores.

In the post-2008 era of cardiovascular outcome trials (CVOTs) mandated by the U.S. Food and Drug Administration (FDA) for any new glucose-lowering drug, severe hypoglycemic events (SHEs) requiring third-party assistance have remained a major challenge complicating diabetes therapy (1). Post hoc analyses of several CVOTs have

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found that SHEs are associated with an increased risk of subsequent cardiovascular (CV) and all-cause mortality (ACM) events (2–9). These findings, and the lack of compelling evidence for CV benefit from intensive glycemic control in patients with established CV disease, have prompted many diabetes management guidelines to suggest relaxing individual glycated hemoglobin (HbA_{1c}) targets in such patients in the anticipation that this will reduce SHEs and associated mortality events (10,11). Higher HbA_{1c} targets, however, may increase the risk of microvascular complications in the longer term, and have not been shown to reduce the risk of SHEs (4,12,13). Indeed, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients with higher HbA_{1c} values had a greater risk of SHEs, irrespective of the treatment group (4), and the risk of ACM was greatest in the participants with the highest average HbA_{1c} values, especially in the intensive treatment arm (14). On the other hand, SHEs did not account for the difference in mortality between the two study arms (4), and transferring the intensive treatment group to less strict HbA_{1c} targets between 7.0% and 7.9% left the increased risk of ACM and CV death unchanged (15). Accordingly, it is unclear to what extent SHEs may play a causative role in ACM and CV events, with common confounders being a realistic alternative explanation. Of note, a strong reverse association, in which nonfatal CV events were associated with a subsequent increased risk of SHEs, was demonstrated in a post hoc analysis of TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) (8).

We sought to confirm in this post hoc analysis of data from EXSCEL (Exenatide Study of Cardiovascular Event Lowering) (16) that there is a bidirectional relationship between an increased risk for CV events after SHEs and an increased risk for SHEs after nonfatal CV events, particularly in patients at dual risk with features of "frailty" as evidenced by a high summary comorbidity score.

RESEARCH DESIGN AND METHODS

Study Design and Participants

EXSCEL was a double-blind, placebo-controlled, randomized, event-driven trial conducted at 687 sites in 35 countries. It was designed to assess the CV safety of extended-release exenatide given once weekly versus placebo when added to usual care in patients with type 2 diabetes; the results have been reported in detail (16). The trial was designed such that ~70% of enrolled patients had previous CV events and 30% did not. EXSCEL was run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit in an academically independent collaboration with the sponsor, Amylin Pharmaceuticals (a wholly owned subsidiary of AstraZeneca). The protocol was approved by the ethics committee at each participating site, and the statistical analyses were performed by the DCRI, independent of the sponsor. All patients provided written informed consent. Eligible patients were adults with type 2 diabetes and with an HbA_{1c} level of 6.5–10.0% (48–96 mmol/mol) inclusive. Previous CV events were defined as a history of major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease. In addition, the summary comorbidity score at baseline was assessed using the Charlson Comorbidity Index (17,18). History of two or more episodes of severe hypoglycemia (defined as hypoglycemia for which a patient received third-party assistance) during the preceding 12 months was a principle exclusion criterion.

Randomization and Study Medication

EXSCEL participants were randomly assigned in a 1:1 ratio to receive subcutaneous injections of once-weekly exenatide (EQW) at a dose of 2 mg or matching placebo. Participants were required to discontinue study medication if they had two or more SHEs between trial visits (despite adjustment of other glucose-lowering agents), had irreversible kidney dysfunction (confirmed by two consecutive estimated glomerular filtration rate [eGFR] values <30 mL/min/1.73 m^2), or received renal replacement therapy. For minimization of potential confounding effects of differential glycemic levels on trial outcomes, the use of open-label glucose-lowering agents (including dipeptidyl peptidase 4 inhibitors but not including glucagon-like peptide 1 receptor agonists) was encouraged to promote glycemic equipoise between the two trial groups and to help patients reach clinically appropriate HbA_{1c} targets.

SHEs

At screening/enrollment, 1 week, 2 months, 6 months, and 12 months, and then at semiannual visits, the symptoms and appropriate management of hypoglycemia were reviewed proactively with participants. All SHEs were recorded systematically as prespecified events of clinical interest. SHEs were defined per protocol as episodes in which a participant was sufficiently disoriented or incapacitated as to require help from either another individual or from medical personnel, i.e., third-party assistance, irrespective of whether this assistance was actually provided. It did not suffice, for example, if a family member or other bystander brought the patient a snack or drink to help raise his or her blood glucose if it was not clear that the patient could not have done this unaided. This category included all patients who had at least one SHE that was reported during the overall period, which was defined as the period from the date of randomization through the last date that the patient was known to be alive.

