Hypoglycemia and Incident Cognitive Dysfunction: A Post Hoc Analysis From the ORIGIN Trial

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OBJECTIVE

Epidemiological studies have reported a relationship between severe hypoglycemia, cognitive dysfunction, and dementia in middle-aged and older people with type 2 diabetes. However, whether severe or nonsevere hypoglycemia precedes cognitive dysfunction is unclear. Thus, the aim of this study was to analyze the relationship between hypoglycemia and incident cognitive dysfunction in a group of carefully followed patients using prospectively collected data in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial.

RESEARCH DESIGN AND METHODS

This prospective cohort analysis of data from a randomized controlled trial included individuals with dysglycemia who had additional cardiovascular risk factors and a Mini-Mental State Examination (MMSE) score ≥24 (*N* = 11,495). Severe and nonsevere hypoglycemic events were collected prospectively during a median follow-up time of 6.2 years. Incident cognitive dysfunction was defined as either reported dementia or an MMSE score of <24. The hazard of at least one episode of severe or nonsevere hypoglycemia for incident cognitive dysfunction (i.e., the dependent variable) from the time of randomization was estimated using a Cox proportional hazards model after adjusting for baseline cardiovascular disease, diabetes status, treatment allocation, and a propensity score for either form of hypoglycemia.

RESULTS

This analysis did not demonstrate an association between severe hypoglycemia and incident cognitive impairment either before (hazard ratio [HR] 1.16; 95% CI 0.89, 1.52) or after (HR 1.00; 95% CI 0.76, 1.31) adjusting for the severe hypoglycemia propensities. Conversely, nonsevere hypoglycemia was inversely related to incident cognitive impairment both before (HR 0.59; 95% CI 0.52, 0.68) and after (HR 0.58; 95% CI 0.51, 0.67) adjustment.

CONCLUSIONS

Hypoglycemia did not increase the risk of incident cognitive dysfunction in 11,495 middle-aged individuals with dysglycemia.

Epidemiological studies have reported that recurrent severe hypoglycemia is associated with dementia and cognitive dysfunction in middle-aged and older people with type 2 diabetes (1–3). Explanations for this relationship include the possibility that *1*) recurrent episodes of hypoglycemia cause and/or accelerate cognitive dysfunction, *2*) cognitive dysfunction promotes episodes of severe hypoglycemia,

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3) factors that increase the propensity of developing severe hypoglycemia also increase the propensity for cognitive dysfunction, or *4*) some combination of these three explanations. Analyses of data from two large randomized controlled trials showing that middle-aged and older people with type 2 diabetes who were allocated to receive intensive glycemic control experienced the same degree of cognitive dysfunction during follow-up as individuals allocated to standard glycemic control despite more frequent severe hypoglycemia (4,5) suggest that hypoglycemia may not promote chronic cognitive dysfunction.

The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial allocated 12,537 middle-aged and older people with dysglycemia and additional cardiovascular risk factors to receive insulin-mediated normoglycemia versus standard care without insulin. During a median follow-up time of 6.2 years, participants allocated to both groups had similar rates of serious health outcomes and similar rates of cognitive dysfunction (6,7). Data on hypoglycemia and cognition were analyzed to assess the relationship between hypoglycemia and incident cognitive dysfunction overall and according to allocated therapy in ORIGIN trial participants who did not have cognitive impairment at baseline.

RESEARCH DESIGN AND METHODS

The design, main results, and cognitive substudy results of ORIGIN have been published previously (6,7). Briefly, 12,537 individuals ≥50 years of age with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes who also had additional cardiovascular risk factors were recruited between 2003 and 2005 from 573 sites in 40 participating countries. Participants were randomly assigned to either the addition of basal insulin glargine titrated to a fasting plasma glucose (FPG) concentration of <95 mg/dL (5.3 mmol/L) or to targets formulated according to local guidelines. All ORIGIN trial participants were asked to complete a Mini-Mental State Examination (MMSE) at baseline and at three additional time points during the trial. Incident dementia was also ascertained. For the purpose of this analysis, only data regarding those participants who had an MMSE score ≥24 (i.e., did not have cognitive impairment) at baseline were included (N = 11,495).

