Increased Risk of Severe Hypoglycemic Events Before and After Cardiovascular Outcomes in TECOS Suggests an At-Risk Type 2 Diabetes Frail Patient Phenotype

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OBJECTIVE

Severe hypoglycemic events (SHEs) in type 2 diabetes are associated with subsequent cardiovascular (CV) event risk. We examined whether CV events were associated with subsequent SHE risk.

RESEARCH DESIGN AND METHODS

Time-dependent associations between SHEs and a composite CV end point (fatal/nonfatal myocardial infarction or stroke, hospitalization for unstable angina, hospitalization for heart failure [hHF]) were examined post hoc in 14,671 TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) participants with type 2 diabetes and CV disease followed for a median of 3.0 years.

RESULTS

SHEs were uncommon and unassociated with sitagliptin therapy (N = 160 [2.2%], 0.78/100 patient-years vs. N = 143 [1.9%], 0.70/100 patient-years for placebo; hazard ratio [HR] 1.12 [95% CI 0.89, 1.40], P = 0.33). Patients with (versus without) SHEs were older with longer diabetes duration, lower body weight, and lower estimated glomerular filtration rate; were more frequently women, nonwhite, and insulin treated; and more often had microalbuminuria or macroalbuminuria. Analyses adjusted for clinical factors showed SHEs were associated with increased risk of the primary composite CV end point (1.55 [1.06, 2.28], P = 0.025), all-cause death (1.83 [1.22, 2.75], P = 0.004), and CV death (1.72 [1.02, 2.87], P = 0.040). Conversely, nonfatal myocardial infarction (3.02 [1.83, 4.96], P < 0.001), nonfatal stroke (2.77 [1.36, 5.63], P = 0.005), and hHF (3.68 [2.13, 6.36], P < 0.001) were associated with increased risk of SHEs. Fully adjusted models showed no association between SHEs and subsequent CV or hHF events, but the association between CV events and subsequent SHEs remained robust.

CONCLUSIONS

These findings, showing greater risk of SHEs after CV events and greater risk of CV events after SHEs, suggest a common at-risk type 2 diabetes frail patient phenotype.

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Post hoc analyses of several large-scale, long-term randomized cardiovascular (CV) outcome trials evaluating glucose-lowering drugs or strategies have identified an association between hypoglycemia and a subsequent increased risk of all-cause mortality or CV mortality in people with type 2 diabetes, as shown in Supplementary Table 1 (1–5). This is particularly the case for patients experiencing severe hypoglycemic events (SHEs), with typically close to twice the risk of CV death in those who have experienced an SHE compared with those who have not. As a result, many diabetes management guidelines have been modified to advocate less aggressive glycemic targets to reduce the incidence of SHEs in the belief that this will minimize mortality risk (6,7), although less strict glycemic targets have not been shown to reduce the risk of SHEs (8). However, it remains unclear whether SHEs have a causal role in increasing CV mortality rates and whether more cautious glycemic targets, which may increase the risk of microvascular disease in the longer term (9), are warranted.

We conducted post hoc analyses of the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) (10) to better elucidate the interrelationship between SHEs and CV events. In TECOS, a wide range of CV outcomes were collected assiduously and adjudicated, along with prospective recording of SHEs as an adverse outcome of special interest in 14,671 participants with type 2 diabetes and CV disease followed for a median of 3.0 years.

RESEARCH DESIGN AND METHODS

Study Design and Participants

TECOS was a multinational, double-blind, placebo-controlled, randomized, event-driven trial designed to assess the CV safety of sitagliptin versus placebo when added to usual care in patients with type 2 diabetes and established CV disease, as reported previously (10). It was designed and 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, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. The database was held at and verified independently by the DCRI. The protocol was approved by the ethics committees associated with all TECOS sites, and all participants provided written informed consent for trial participation.