Clinical Outcomes

Major adverse CV events (MACE) constituted the EXSCEL primary composite outcome, defined as the first occurrence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, which was evaluated in a time-to-event analysis. Secondary outcomes, also evaluated in time-to-event analyses, included ACM, CV death, the first occurrence of nonfatal or fatal MI, nonfatal or fatal stroke, hospitalization for acute coronary syndrome (hACS), and hospitalization for heart failure (hHF). An independent clinical events classification committee whose members were unaware of the trial-group assignments adjudicated all the components of the primary and secondary outcomes, ventricular arrhythmias that led to intervention, neoplasms, and pancreatitis. Prespecified events of clinical interest for which information was collected systematically at every follow-up visit, regardless of seriousness, were pancreatitis, neoplasm, SHEs, and expected CV or diabetes-related complications.

Statistical Analysis

Categorical variables are presented as *n* (%), and continuous variables are presented as median (25th, 75th percentile).

Risk of first SHE as a function of time is shown with Kaplan-Meier plots, with study treatment differences tested using Cox proportional hazards regression models stratified by prior CV disease. Treatment effects for EQW versus placebo are presented as hazard ratios (HRs) and 95% CIs, with numbers of events and events per 100 patient-years of follow-up reported. Using the same approach, we further subdivided both treatment arms, considering patients on "insulinotropic" therapies (insulin, sulfonylureas, or nonsulfonylurea insulin secretagogues) compared with those without such drugs, and the randomized treatment–by–insulinotropic therapy interaction was evaluated.

For investigation of the association between SHEs and CV events, Cox proportional hazards regression models were fitted with SHEs as time-dependent variables and subsequent MACE, as well as fatal/nonfatal MI or stroke, hACS, hHF, and ACM, as outcomes. For investigation of the reverse association, Cox models were fitted with nonfatal CV events as time-dependent variables and subsequent SHEs as outcomes. For both analyses, unadjusted as well as partially and fully adjusted models were used. Partially adjusted models included randomized treatment and clinical factors of age, sex, ethnicity, weight, and current smoking, while models fully adjusted for independent predictors of MACE and ACM in EXSCEL (19) included age, sex, ethnicity, HbA_{1c}, New York Heart Association class, current smoking, randomized treatment, MI, CV disease, stroke, ≥50% stenosis in carotid artery, atrial fibrillation or flutter, systolic blood pressure, diastolic blood pressure, heart rate, height, BMI, eGFR, diabetes duration, insulin therapy at baseline, time-dependent insulin use during the trial, chronic respiratory disease, amputation, diabetic neuropathy, and foot ulcers as covariates. Models for SHE outcomes were also adjusted for baseline β-blockers and sulfonylureas. For the continuous variables, we checked whether nonlinear terms (piecewise splines) needed to be included in the models. Where piecewise splines for continuous variables were necessary, a cut point was selected that would work reasonably well for all end points. The proportional hazards assumption was checked for the full adjustment model with no major violations being identified.

Models for CV outcomes used only the first SHE per patient and assumed that there were no time-dependent confounders associated with both SHEs and clinical outcomes. Events per 100 patient-years of follow-up are presented separately for the time from first SHE to clinical outcome and for time to clinical outcome or censor without an SHE. Results are displayed as forest plots. Analyses of the association between nonfatal CV outcomes and subsequent SHEs were conducted and presented similarly.

To investigate the time dependence of the risk of CV events after SHEs, nonlinear restricted cubic spline functions of time since SHE were included in fully adjusted proportional hazards regression models. These functions were exponentiated to get HRs associated with SHE as a function of time since SHE and plotted for the range of follow-up times postevent. Risk of SHE as a function of time since nonfatal CV events was investigated using the same approach. *P* values for whether the HRs were constant over time are provided. Data were analyzed using SAS software, version 9.4 (SAS Institute, Cary, NC), with *P* values <0.05 considered statistically significant.

RESULTS

The EXSCEL intention-to-treat population consisted of 14,752 patients (of whom 10,782 [73.1%] had previous CV disease) with a median follow-up of 3.2 years (interquartile range 2.2−4.4). A total of 14,187 participants (96.2%) completed the trial, and vital status was obtained for 98.8% of the participants. The median duration of exposure to study medication was 2.4 years (1.4−3.8) in the EQW group and 2.3 years (1.2−3.6) in the placebo group. No patients were excluded from the trial because of a history of two SHEs.

SHEs were relatively uncommon and not associated with EQW therapy ($N = 247$ [3.4%], 1.0/100 patient-years, vs. $N = 219$ [3.0%], 0.9/100 patient-years for placebo; HR 1.13 [95% CI 0.94−1.36], $P = 0.179$) (Fig. 1*A*). Subgroups with or without baseline therapy that included insulin, sulfonylurea, or nonsulfonylurea secretagogues also showed no difference between the two treatment arms (HR 1.12 [95% CI 0.93−1.36]) for the subgroup with insulin, sulfonylurea, or nonsulfonylurea secretagogues and HR 1.24 [95% CI 0.61−2.51] for the group without; $P = 0.80$ for interaction) (Fig. 1*B*). Incidence rates for SHEs were higher in the 1st year than thereafter in both treatment groups and were highest in the subgroup with insulin, sulfonylurea, or nonsulfonylurea secretagogue therapy at baseline compared with those on other therapies at baseline (HR 4.17 [95% CI 2.90–6.02]). Recurrent SHEs were balanced between treatment arms, seen in 71 placebo participants and 62 EQW participants. There was a total of 450 events (1.8/100 patient-years) in the placebo group and 404 in the EQW group (1.6/100 patient-years). Two participants in the placebo group and four in the EQW group discontinued study drug because of SHEs.