All participants were provided with glucose meters and diaries and were instructed to record episodes of hypoglycemia along with capillary glucose values. During each visit, study personnel reviewed these diaries and explicitly asked about hypoglycemic episodes and recorded them on specific case report forms. Nonsevere hypoglycemia was defined as an event associated with symptoms consistent with hypoglycemia and confirmed by a capillary glucose reading of ≤54 mg/dL (3 mmol/L). The definition of severe hypoglycemia used in this analysis was identical to that used and previously reported in the ORIGIN trial (6,8,9). Specifically, it was defined as a symptomatic hypoglycemic event in which the participants required the assistance of another person (10) and there was *1*) prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration and/or *2*) a documented self-measured or laboratory-measured plasma glucose level of ≤36 mg/dL (2 mmol/L) (9).

All ORIGIN trial participants were asked to complete the MMSE at baseline, 2 years, 4 years, and the penultimate visit. The MMSE is a measure of global cognitive function. It contains 30 items pertaining to the following six cognitive domains: orientation, registration, attention and calculation, recall, language, and visual-spatial ability. For each of the 30 items, 0 denotes an incorrect answer and 1 denotes a correct answer. When English was not the participant's first language, a validated translation was provided. The test administrator was required to score the individual items and then fax the score sheet to the coordinating center. To ensure completeness of the data, sites were queried if any item was not scored and were asked to provide the appropriate score. Scoring of the complete test (only when a test was administered) was done centrally according to the number of correct items; missing items were assigned a score of 0 (11). Scoring in this manner has been previously validated with reported high correlations between the score obtained and the score on other cognitive measures as well as activities of daily living (12).

Incident cognitive dysfunction was defined as either reported dementia (i.e., the first occurrence of an affirmative answer to a case report form question regarding whether the participant had received a diagnosis of dementia since the last study visit) or a postrandomization MMSE score of <24 (7). In addition, sensitivity analysis using a more restricted definition of cognitive dysfunction (i.e., reported dementia or two consecutive MMSE scores of <24 or a last available MMSE score of <24) was conducted. Participants were considered to have probable depression if they indicated during the randomization visit that they were feeling "sad, low in spirits, or depressed for 2 or more weeks" and if they also indicated that during that time they "thought a lot about death or required treatment for depression." Previous cardiovascular disease (CVD) was defined as prior myocardial infarction, stroke, or previous revascularization, and alcohol consumption was defined as more than two drinks per week.

Statistical Analysis

Continuous variables were summarized using the mean with SD, and binary variables were summarized using counts with percentages. The difference in the distribution of the baseline variables was determined using a χ^2 test for counts (percentages) and a t test for means.

Hypoglycemia propensity scores were used to account for a range of variables that may be confounded with both hypoglycemia and changes in cognitive status. As previously reported (9), these propensity scores were calculated separately for severe and nonsevere hypoglycemia. Each score was calculated using logistic regression in which hypoglycemia was the dependent variable and the independent variables were age, sex, ethnicity, education, prior cardiovascular event, hypertension, depression, smoking, more than two drinks of alcohol per week, an albumin/creatinine ratio ≥30 mg/g, BMI, waist-to-hip ratio, A1C, FPG at baseline, glucose-lowering medication use, statin use, ACE/angiotensin receptor blocker use, β-blocker use, thiazide use, anti-platelet agent use, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride levels, systolic blood pressure, diastolic blood pressure, serum creatinine, prior diabetes, and MMSE score at baseline.

The hazard of at least one episode of severe hypoglycemia for incident

Table 1—Baseline characteristics according to severe hypoglycemia status among 11,495 participants with a baseline MMSE score ≥24

Variable	Severe hypoglycemia	No severe hypoglycemia
Total *n*	427	11,068
Age, years	65.5 (8.1)	63.2 (7.7)[A]
Female	112 (26.2)	3,663 (33.1)[B]
Education		
<8 years	139 (32.6)	3,564 (32.2)
9–12 years	146 (34.2)	3,047 (27.5)[B]
>12 years	142 (33.3)	4,455 (40.2)[B]
Ethnicity		
White	252 (59.0)	6,784 (61.3)
Black	9 (2.1)	295 (2.7)
South Asian	9 (2.1)	419 (3.8)
Other Asian	26 (6.1)	707 (6.4)
Latin	121 (28.3)	2,588 (23.4)[B]
Other	10 (2.3)	274 (2.5)
Depression[3]	72 (16.9)	1,546 (14.0)
Mean BMI	29.2 (4.6)	29.9 (5.3)[B]
Previous CVD[1]	279 (65.3)	6,548 (59.2)[B]
Hypertension	356 (83.4)	8,717 (78.8)[B]
Hyperlipidemia	301 (70.5)	7,385 (66.7)
Current smoker	53 (12.4)	1,410 (12.7)
Alcohol[2]	126 (29.5)	2,612 (23.6)[B]
Previous DM	395 (92.5)	9,736 (88.0)[B]
DM duration, years	7.5 (7.5)	5.3 (5.8)[A]
Mean A1C, %	6.6 (1.0)	6.5 (0.9)[B]
Mean FPG, mmol/L	7.5 (2.1)	7.3 (2.0)[B]
Glargine allocation	329 (77.0)	5,428 (49.0)[A]
Standard allocation	98 (23.0)	5,640 (51.0)[A]
n-3 allocation	214 (50.1)	5,571 (50.3)
Placebo allocation	213 (49.9)	5,496 (49.7)
Metformin	114 (26.7)	3,018 (27.3)
Sulfonylurea	155 (36.3)	3,141 (28.4)[A]
Other glucose-lowering drugs	20 (4.7)	315 (2.8)[B]
Mean MMSE score	28.2 (1.9)	28.5 (1.7)[A]