Eligible patients had type 2 diabetes and preexisting coronary, cerebrovascular, or peripheral atherosclerotic vascular disease, were ≥50 years of age, and had a baseline glycated hemoglobin (HbA_{1c}) of 48–64 mmol/mol (6.5–8.0%) on stable antihyperglycemic medication, i.e., monotherapy or dual-combination therapy with metformin, pioglitazone, or sulfonylurea, or insulin with or without metformin. Trial exclusions included use of a dipeptidyl peptidase 4 inhibitor, glucagon-like peptide 1 receptor agonist, or rosiglitazone during the preceding 3 months; ≥2 SHEs in the previous 12 months; or estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 at baseline. Patients with previous heart failure were not excluded.

Randomization and Study Medication

Participants were assigned randomly 1:1 to treatment with sitagliptin 100 mg daily (50 mg daily if baseline eGFR was ≥30 and <50 mL/min/1.73 m^2) or matching placebo, with predefined dose adjustments throughout the trial based on eGFR levels. HbA_{1c} was measured locally at enrollment, at 4 and 8 months, and then annually. Open-label addition and/or titration of antihyperglycemic medication (other than a dipeptidyl peptidase 4 inhibitor or glucagon-like peptide 1 receptor agonist) was encouraged throughout the trial, targeting HbA_{1c} levels in accord with regional standards of care and individualized treatment goals.

SHEs

At screening/enrollment, 4- and 8-month visits, and then annual visits, the symptoms and appropriate management of hypoglycemia were reviewed proactively with participants. All SHEs were recorded systematically as prespecified events of clinical interest. They 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 participant 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. Patients who had ≥2 SHEs between study visits, despite adjustment of open-label glucose-lowering agents, were required to discontinue study medication.

Clinical Outcomes

The TECOS primary 4-point composite major adverse cardiovascular event (MACE) was defined as the first confirmed event of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for unstable angina. Other TECOS secondary outcomes included 3-point MACE (CV death, nonfatal MI, or nonfatal stroke), fatal/nonfatal MI, fatal/nonfatal stroke, all-cause death, and hospitalization for heart failure (hHF). All of these events were adjudicated by an independent clinical events classification committee, whose members were unaware of study group assignments. Additional prespecified exploratory outcomes included changes in HbA_{1c} and eGFR levels, initiation of additional glucose-lowering agents or long-term insulin therapy, and frequency of SHEs.

Statistical Analysis

Categorical variables are presented as number and percentage, and continuous variables are presented as median (interquartile range). Time to first SHE is shown with Kaplan-Meier plots, with study treatment differences tested using Cox proportional hazards regression models stratified by region. Treatment effects for sitagliptin 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.

To investigate the association between SHEs and subsequent CV or mortality outcomes, Cox regression models were fitted with SHE as a time-dependent variable. Models were repeated with partial adjustment for selected clinical factors (age, sex, race, smoking, and weight) and with full adjustment. Covariates were chosen for inclusion in the full adjustment model if they were selected for the 3-point MACE end point using Cox models with backward elimination, with $\alpha = 0.05$ required for retention. Because common risk factors often underlie multiple conditions, it is reasonable to assume that modeling a composite end point would select the major confounders. Significant variables were age, sex, race, ethnicity, HbA_{1c}, New York Heart Association class, smoking, MI, chronic obstructive pulmonary disease, coronary artery disease, stroke, ≥50% stenosis of carotid artery, atrial fibrillation or flutter, insulin therapy, amputation, diabetic neuropathy, foot ulcer, blood pressure, heart rate, height, BMI, and eGFR. Randomized treatment and diabetes

Table 1—Baseline characteristics for participants with and without SHEs (intention-to-treat population)