Baseline characteristics for those with and without an SHE during the trial are listed in Table 1. Participants with an SHE, compared with those without, had longer diabetes duration and lower eGFR, more frequently had prior CV or heart failure events, and were more often nonwhite or insulin treated and with a higher daily dose per kilogram of body weight. Furthermore, participants with SHEs were more often treated with diuretics, statins, β-blockers, and antithrombotic agents. Of the 466 participants with SHEs, 15 (3.2%) died of non-CV causes and 116 (24.9%) had a CV event (i.e., MI, stroke, hHF, hACS, or CV death). Of these 116 participants, 66 had these events after an SHE during the trial (with four participants having an SHE on the same day) and 50 participants had an SHE after a nonfatal CV or hHF event during the trial. The baseline characteristics of the latter two groups are also listed in Table 1, compared with the 14,636 EXSCEL participants who did not have an SHE or a CV event during the trial. Those two groups with, compared with those without, concomitant SHEs and CV events during the trial showed rather similar characteristics and were ∼4 years older, had a 4-year longer duration of diabetes, and were almost twice as likely to be insulin treated. In addition, their daily insulin dose at baseline was higher compared with those without the dual risk (0.82 vs. 0.62 units/kg body wt) (see also Supplementary Table 1). They comprised fewer women; were more often black; tended to have a higher BMI and HbA_{1c}; had twice the proportion with chronic kidney disease stage 3 (eGFR 30–59 mL/min/1.73 m^2); more frequently

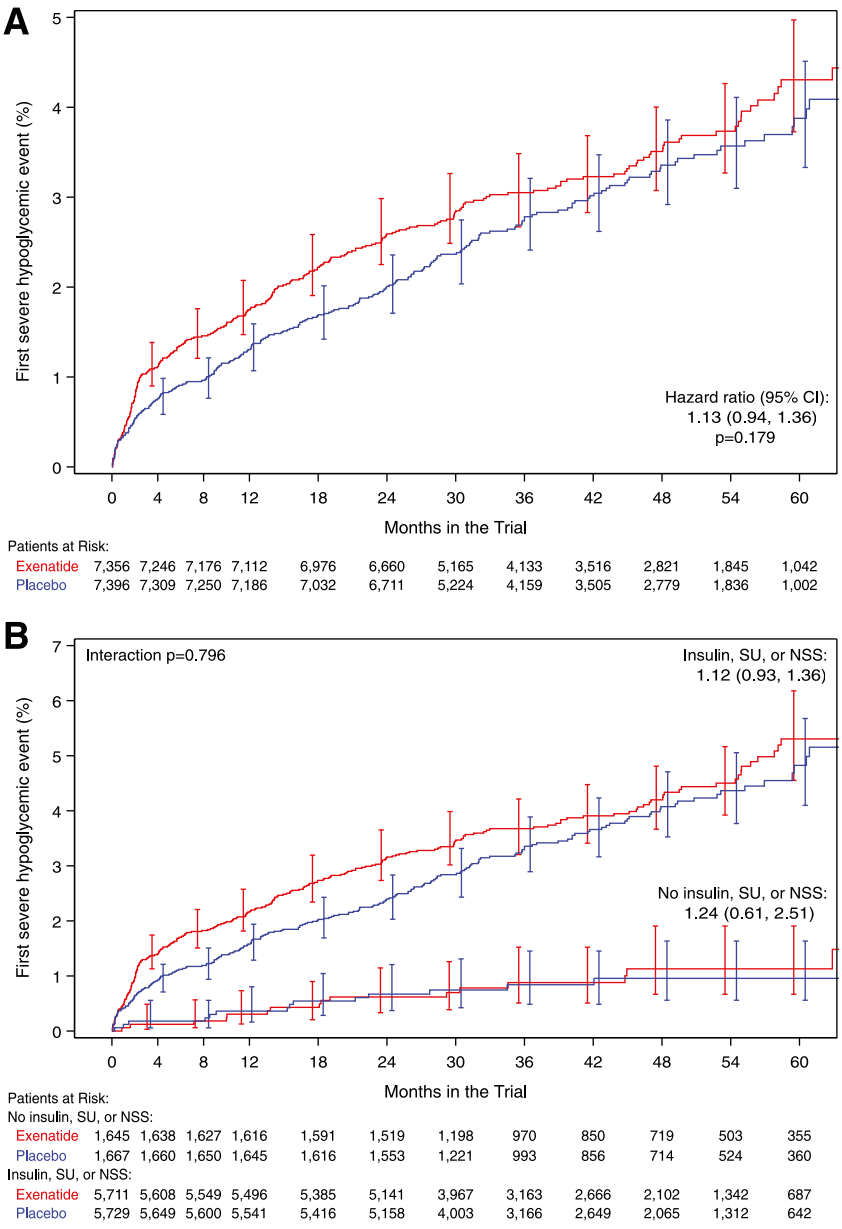

Figure 1—Kaplan-Meier plots of time to first SHE for participants assigned to exenatide or placebo. *A*: In the intention-to-treat population. *B*: Split by those with or without therapy with insulin, sulfonylurea (SU), or nonsulfonylurea secretagogues (NSS) at baseline.