For categorical outcomes, values are presented as *n* (%). For continuous variables, values are presented as the mean (SD). DM, diabetes mellitus. [1]Defined as previous revascularization, myocardial infarction, or stroke. [2]More than two drinks consumed in a week. [3]Defined as an affirmative answer regarding the question of feeling "sad, low in spirits, or depressed for 2 or more weeks" and during that time also having "thought a lot about death or required treatment for depression." [A]$P < 0.001$. [B]$P \leq 0.05$.

cognitive dysfunction (i.e., the dependent variable) from the time of randomization was estimated using a Cox proportional hazards model adjusted for baseline CVD, diabetes status (impaired fasting glucose/impaired glucose tolerance or diabetes), allocation to glargine, and allocation to n-3 fatty acids; these variables and a propensity score for severe hypoglycemia; and these variables, the propensity score, and the interaction of glargine allocation with severe hypoglycemia if the interaction term was significant. An individual was counted as having had an episode of severe hypoglycemia if one or more episodes were reported between the day of randomization and the time that individual was classified as having cognitive dysfunction or the end of the study if cognitive dysfunction did not develop in the individual. The same analyses were repeated after replacing severe hypoglycemia with nonsevere hypoglycemia, after accounting for the competing risk of death (10), after adjusting for age at the time that data were censored for each participant, and after additionally adjusting for A1C as a time-varying covariate.

Finally, the effect of severe and nonsevere hypoglycemia on cognitive dysfunction in six prespecified subgroups (with/without prior diabetes; male/female; with/without prior CVD; ≤8, 9–12, or >12 years of education; <65/≥65 years of age; and allocated to glargine/standard arm) was also explored. Because a total of 12 subgroup interactions were tested (i.e., six for severe hypoglycemia and six for nonsevere hypoglycemia), a subgroup interaction was deemed significant if its *P* value was $<0.05/12 = 0.0042$.

RESULTS

Baseline characteristics of the 11,495 people whose baseline MMSE score was ≥24 are summarized in Table 1 for severe hypoglycemia and in Table 2 for nonsevere hypoglycemia. Compared with individuals who did not have episodes of hypoglycemia, those who had episodes were more likely to be male and of Latin origin, to have previously received a diagnosis of diabetes, to be lighter, and to be taking a sulfonylurea. They also reported lower educational attainment (severe hypoglycemia only), higher alcohol use, higher A1C, longer diabetes duration, and more depression and were more likely to be allocated to the glargine arm and to have a lower baseline MMSE score.

During a median follow-up time of 6.2 years, 1,387 (12%) developed incident cognitive dysfunction; dementia was reported to have developed in 100 of these individuals (0.9%) and 1,333 (11.6%) had a postrandomization MMSE score <24. The incidence of cognitive dysfunction (and its components) in those individuals who did and did not experience severe and nonsevere hypoglycemia is depicted in the Supplementary Data.