	With SHEs (*N* = 303)	Without SHEs (*N* = 14,368)
Age at randomization, years*	67 (62, 73)	65 (60, 71)
<65	109 (36.6)	6,507 (46.3)
≥65	189 (63.4)	7,546 (53.7)
<70	176 (59.1)	9,666 (68.8)
≥70	122 (40.9)	4,387 (31.2)
Sex		
Male	193 (63.7)	10,181 (70.9)
Female	110 (36.3)	4,187 (29.1)
Race		
White	176 (58.1)	9,781 (68.1)
Black	21 (6.9)	426 (3.0)
Asian	74 (24.4)	3,191 (22.2)
Other	32 (10.6)	970 (6.8)
Duration of type 2 diabetes, years†	14 (8, 22)	10 (5, 16)
Duration of type 2 diabetes ≥15 years	146 (48.2)	4,144 (28.9)
Diabetes therapy at baseline (alone or in combination)		
Sulfonylurea	140 (46.2)	6,505 (45.3)
Metformin	226 (74.6)	11,740 (81.7)
Thiazolidinedione (includes pioglitazone)	8 (2.6)	388 (2.7)
Insulin	129 (42.6)	3,279 (22.8)
Not on sulfonylurea or insulin	40 (13.2)	4,679 (32.6)
Preexisting vascular disease	302 (99.7)	14,288 (99.4)
Previous MI	118 (38.9)	6,137 (42.7)
Previous congestive heart failure	54 (17.8)	2,589 (18.0)
Current smoking	25 (8.3)	1,653 (11.5)
Qualifying HbA_{1c}		
mmol/mol	56 (52, 61)	55 (51, 60)
%	7.3 (6.9, 7.7)	7.2 (6.8, 7.6)
Qualifying HbA_{1c} categories, %		
<7	87 (28.7)	4,895 (34.1)
≥7 to <7.5	97 (32.0)	4,410 (30.7)
≥7.5	119 (39.3)	5,058 (35.2)
eGFR, mL/min/1.73 m^2	64.0 (52.0, 82.3)	73.0 (60.0, 88.0)
eGFR categories, mL/min/1.73 m^2‡		
≥60	189 (63.0)	11,015 (77.4)
<60	111 (37.0)	3,213 (22.6)
UACR categories, g/mol§		
Normoalbuminuria, <30	73 (56.2)	3,605 (71.8)
Microalbuminuria, ≥30 to <300	46 (35.4)	1,173 (23.4)
Macroalbuminuria, ≥300	11 (8.5)	240 (4.8)
Blood pressure, mmHg		
Systolic	134 (125, 149)	134 (124, 145)
Diastolic	75 (67, 82)	79 (70, 84)
BMI categories, kg/m^2		
<25	55 (18.3)	2,348 (16.5)
≥25 to <30	121 (40.2)	5,211 (36.6)
≥30 to <35	76 (25.2)	4,174 (29.3)
≥35	49 (16.3)	2,500 (17.6)
Weight, kg	79.8 (69.0, 92.5)	83.0 (71.7, 97.0)
Medications taken at time of randomization		
Statins	257 (84.8)	11,462 (79.8)
ACE inhibitors or ARBs	241 (79.5)	11,314 (78.7)
Diuretics	144 (47.5)	5,876 (40.9)
Calcium channel blockers	109 (36.0)	4,852 (33.8)
β-Blockers	194 (64.0)	9,128 (63.5)
Aspirin	245 (80.9)	11,273 (78.5)
Other platelet antagonists	77 (25.4)	3,110 (21.6)

Data are *n* (%) or median (Q1, Q3). UACR, urine albumin-to-creatinine ratio. *Age is missing among patients enrolled in Lithuania because the entire birth date including year was not available. †Duration = (year of randomization – year of diagnosis) + 1. ‡MDRD formula was used to calculate the eGFR. Site-reported values are presented in the table. §Available for 130 patients with SHEs and 5,018 without SHEs.

duration were included due to clinical relevance, and region was included as a strata variable for consistency with the TECOS primary results article (10). For the continuous variables, the linearity assumption of Cox proportional hazards regression models was checked for all end points. 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, and no major violations were identified. Multiple imputation by the fully conditional specification method with regression was used, via SAS PROC MI (SAS Institute, Inc., Cary, NC), to create 25 imputed data sets of baseline characteristics. No more than 3% of data were missing for any particular variable, so for simplicity only the first imputed data set was used in modeling.