reported a history of CV disease, heart failure, and prior CV events; showed a markedly higher Charlson Comorbidity Index; and were more often treated with acetylsalicylic acid, thienopyridines, statins, diuretics, and β-blockers. These trends were most pronounced in the group with an SHE before a CV event, with 97% having experienced a prior CV event, 41% with a prior heart failure history, and 46% with chronic kidney disease stage 3. Those patients also had the highest daily insulin dose (0.87 units/kg body wt). Of the four participants with an SHE and a CV event occurring on the same day, three were taking insulin at baseline and the other had commenced insulin therapy prior to the events. Two died within 2 days from CV death and non-CV death, while the other two remained free from further events.

In analyses adjusted for selected clinical factors, SHEs were associated with a subsequent increased risk of the primary MACE end point (HR 1.43 [95% CI 1.08–1.91], $P = 0.013$), ACM (HR 2.06 [95% CI 1.57–2.71], $P < 0.001$), CV death (HR 1.84 [95% CI 1.28–2.62], $P = 0.001$), MI (HR 1.68 [95% CI 1.18–2.39], $P = 0.004$), hACS (HR 1.66 [95% CI 1.19–2.30], $P = 0.003$), and hHF (HR 2.88 [95% CI 1.92–4.33], $P < 0.001$) (Fig. 2*A*). Conversely, nonfatal MI or stroke (HR 2.50 [95% CI 1.75–3.56], $P < 0.001$), nonfatal MI (HR 2.52 [95% CI 1.70–3.74], $P < 0.001$), nonfatal stroke (HR 2.56 [95% CI 1.40–4.70], $P = 0.002$), hACS (HR 2.42 [95% CI 1.68–3.48], $P < 0.001$), and hHF (HR 4.40 [95% CI 2.70–7.15], $P < 0.001$) were associated with a subsequent increased risk of SHEs (Fig. 2*B*).

In fully adjusted models, statistically significant associations of SHEs with subsequent events were limited to CV death, ACM, and hHF events (Fig. 2*C*), while all associations between nonfatal CV events and subsequent increased risk of SHEs remained statistically significant (Fig. 2*D*).

After adjustment for the full list of covariates, the elevated hazards of combined CV events (MACE/hACS/hHF) following SHEs and of SHEs following combined nonfatal CV events (nonfatal MACE/hACS/hHF) were approximately constant over time (Fig. 3*A* and *B*). The hazard for ACM following hypoglycemia, however, changed over time ($P < 0.001$), being greatest (approximately fivefold) soon after an SHE, decreasing over the first 2 years to about normal levels and increasing again after ~3 years post-SHE, although the numbers at risk beyond 3 years decreased and 95% CIs widened substantially (Fig. 3*C*). A similar pattern—albeit only of borderline significance—was seen with single time-dependent hazard plots for MACE and CV death after an SHE ($P = 0.031$ for MACE and 0.056 for CV death) (Supplementary Fig. 1) but not for hACS or hHF.

CONCLUSIONS

The primary objective of this work—to validate the hypothesis of a bidirectional relationship for an increased risk of CV events after SHEs as well as an increased risk of SHEs after CV events in patients with type 2 diabetes—was met. We found consistent evidence again confirming a greater risk of CV death, ACM, or hHF after SHEs, with also a substantially higher risk of SHEs after a nonfatal CV event such as nonfatal MI, stroke, hACS, or hHF. Moreover, we have demonstrated that the elevated hazards of combined CV events following SHEs and SHEs following combined nonfatal CV events were approximately constant over time, while the specific hazard for all-cause death—and to some extent also

Table 1—Baseline patient characteristics according to CV and SHEs occurring during the study