Severe Hypoglycemia

There were 427 participants (3.7%) who experienced severe hypoglycemia. The analysis failed to demonstrate a relationship between severe hypoglycemia and incident cognitive impairment after adjusting for baseline CVD, diabetes status, and treatment allocation (hazard ratio [HR] 1.16; 95% CI 0.89, 1.52) and after adjusting for these variables and a propensity score for severe hypoglycemia (HR 1.00; 95% CI 0.76, 1.31). There was no evidence of an interaction between glargine allocation and severe hypoglycemia

Table 2—Baseline characteristics according to nonsevere hypoglycemia status among 11,495 participants with a baseline MMSE ≥24

Variable	Nonsevere hypoglycemia	No nonsevere hypoglycemia
Total *n*	3,256	8,239
Age, years	62.8 (7.4)	63.5 (7.8)[A]
Female	1,013 (31.1)	2,762 (33.5)[B]
Education		
<8 years	1,066 (32.7)	2,637 (32.0)
9–12 years	914 (28.0)	2,279 (27.7)
>12 years	1,276 (39.2)	3,321 (40.3)
Ethnicity		
White	1,843 (56.6)	5,193 (63.0)[A]
Black	86 (2.6)	218 (2.6)
South Asian	112 (3.4)	316 (3.8)
Other Asian	183 (5.6)	550 (6.7)[B]
Latin	966 (29.7)	1,743 (21.2)[A]
Other	66 (2.0)	218 (2.6)
Depression[3]	547 (16.8)	1,071 (13)[A]
Mean BMI	29.6 (5.1)	30.0 (5.3)[A]
Previous CVD[1]	1,947 (59.8)	4,880 (59.2)
Hypertension	2,562 (78.7)	6,511 (79.0)
Hyperlipidemia	2,198 (67.5)	5,488 (66.6)
Current smoker	445 (13.7)	1,018 (12.4)
Alcohol[2]	810 (24.9)	1,928 (23.4)
Previous DM	3,049 (93.6)	7,082 (86.0)[A]
DM duration, years	6.3 (6.4)	4.9 (5.6)[A]
Mean A1C, %	6.7 (1.0)	6.4 (0.9)[A]
Mean FPG, mmol/L	7.6 (2.1)	7.2 (1.9)[B]
Glargine allocation	2,429 (74.6)	3,328 (40.4)[A]
Standard allocation	827 (25.4)	4,911 (59.6)[A]
n-3 allocation	1,621 (49.8)	4,164 (50.5)
Placebo allocation	1,635 (50.2)	4,074 (49.4)
Metformin	879 (27.0)	2,253 (27.3)
Sulfonylurea	1,310 (40.2)	1,986 (24.1)[A]
Other glucose-lowering drugs	101 (3.1)	234 (2.8)
Mean MMSE score	28.4 (1.8)	28.5 (1.7)[B]

For categorical outcomes, values are *n* (%). For continuous variables, the mean (SD) is given. DM, diabetes mellitus. [1]Defined as previous revascularization, myocardial infarction, or stroke. [2]More than two drinks consumed in a week. [3]Defined as an affirmative answer regarding the question of feeling "sad, low in spirits, or depressed for 2 or more weeks" and during that time also having "thought a lot about death or required treatment for depression." [A]$P < 0.001$. [B]$P = < 0.05$.

(P for interaction = 0.23). Sensitivity analysis accounting for the competing risk of death yielded similar results (HR 1.16; 95% CI 0.89, 1.51; and HR 1.02; 95% CI 0.78, 1.34; respectively) (Fig. 1*A*) as did the addition of age at the time that data were censored for each participant (HR 0.99; 95% CI 0.75, 1.30). Finally, in a sensitivity analysis that used a more restricted definition of cognitive dysfunction (i.e., either reported dementia or two consecutive MMSE scores <24 or a last available MMSE score <24), a similar, nonsignificant propensity score and adjusted hazard ratio was calculated (HR 1.21; 95% CI 0.9, 1.63).

Nonsevere Hypoglycemia

There were 3,256 participants (28.3%) who experienced nonsevere hypoglycemia. There was an inverse relationship between nonsevere hypoglycemia and the risk for incident cognitive dysfunction. Thus, those individuals who experienced at least one episode of nonsevere hypoglycemia were less likely to develop cognitive dysfunction than were those who did not experience an episode, after adjustment for baseline CVD, diabetes status, and treatment allocation (HR 0.59; 95% CI 0.52, 0.68) and for these variables plus a propensity score for nonsevere hypoglycemia (HR 0.58; 95% CI 0.51, 0.67). There was no evidence of an interaction between glargine allocation and nonsevere hypoglycemia (P for interaction = 0.042; due to multiple interactions, $P < 0.0042$ considered to be significant). A sensitivity analysis that accounted for the competing risk of death yielded similar results (HR 0.63; 95% CI 0.55, 0.72; and HR 0.62; 95% CI 0.54, 0.72; respectively) (Fig. 1*B*), as did the addition of A1C as a time-varying covariate (HR 0.59; 95% CI 0.52, 0.68; and HR 0.59; 95% CI 0.51, 0.67; respectively) and the addition of age at the time that data were censored for each participant (HR 0.58; 95% CI 0.50, 0.66). Finally, in a sensitivity analysis that used a more restricted definition of cognitive dysfunction (reported dementia or two consecutive MMSE scores <24 or a last available MMSE score <24), a similar propensity score–adjusted HR was calculated (HR 0.62; 95% CI 0.52, 0.73).