Models used only the first SHE per patient and assumed that there were no time-dependent covariates 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. Similar models were fitted to investigate the association between nonfatal CV outcomes and subsequent SHEs. All models included randomized treatment and were stratified by region. Data were analyzed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC) with P values <0.05 considered statistically significant.

RESULTS

The TECOS intention-to-treat population consisted of 14,671 participants with a median follow-up of 3.0 years (interquartile range 2.3, 3.8; maximum 5.7). Of participants allocated to sitagliptin and placebo, 95.1% and 94.1%, respectively, completed the study, with premature discontinuation of study medication in 26.1% and 27.5%, respectively. Vital status was available for 97.5% of participants at study end.

SHEs were uncommon, with 303 (2.1%) TECOS participants reporting one or more (10). Table 1 lists the baseline characteristics of those with and without SHEs during the trial. Participants with SHEs, compared with those without, tended to be older with longer mean duration of diabetes, lower mean body weight, and lower mean eGFR. They were also more frequently women,

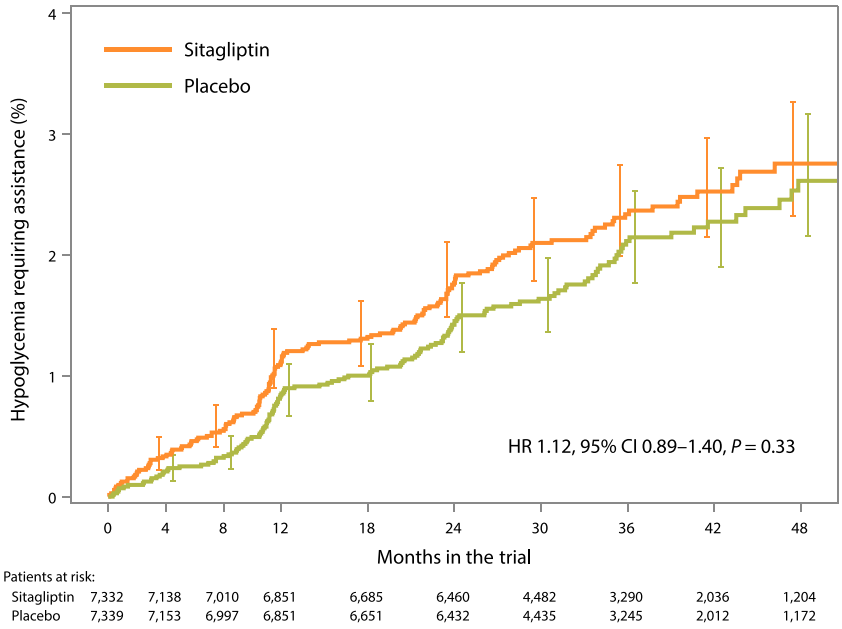

Figure 1—Kaplan-Meier plot of time to first SHE for sitagliptin- and placebo-assigned participants (intention-to-treat population).

nonwhite, and on insulin treatment and more often had microalbuminuria or macroalbuminuria. Rates of reported previous MI and congestive heart failure were similar between the two groups, but participants with SHEs were more often being treated with diuretics, statins, and antithrombotic agents.

The incidence of SHEs did not differ between those assigned to the sitagliptin (*N* = 160 [2.2%], 0.78 per 100 patient-years) or placebo (*N* = 143 [1.9%], 0.70 per 100 patient-years) groups (HR 1.12 [95% CI 0.89, 1.40], *P* = 0.33), as shown in Fig. 1. SHE rates were higher in the first year than in the second and third years in both groups (Fig. 1). Only one patient per treatment arm discontinued study drug due to two SHEs occurring between study visits. Of the 303 participants with SHEs, 68 (22.4%) also had a 4-point MACE or hHF event. They tended to be older with higher mean body weight and lower mean eGFR and were more often on insulin therapy or more likely to have had an MI or heart failure with more prevalent use of β-blockers, diuretics, and statins at baseline (Supplementary Table 2).