	No SHE during trial (N = 14,286)	SHE during trial (N = 466)	CV event before SHE during trial (N = 50)	SHE before CV event during trial (N = 66)*	Did not have SHE and CV event during trial (N = 14,636)
Age at randomization (years)	62 (56, 68)	63 (57, 70)	67 (59, 71)	65 (61, 70)	62 (56, 68)
Female sex	5,422 (38.0)	181 (38.8)	15 (30.0)	16 (24.2)	5,572 (38.1)
Race					
White	10,865 (76.1)	310 (66.5)	33 (66.0)	50 (75.8)	11,092 (75.8)
Black	832 (5.8)	46 (9.9)	6 (12.0)	5 (7.6)	867 (5.9)
Asian	1,402 (9.8)	50 (10.7)	4 (8.0)	6 (9.1)	1,442 (9.9)
Other	1,182 (8.3)	60 (12.9)	7 (14.0)	5 (7.6)	1,230 (8.4)
Duration of type 2 diabetes (years)	12 (7, 17)	14 (9, 22)	16 (11, 22)	17 (10, 24)	12 (7, 18)
History of CV disease					
Coronary artery disease	7,505 (52.5)	289 (62.0)	36 (72.0)	55 (83.3)	7,703 (52.6)
Cerebrovascular disease	2,419 (16.9)	90 (19.3)	11 (22.0)	23 (34.8)	2,475 (16.9)
Peripheral artery disease	2,712 (19.0)	88 (18.9)	13 (26.0)	12 (18.2)	2,775 (19.0)
CV event					
Prior CV event	10,421 (72.9)	361 (77.5)	43 (86.0)	64 (97.0)	10,675 (72.9)
CV disease without prior event	143 (1.0)	6 (1.3)	0 (0)	0 (0)	149 (1.0)
Neither prior CV event nor disease	3,722 (26.1)	99 (21.2)	7 (14.0)	2 (3.0)	3,812 (26.0)
Heart failure	2,291 (16.0)	98 (21.0)	16 (32.0)	27 (40.9)	2,346 (16.0)
Charlson Comorbidity Index	5 (4, 7)	6 (5, 8)	7 (5, 9)	8 (6, 9)	5 (4, 7)
Systolic blood pressure (mmHg)	135 (124, 145)	135 (125, 148)	136 (127, 145)	131 (120, 145)	135 (124, 145)
Diastolic blood pressure (mmHg)	80 (70, 85)	78 (70, 82)	77 (68, 82)	77 (65, 81)	80 (70, 85)
Heart rate (bpm)	72 (66, 80)	72 (65, 80)	74 (64, 80)	73 (66, 84)	72 (66, 80)
BMI (kg/m^2)	31.8 (28.3, 36.2)	31.6 (27.9, 36.5)	32.7 (29.7, 36.9)	33.3 (28.6, 37.5)	31.8 (28.2, 36.2)
HbA_{1c} (%)	8.0 (7.3, 8.9)	8.1 (7.5, 8.9)	8.6 (7.7, 9.4)	8.0 (7.3, 9.1)	8.0 (7.3, 8.9)
Total cholesterol (mg/dL)	166 (138, 201)	163 (137, 197)	164 (138, 200)	146 (123, 176)	166 (138, 201)
LDL (mg/dL)	88 (66, 116)	87 (65, 119)	80 (60, 104)	77 (62, 104)	88 (66, 116)
HDL (mg/dL)	42 (35, 50)	42 (35, 49)	42 (34, 49)	38 (32, 44)	42 (35, 50)
Triglycerides (mg/dL)	159 (114, 228)	163 (106, 230)	170 (106, 255)	162 (104, 222)	159 (114, 228)
eGFR (mL/min/1.73 m^2)	77 (61, 92)	70 (55, 86)	64 (54, 87)	61 (45, 80)	76 (61, 92)
≥90	4,172 (29.3)	96 (20.6)	11 (22.0)	9 (13.6)	4,248 (29.1)
60–89	7,027 (49.3)	219 (47.1)	19 (38.0)	27 (40.9)	7,200 (49.4)
30–59	3,027 (21.3)	150 (32.3)	20 (40.0)	30 (45.5)	3,127 (21.4)
<30	14 (0.1)	0 (0)	0 (0)	0 (0)	14 (0.1)
CV medications					
Aspirin	9,055 (63.4)	325 (69.7)	38 (76.0)	58 (87.9)	9,284 (63.4)
Thienopyridines	2,426 (17.0)	98 (21.0)	16 (32.0)	24 (36.4)	2,484 (17.0)
Any antiplatelets	10,472 (73.4)	363 (77.9)	45 (90.0)	60 (90.9)	10,730 (73.4)
ACEI or ARB	11,024 (77.2)	374 (80.3)	38 (76.0)	52 (78.8)	11,308 (77.3)
β-Blockers	7,933 (55.5)	278 (59.7)	36 (72.0)	49 (74.2)	8,126 (55.5)
Calcium channel blockers	4,550 (31.8)	160 (34.3)	14 (28.0)	28 (42.4)	4,668 (31.9)
Any antihypertensive	12,894 (90.3)	429 (92.1)	49 (98.0)	65 (98.5)	13,209 (90.3)
Statin	10,479 (73.4)	366 (78.5)	41 (82.0)	59 (89.4)	10,745 (73.4)
Any lipid-lowering medication	10,992 (76.9)	378 (81.1)	42 (84.0)	59 (89.4)	11,269 (77.0)
Diuretics	6,208 (43.5)	235 (50.4)	34 (68.0)	46 (69.7)	6,363 (43.5)

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Table 1—Continued

	No SHE during trial (N = 14,286)	SHE during trial (N = 466)	CV event before SHE during trial (N = 50)	SHE before CV event during trial (N = 66)*	Did not have SHE and CV event during trial (N = 14,636)
Diabetes medications					
Biguanide	10,982 (76.9)	313 (67.2)	29 (58.0)	39 (59.1)	11,227 (76.7)
Sulfonylurea	5,253 (36.8)	148 (31.8)	11 (22.0)	14 (21.2)	5,376 (36.7)
Insulin	6,509 (45.6)	327 (70.2)	40 (80.0)	52 (78.8)	6,744 (46.1)
Dose (units/kg body wt)	0.62 (0.39, 0.89)	0.73 (0.45, 1.07)	0.72 (0.43, 1.12)	0.87 (0.52, 1.19)	0.62 (0.39, 0.90)
DPP-4i	2,148 (15.0)	55 (11.8)	1 (2.0)	6 (9.1)	2,196 (15.0)
TZD	565 (4.0)	14 (3.0)	0 (0)	4 (6.1)	575 (3.9)
Other	610 (4.3)	14 (3.0)	0 (0)	3 (4.5)	621 (4.2)
Insulin/sulfonylurea/ NSS	11,005 (77.0)	435 (93.3)	48 (96.0)	63 (95.5)	11,329 (77.4)