Subgroup Analyses

Figure 2 displays the relationship between hypoglycemia and incident cognitive dysfunction overall and within predefined subgroups after adjustment for baseline CVD, diabetes status, treatment allocation, and a propensity score for severe hypoglycemia. There was no evidence of a statistically significant interaction among subgroups and the risk of cognitive dysfunction with either severe or nonsevere hypoglycemia (all P values for interaction ≥0.0042).

CONCLUSIONS

In this long-term prospective analysis of data from 11,495 people, neither severe nor nonsevere hypoglycemia was associated with a higher incidence of cognitive dysfunction either before or after adjusting for confounding variables, including hypoglycemia propensity scores, and the competing risk of death. The facts that all participants were cognitively intact enough at baseline to understand and sign a consent form and that the analyses were limited to individuals whose baseline MMSE score was ≥24 ensure that the relationship of hypoglycemia with incident, as opposed to prevalent, cognitive dysfunction was assessed.

These findings are similar to those from two large clinical trials in which

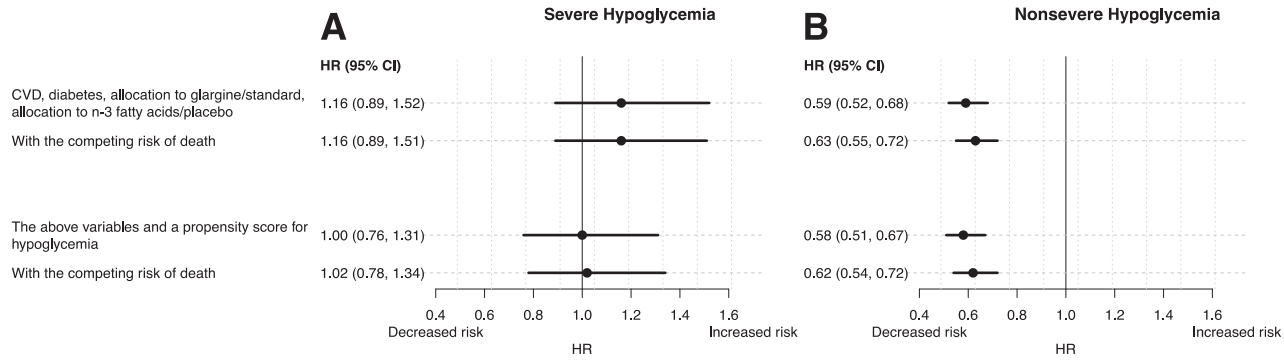

Figure 1—The risk for incident cognitive dysfunction after an episode of severe (*A*) or nonsevere (*B*) hypoglycemia with and without accounting for the competing risk of death after adjusting for consecutive models that include the following: CVD, diabetes status, treatment allocation, and a propensity score (for severe and nonsevere hypoglycemia).

participants had to be cognitively intact enough at baseline to understand and sign an informed consent form. These include the ACCORD MIND (Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes) substudy, in which no relationship between severe hypoglycemia and cognitive decline was observed in 2,977 individuals, and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial in 11,140 people, in which people allocated to the intensive glucose-lowering group had more episodes of severe hypoglycemia than those allocated to standard care, but a similar rate of cognitive decline (5). Conversely, these findings do not support some previous reports (1–3) that hypoglycemia increases the risk of cognitive dysfunction. Cognitive status at baseline was unavailable in some of these reports, which raises the possibility that in those analyses hypoglycemia may have occurred more frequently in those with reduced cognitive function. Indeed, we previously reported that baseline MMSE score was an independent risk factor for severe hypoglycemia in ORIGIN participants (8).

The observation that individuals who experienced nonsevere hypoglycemia had a lower incidence of cognitive impairment than those who did not experience any such episodes may have been a chance finding. Alternatively, those people who experienced such episodes may have been those with better cognitive function at baseline, thus motivating them to strive for lower glucose levels leading to more nonsevere hypoglycemia. The fact that sensitivity analysis with further adjustment for A1C as a time-varying covariate did not alter the relationship reduces but does not eliminate this possibility.