Of these 68 participants with SHEs and a 4-point MACE or hHF event, 34 had an SHE with a subsequent MACE or hHF event, 38 had a 4-point MACE or hHF event with a subsequent SHE, and 7 had an SHE both before and after a 4-point MACE or hHF event. In three cases, participants had a single SHE and a 4-point MACE or hHF event on the same day, so which event developed first could not be determined.

Association Between SHEs and Subsequent CV or hHF Events or Death

In unadjusted analyses (Fig. 2*A*), SHEs were associated with a subsequent 4-point MACE (HR 1.57 [95% CI 1.07, 2.31], *P* = 0.020), all-cause death (1.91 [1.27, 2.88], *P* = 0.002), and CV death (1.81 [1.08, 3.02], *P* = 0.024). There was also a significant association with a subsequent 3-point MACE.

After adjustment for selected clinical (demographic) factors (Fig. 2*B*), all of these associations remained statistically significant: 4-point MACE (HR 1.55 [95% CI 1.06, 2.28], *P* = 0.025), all-cause death (1.83 [1.22, 2.75], *P* = 0.004), and CV death (1.72 [1.02, 2.87], *P* = 0.040). However, these associations all became nonsignificant after further adjustment for baseline variables that were significantly associated with CV events (Fig. 2*C*). No associations were seen between SHEs and a subsequent fatal/nonfatal MI, hospitalization for unstable angina, fatal/nonfatal stroke, or hHF in any of the models.

Association Between Nonfatal CV or hHF Events and Subsequent SHEs

In unadjusted analyses (Fig. 3*A*), SHEs were associated with a previous nonfatal MI, hospitalization for unstable angina, or nonfatal stroke (HR 2.46 [95% CI 1.63, 3.70], $P < 0.001$), nonfatal MI (2.99 [1.82, 4.90], $P < 0.001$), nonfatal stroke (2.75 [1.35, 5.57], *P* = 0.005), and hHF (3.90 [2.27, 6.70], $P < 0.001$).

After adjustment for clinical factors (Fig. 3*B*), all of these associations remained statistically significant: nonfatal CV event or hospitalization for unstable angina (2.48 [1.65, 3.75], $P < 0.001$), nonfatal MI (3.02 [1.83, 4.96], $P < 0.001$), nonfatal stroke (2.77 [1.36, 5.63], *P* = 0.005), and hHF (3.68 [2.13, 6.36], $P < 0.001$).

These associations remained statistically significant after further adjustment for the wider range of baseline variables (Fig. 3*C*): nonfatal CV event or hospitalization for unstable angina (1.96 [1.29, 2.98], *P* = 0.001), nonfatal MI (2.31 [1.39, 3.82], *P* = 0.001), nonfatal stroke (2.07 [1.01, 4.23], *P* = 0.046), and hHF (2.26 [1.28, 3.99], *P* = 0.005).

CONCLUSIONS

Our post hoc analysis of TECOS data found a relatively low rate of SHEs among participants with type 2 diabetes and established CV disease, with no increased SHE risk in those randomized to sitagliptin. A novel finding was a robust association between SHEs and previous major CV events, with a near doubling in the risk of an SHE following a nonfatal CV or hHF event, even after full statistical adjustment. The bidirectional relationship between SHEs and CV outcomes suggests that there may be a common "frail" type 2 diabetes phenotype of patients who are susceptible to both of these events. Thus SHEs, rather than being causative of MACE, hHF, or all-cause death events, may simply be indicative of patients with a frail type 2 diabetes phenotype who are at high risk of both outcomes likely due to a multitude of coexisting risk factors.