Data are *n* (%) or median (25th, 75th percentile). ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; DPP-4i, dipeptidyl peptidase 4 inhibitor; NSS, nonsulfonylurea secretagogues; TZD, thiazolidinedione. *Four patients with CV event and SHE on the same day are included with the SHE before CV event group.

for CV death and MACE—following an SHE changed in a time-dependent way, with highest excess risk closest to the time the SHE occurred. Notably, those individuals at dual risk of SHEs and CV events—regardless of the time sequence—were characterized by much higher Charlson Comorbidity Index scores compared with those without.

These EXSCEL-derived results are more robust than those for TECOS (8), as the number of patients with concomitant SHEs and a CV event was ~70% larger. As with the TECOS results, but unlike most other reports regarding SHEs and CV events, these EXSCEL results were adjusted for all major predictors of CV outcomes in the trial including prior CV disease, heart failure, eGFR, duration of diabetes, insulin therapy at baseline, and new insulin use during the trial. Also, the plots of time-dependent HRs were done with full adjustment. Nevertheless, the finding of a two- to threefold increased risk for SHEs after nonfatal CV events persisted and remained approximately constant over time, while the

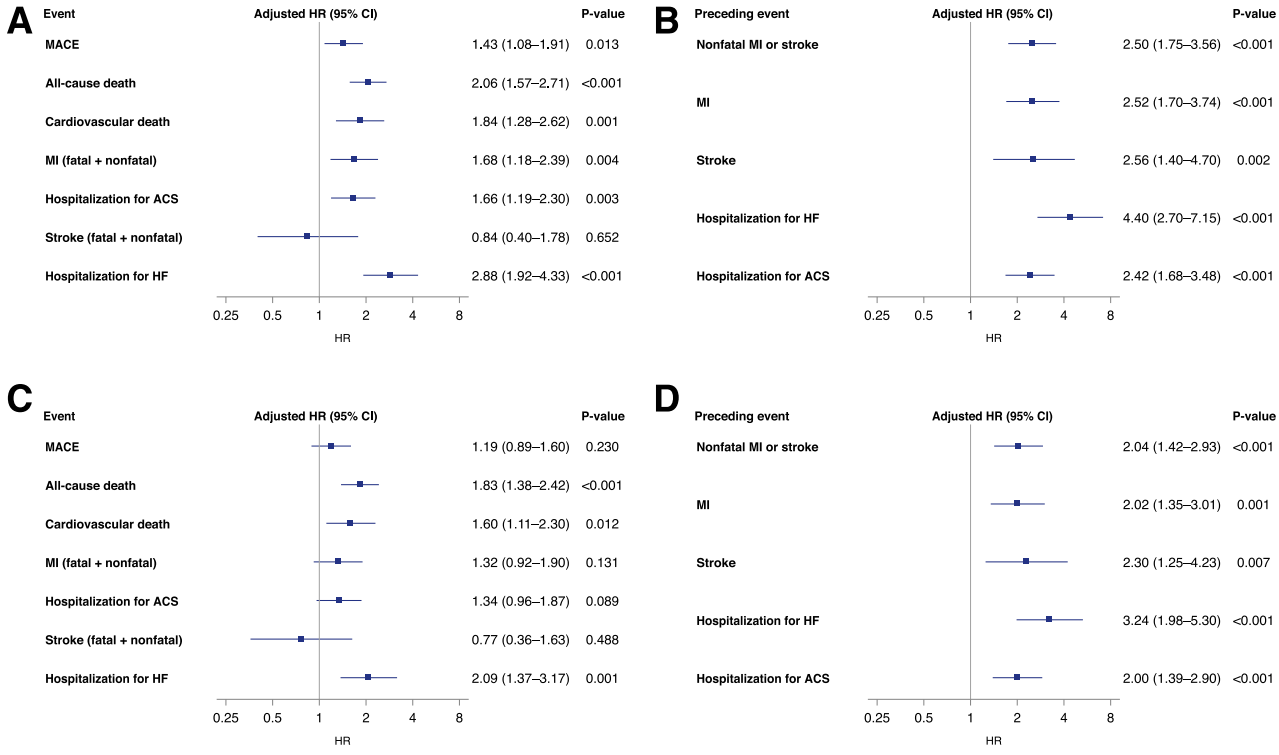
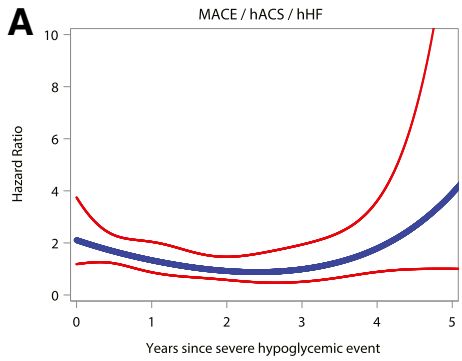
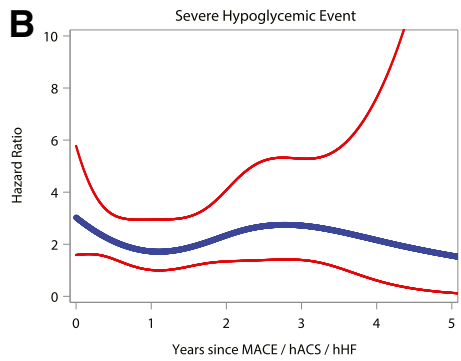