Our study has several limitations. First, despite adjustment for a propensity score that included many variables, the possibility of residual confounding cannot be eliminated. Indeed, as noted in Table 1, people who experienced a hypoglycemic event differed in several ways from those who did not. Second, as

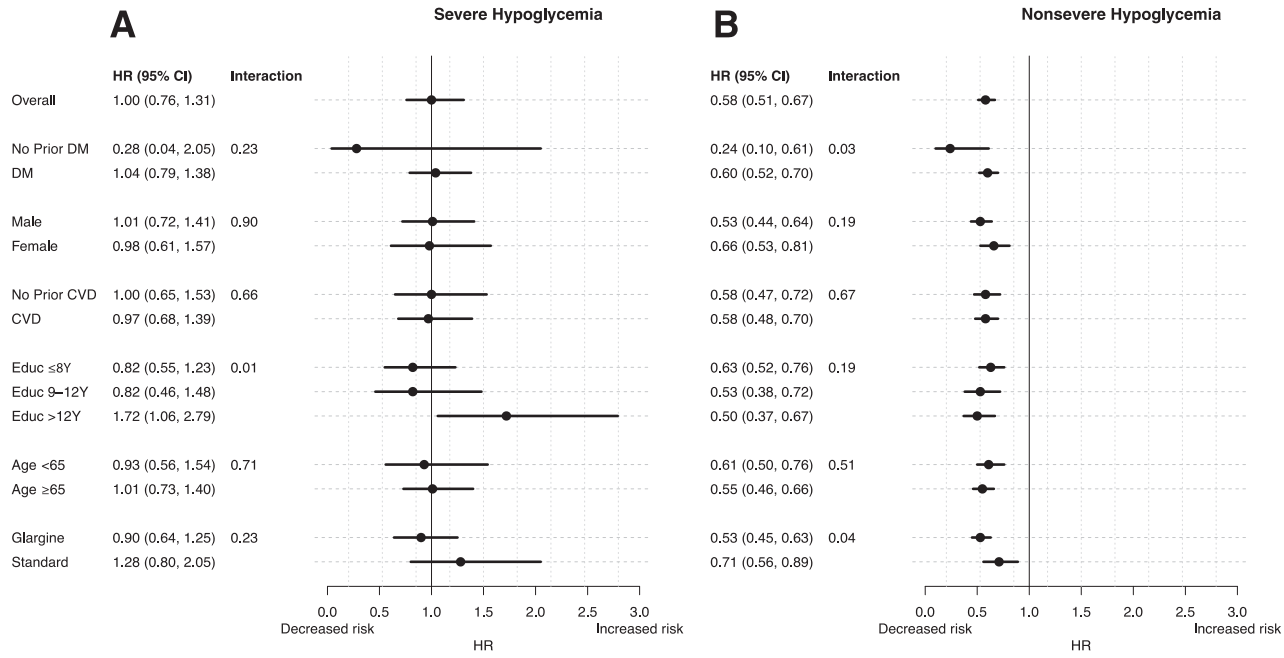

Figure 2—The risk for incident cognitive dysfunction after an episode of severe (*A*) and nonsevere (*B*) hypoglycemia after adjusting for CVD, diabetes (DM) status, treatment allocation, and a propensity score (for severe and nonsevere hypoglycemia) in subgroups of participants. Educ, education; Y, years.

ORIGIN trial participants had a mean age of 64 years with a fairly low A1C at baseline, these results may not apply to an older, less well-controlled population. Third, hypoglycemia was based on the interrogation of participants and their logbook, and not on independent measures of glucose, thus reducing, but not eliminating, the possibility of misclassification in the ascertainment of the hypoglycemia episodes.

These findings provide no support for the hypothesis that hypoglycemia causes long-term cognitive decline and are therefore reassuring for patients and their health care providers. When viewed in the context of previous reports that cognitive dysfunction is a risk factor for future hypoglycemia, they highlight the importance of assessing cognitive status in all patients and tailoring therapy appropriately.

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Author Contributions. T.C.-Y. and H.C.G. were responsible for study concept and design, statistical analysis, the plan for interpretation of the data, and drafting and redrafting of the manuscript. J.B. and Z.P. contributed to critical revision of the manuscript. H.J. was responsible for statistical analysis and contributed to critical revision of the manuscript. T.C.-Y. and H.C.G. 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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