Post hoc analyses of other large-scale CV outcome trials have also reported associations between SHEs and subsequent CV events, primarily related to fatal outcomes (1–3,5). The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study observed an association of SHEs with MACE that became nonsignificant when considering the time sequence of SHE and MACE (Supplementary Table 1) (11). The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial found

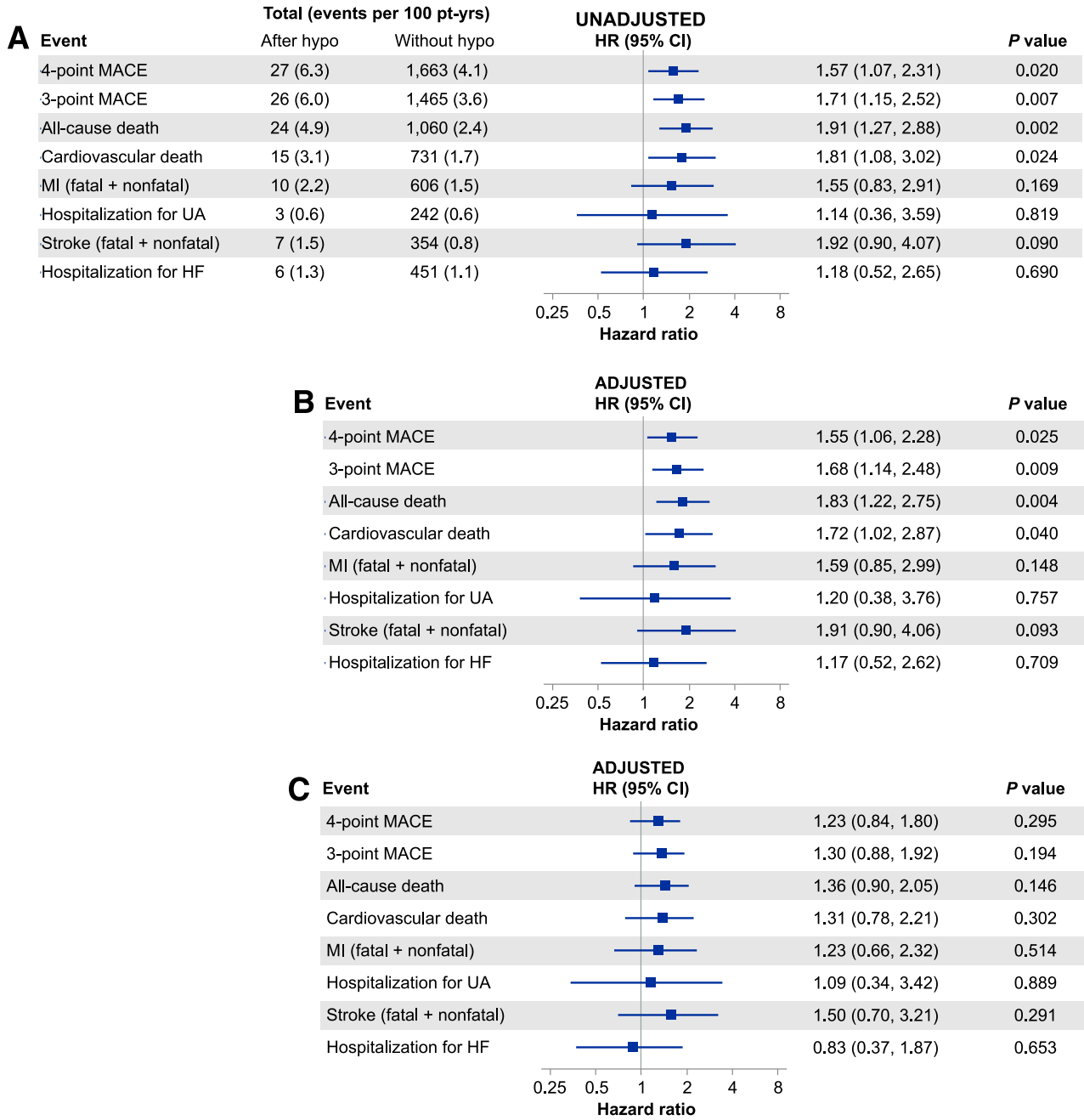

Figure 2—Association between SHEs and subsequent risk of CV events or death. *A*: Unadjusted. *B*: Adjusted for clinical factors (randomized treatment, age, sex, race, weight, and smoking). *C*: Full adjustment. HF, heart failure; UA, unstable angina; pt-years, patient-years.

an association of SHEs with CV death but not with MI (12). These findings to some extent may be consistent with the results in TECOS, but the time-dependent aspects remain presently unclear.