Figure 2—Forest plots showing the association of SHEs and subsequent risk of CV outcomes (*A* and *C*) and nonfatal CV events and subsequent risk of SHEs (*B* and *D*). Models for *A* and *B* were adjusted for clinical factors (randomized treatment, age, sex, ethnicity, weight, and smoking), whereas models for *C* and *D* were fully adjusted for age, sex, ethnicity, HbA_{1c} level, New York Heart Association class, current smoking, history of MI, coronary artery disease, stroke, stenosis of carotid artery, atrial fibrillation, chronic obstructive pulmonary disease, amputation, diabetic neuropathy, foot ulcers, baseline insulin therapy, systolic blood pressure, diastolic blood pressure, heart rate, height, BMI, eGFR, diabetes duration, randomized treatment, and insulin use as a time-dependent variable. Models for panel *D* were additionally adjusted for baseline β-blockers and baseline sulfonylurea. ACS, acute coronary syndrome; HF, heart failure.



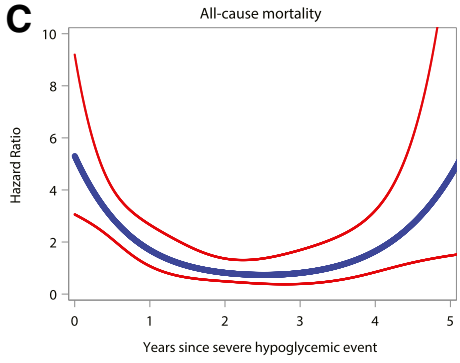
P=0.12

Year following SHE	Number at risk	Events in last 6 months
0.0	403	-
0.5	330	22
1.0	277	13
1.5	234	7
2.0	182	8
2.5	145	3
3.0	107	1
3.5	78	2
4.0	40	4
4.5	22	1
5.0	6	0
5.5	3	1



P=0.67

Year following SHE	Number at risk	Events in last 6 months
0.0	1599	-
0.5	1294	18
1.0	1069	8
1.5	820	6
2.0	603	6
2.5	442	6
3.0	319	2
3.5	206	1
4.0	116	2
4.5	54	0
5.0	20	1
5.5	4	0



P<0.0001

Year following SHE	Number at risk	Events in last 6 months
0.0	452	-
0.5	381	23
1.0	335	6
1.5	287	9
2.0	235	5
2.5	192	1
3.0	141	2
3.5	106	0
4.0	61	5
4.5	35	2
5.0	13	2
5.5	7	0

Figure 3—Time-dependent HR plots with 95% CIs and numbers at risk for combined CV events (MACE/hACS/hHF). *A*: Occurring after an SHE. *B*: For an SHE after a nonfatal CV event (MACE/hACS/hHF). *C*: For all-cause death after an SHE. *P* values for the test of constant HR over time are provided.

increased risk of 60% for CV death and ~80% for all-cause death after an SHE is quite comparable with other publications including the finding of these hazards being most frequent close to an SHE (3,4,6,7,9,20,21). The significant association of hHF in both directions with SHEs is another interesting new observation. Importantly, assigned treatment with EQW was not associated with different rates of SHEs between randomized study groups.

Although associations found in epidemiologic patient cohorts are not able to prove a causal relationship between the

parameters studied, the bidirectional relationship between SHEs and CV outcomes, together with a higher Charlson Comorbidity Index of ~8 in those at dual risk of SHEs and CV events, suggests that there may be a common type 2 diabetes phenotype of patients with multiple comorbidities and likely features of "frailty" who are susceptible to both of these events. Thus, SHEs in many, if not most, instances—rather than being causative of CV death, hHF, or all-cause death events—may simply be indicative of multimorbid or "frail" patients who are at higher risk of both outcomes likely due to a large accumulation of coexisting risk factors. That there were four patients in EXSCEL with same-day events does not seem to exclude or confirm a causal role of SHEs for CV outcomes.