Considerable efforts have been made to provide biologically plausible mechanisms whereby SHEs might indicate higher risks of CV events and mortality. Severe hypoglycemia is known to induce a wide range of potentially adverse effects in the vasculature and the heart, such as neurosympathetic overdrive with the risk of arrhythmias, activation of proinflammatory and prothrombotic pathways, and endothelial dysfunction (13–18). In this context, a link of SHEs with fatal CV and all-cause death outcomes may seem reasonable; however CV outcome trials are not designed to elucidate pathophysiologic mechanisms, and the link between SHEs and MACE or hHF outcomes may be quite complex. Our results suggest that the association seems to be bidirectional, with a common frail phenotype explaining the susceptibility to both SHEs and worse clinical outcomes.

In TECOS, baseline characteristics for participants who suffered within-study SHEs suggested that they did indeed differ from those without SHEs, being older, more likely to be insulin treated, women, and nonwhite, and with a longer diabetes duration, lower eGFR, and lower weight. These observations are in accord with published information from other CV outcome trials. Of note, previous history of

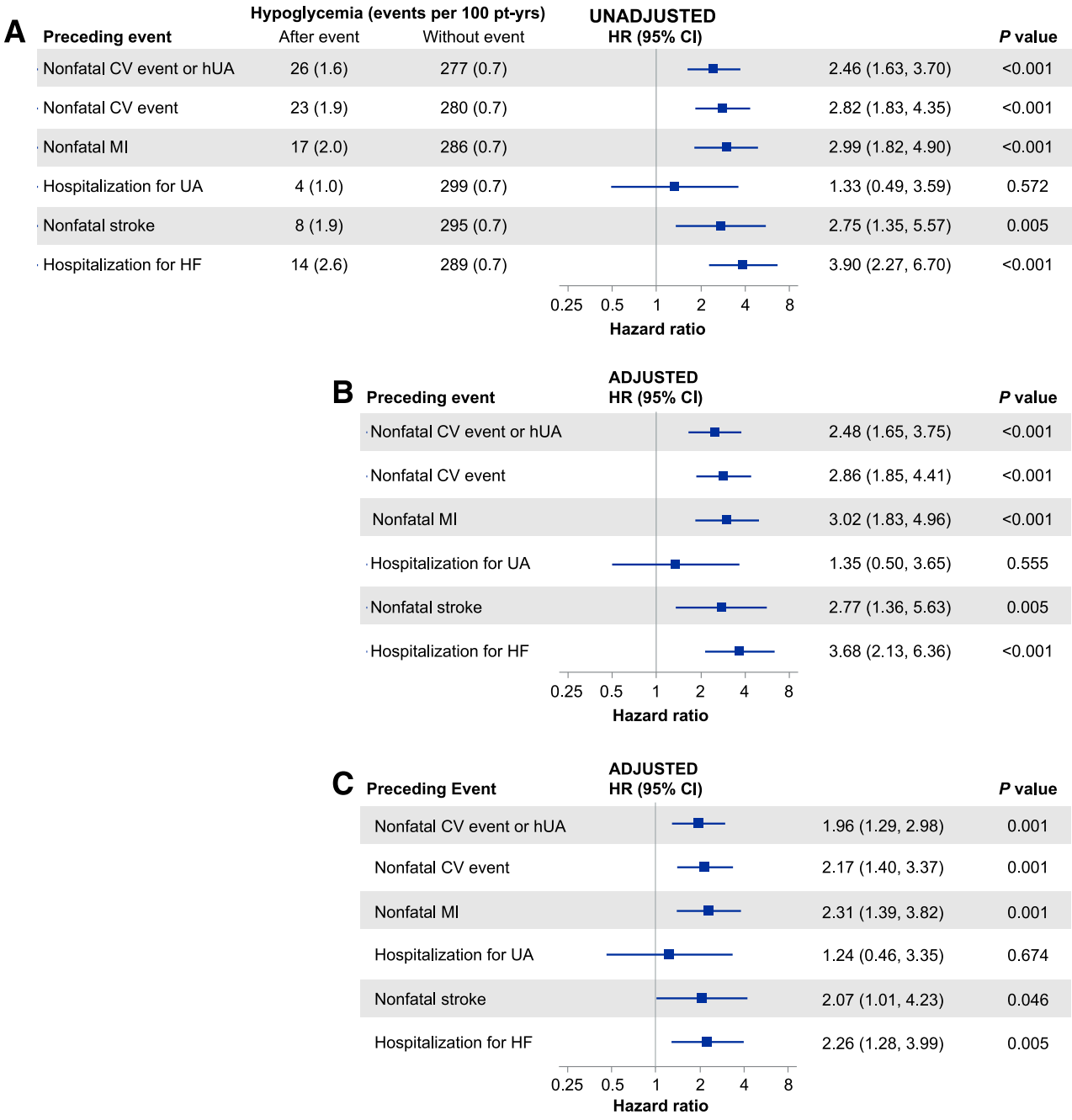

Figure 3—Association between nonfatal CV events or hospitalization for unstable angina (hUA) or hospitalization for heart failure (HF) and subsequent SHEs. *A*: Unadjusted. *B*: Adjusted for clinical factors (randomized treatment, age, sex, race, weight, and smoking). *C*: Full adjustment.

CV disease or heart failure was not related to SHEs, nor was the use of β-blockers, ACE inhibitors, or angiotensin II receptor blockers (ARBs) at baseline—factors that could have influenced the occurrence of SHEs in light of the present findings or earlier publications (13–20). Given that established CV disease was an inclusion criterion for enrollment in TECOS, it is not unreasonable to see no differences. Among the 303 patients with SHEs in TECOS, however, those with CV events and hHF versus those without did show higher baseline rates of previous MI and HF, more frequent use of diuretics, β-blockers, statins, ACE inhibitors or ARBs, and insulin together with a lower eGFR (Supplementary Table 2), again alluding to a common particularly frail type 2 diabetes phenotype of patients susceptible to both SHEs and CV events or hHF events. Epidemiologic observations from the Hong Kong Diabetes Registry seem to support this novel concept (21,22).

Strengths of our study include its size and length of follow-up, adjudication of all relevant events, and that SHEs were captured proactively by a structured process. Weaknesses include its post hoc nature, with any findings from this subgroup identified in postrandomization data being no more than hypothesis generating, as well as the low SHE rates and the lack of biomarkers that could provide greater mechanistic insights. There could also be possible confounding from changes in therapy

following SHEs, MACE, or hHF events, e.g., switch to insulin from oral agents, that could impact future risk of SHEs and/or CV events.

In conclusion, while it remains important to seek to minimize the risk of SHEs in people with type 2 diabetes, the focus on attaining good glycemic control to minimize the risk of diabetes complications should not be unduly compromised. A precision medicine approach is required to delineate those with a frail phenotype who need special consideration from those likely to benefit from more aggressive glycemic targets.

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All analyses were performed by DCRI and the University of Oxford Diabetes Trials Unit independent of the sponsor. The authors are solely responsible for the design and conduct of this study, all analyses, the drafting and editing of the manuscript, and its final contents. All authors agreed to submit the report for publication, and the funder had no role in this decision.

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Author Contributions. E.S. contributed to the study design and data analysis and interpretation and drafted and edited the manuscript. S.R.S. performed the statistical analysis and edited the manuscript. P.W.A., J.B.B., J.C.N.C., J.B.G., J.M.L., A.S., F.T., F.V.d.W., and E.D.P. edited the manuscript. R.R.H. contributed to the study design and data analysis and interpretation and edited the manuscript. All authors reviewed and approved the final submitted report. E.S. and R.R.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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