These observations of EXSCEL data also shed light on the emerging characteristics of this patient phenotype at dual risk for SHEs and CV events. Compared with those without this dual risk, patients are considerably older, have a 4-year-longer duration of diabetes, and are more likely (80% vs. 37%) to be insulin treated (and with a higher dose) at study entry, with a further increase of insulin users within the trial. Almost all had a prior CV event either at study baseline preceding the first SHE in the study or occurring before an SHE during the study. Some 43% had chronic kidney disease stage 3 at study entry, and more than one-third had a history of heart failure, with all these factors adding up to increased SHE risk and risk of fatal and nonfatal CV events, hHF events, and ACM. The high comorbidity score for these patients, as evidenced by a high Charlson Comorbidity Index, seems also to be reflected by their much greater use of CV medications, especially of antiplatelet therapies, β-blockers, diuretics, and statins. Of note, baseline HbA_{1c} concentrations of these patients did not differ from those without dual risk or even showed a trend to higher levels.

These characteristics of an emerging "vulnerable" phenotype at dual risk for SHEs and CV events are mirrored by the recently studied populations at dual SHE and CV event risk in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE), as well as in TECOS and the Veterans Affairs Diabetes Trial (VADT) (7–9,20). Epidemiological observations from the Hong Kong Diabetes Registry also seem to support the novel concept of the existence of such a particularly frail or vulnerable patient phenotype (22,23). Remarkably, a recent publication from the Atherosclerosis Risk in Communities (ARIC) cohort study group looking at severe hypoglycemia, mild cognitive impairment, dementia, and brain volumes in older adults with type 2 diabetes described a very similar at-risk patient phenotype with longer diabetes duration, older age, and more common insulin use (24). Finally, the characteristics of a vulnerable patient phenotype at dual risk for SHEs and CV events seemingly resemble a recently suggested "renal" subphenotype cluster of adult-onset diabetes (25).

Mechanistically, SHEs have been associated with hypokalemia, prolongation of the QTc interval on electrocardiogram, and neuro-sympathetic overdrive with marked increase of blood pressure, tachycardia, and various kinds of arrhythmias (18,26–29). Moreover, SHEs activate prothrombotic and proinflammatory pathways, factors that all add up to a theoretical increased CV risk (21,30–33). Our results are compatible with the notion that these pathophysiological mechanisms may have been critical to some individual patients—perhaps even beyond the CV context—especially when considering the segment section closest to the SHE of the time relationship with all-cause death and, to a lesser extent, with CV death. Alternatively, the close time association between an SHE and non-CV death in some patients may just indicate excessive comorbidities in those. In this context, the example of the four patients with same-day dual SHEs and CV events shows the complexity and diversity of such a potential interaction. Furthermore, in others, an SHE had occurred long before a CV event, rendering a causative role of SHEs for CV events in these patients rather unlikely. The gradual recurrence of an increased risk for ACM beyond 3 years after an SHE—although with numbers at risk declining, which limits any firm conclusions—was an unexpected finding potentially alluding to a persisting high comorbidity score that should be further explored.

In terms of SHEs occurring after a CV event including hHF, brain natriuretic peptides may play an important role, as they—among many other effects—activate insulin-sensitizing mechanisms at the level of skeletal muscle and adipose tissue and increase circulating concentrations of the insulin-sensitizing hormone adiponectin (34,35). An augmenting effect of atrial natriuretic peptide on insulin-induced hypoglycemia has long been known (36). The strongest associations seen in our analyses were between hHF and SHEs in both settings of SHEs, before and after a CV event. History of known heart failure at baseline was rather frequent at baseline in both groups with dual SHE and CV events (32% and 41%, respectively). Potentially, a similarly high proportion of patients with heart failure go unrecognized in most CVOTs focusing on patients with established CV disease unless natriuretic peptide levels are measured (37). Heart failure patients with the highest levels of both natriuretic peptides and adiponectin have been found to have the highest mortality risk (38). In this context, continued use of insulin in those patients may be questioned.

Strengths of our study include the size and length of follow-up with proactive collection and independent, blinded adjudication of all relevant events in the context of a CVOT. The number of patients with dual SHEs and CV events ($n = 116$) is to our knowledge the largest reported from a CVOT thus far. Moreover, our results appear to be particularly robust because of adjustment for a rather comprehensive list of potential confounders. Though an evaluation of an a priori hypothesis, study weaknesses include the post hoc nature of the analysis and the lack of available biomarkers such as measurements of natriuretic peptides to further substantiate potential pathogenic links. Moreover, whether less severe hypoglycemic episodes also might have impacted the results could not be evaluated, as they were not systematically evaluated in the pragmatic EXSCEL trial. This seems, however, rather unlikely in light of neutral findings related to less severe hypoglycemia in studies such as the Outcome Reduction With Initial Glargine Intervention (ORIGIN) or LEADER trials (6,9). Nevertheless, residual confounding cannot be excluded. Finally, a formal assessment of frailty was not included in the EXSCEL study protocol.

In summary, we report a robust bidirectional association in EXSCEL participants confirming a greater risk of SHEs after CV events as well as a greater risk of CV or all-cause death events after SHEs. These findings support our view of an existing common at-risk polymorbid and potentially frail type 2 diabetes patient phenotype, susceptible to both SHEs and CV events. These vulnerable patients with high comorbidity scores after a first CV event in conjunction with heart failure, advanced kidney disease, older age, longer duration of diabetes, and tendency to be on insulin and on higher doses warrant special consideration, including careful dosing of insulin therapy.

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