The Association of Severe Hypoglycemia With Incident Cardiovascular Events and Mortality in Adults With Type 2 Diabetes

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

There is suggestive evidence linking hypoglycemia with cardiovascular disease, but few data have been collected in a community-based setting. Information is lacking on individual cardiovascular outcomes and cause-specific mortality.

RESEARCH DESIGN AND METHODS

We conducted a prospective cohort analysis of 1,209 participants with diagnosed diabetes from the Atherosclerosis Risk in Communities (ARIC) study (analytic baseline, 1996–1998). Severe hypoglycemic episodes were identified using first position ICD-9 codes from hospitalizations, emergency department visits, and ambulance calls through 2013. Cardiovascular events and deaths were captured through 2013. We used adjusted Cox regression models with hypoglycemia as a time-varying exposure.

RESULTS

There were 195 participants with at least one severe hypoglycemic episode during a median fellow-up of 15.3 years. After severe hypoglycemia, the 3-year cumulative incidence of coronary heart disease was 10.8% and of mortality was 28.3%. After adjustment, severe hypoglycemia was associated with coronary heart disease (hazard ratio [HR] 2.02, 95% CI 1.27–3.20), all-cause mortality (HR 1.73, 95% CI 1.38–2.17), cardiovascular mortality (HR 1.64, 95% CI 1.15–2.34), and cancer mortality (HR 2.49, 95% CI 1.46–4.24). Hypoglycemia was not associated with stroke, heart failure, atrial fibrillation, or noncardiovascular and noncancer death. Results were robust within subgroups defined by age, sex, race, diabetes duration, and baseline cardiovascular risk.

CONCLUSIONS

Severe hypoglycemia is clearly indicative of declining health and is a potent marker of high absolute risk of cardiovascular events and mortality.

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There is suggestive evidence that hypoglycemia is associated with a substantially increased risk of cardiovascular disease; however, the mechanisms underlying this association remain unclear (1–6). Severe hypoglycemia, defined as hypoglycemia requiring assistance (7), could be merely a marker of vulnerability or could play a causal role in the development of cardiovascular disease. Severe hypoglycemia has been associated with a wide range of conditions, including respiratory, digestive, and skin diseases (6),

and this lack of specificity to cardiovascular disease suggests that poor or failing health may be the underlying cause of both hypoglycemia and other diseases. Hypoglycemia is also likely a marker of the severity and duration of diabetes, because it is more common among those with poor glycemic control and who use insulin (8–10). However, several prior studies of severe hypoglycemia and cardiovascular disease have not accounted for these characteristics (1,11).

There are several pathways through which episodes of hypoglycemia may trigger arrhythmic events or promote atherosclerosis. During hypoglycemia, the sympathetic nervous system releases catecholamines, which induce tachycardia and stimulate cardiac contraction (12). In addition, the activated sympathetic nervous system leads to hypokalemia in the myocardium, potentially causing arrhythmias (13,14). Hypoglycemia also triggers an acute inflammatory response, promoting coagulation through factor VIII and von Willebrand factor (12,15). Endothelial dysfunction may also be increased by an increase in C-reactive protein and platelet activation, promoting atherosclerosis (12).

Much of the epidemiologic evidence on this topic comes from secondary analyses of randomized clinical trials, which often recruit high-risk populations that are less representative of the general population (16). Some have suggested that the association of severe hypoglycemia with cardiovascular disease may be limited to those at high cardiovascular risk, and few studies have been conducted in relatively low-risk populations with diabetes (2,5). Another source of evidence is from retrospective analyses of medical claims databases, which often lack data on important characteristics such as duration of diabetes and kidney function. Thus, evidence is needed from community-based cohort studies that are both representative of the general population and have standardized, high-quality data on clinical characteristics.

The objective of our study was to rigorously quantify and compare associations of severe hypoglycemia with cardiovascular outcomes, including coronary heart disease, stroke, heart failure, atrial fibrillation, and peripheral artery disease, as well as all-cause and cause-specific mortality in a community-based population with diabetes. We also sought to determine whether the association of severe hypoglycemia with these outcomes varied by baseline characteristics, such as cardiovascular risk.

RESEARCH DESIGN AND METHODS
Study Population
The Atherosclerosis Risk in Communities (ARIC) study recruited 15,792 participants from four U.S. communities (17). After the first study visit in 1987–1989, participants returned for subsequent study visits and received annual telephone calls. The fourth study visit in 1996–1998 is the baseline visit for this analysis and was selected to maximize the number of participants with Medicare claims at baseline. Our study population was participants with diagnosed diabetes identified by self-report of a physician diagnosis or use of glucose-lowering medication use ($n = 1,511$) among 11,656 participants at visit 4. To avoid having groups too small for analysis, we excluded four participants who did not identify as black or white and six black participants from the Minnesota or Maryland study sites. We also excluded those missing covariates ($n = 292$). There were some differences between participants who were excluded for missing covariates and those included in the final study population (Supplementary Table 1). Our final analytic population for analyses of mortality was 1,209 participants. For analyses of the different cardiovascular events, we excluded participants with prevalent disease at visit 4, resulting in sample sizes ranging from 992 to 1,190.

Each study site had institutional review board approval, and all participants provided informed written consent.

Severe Hypoglycemia
Severe hypoglycemic events were identified from hospitalizations, emergency department visits, and ambulance calls with a validated algorithm, using ICD-9 codes in the primary position through 31 December 2013 (18). Hospitalization records were available from ARIC surveillance of local hospitals. Linked Medicare claims for hospitalizations, emergency department visits, and ambulance use were available for participants enrolled in Medicare fee-for-service part B.

Cardiovascular Outcomes and Mortality
Coronary heart disease was defined as nonfatal myocardial infarction and fatal coronary heart disease. Stroke was defined as definite or probable ischemic or hemorrhagic strokes. An expert committee adjudicated all coronary heart disease and stroke events since the inception of the study (17).

Adjudication for heart failure began in 2005; all heart failure events before 2005 were based on hospitalization with a primary position ICD-9 code (428) (19). Incident atrial fibrillation was based on hospitalizations with ICD-9 codes for atrial fibrillation or atrial flutter (327.31 or 437.32) in the absence of cardiac surgery (procedure codes 35.x or 36.x) (20). Prevalent atrial fibrillation at visit 4 was also identified from electrocardiograms conducted at visits 1–4 ($n = 47$). Peripheral artery disease events were identified from hospitalizations on the basis of ICD-9 diagnosis codes for peripheral artery disease (440.2, 440.3, 440.4) or ICD-9 procedure codes for leg revascularization (38.18, 39.25, 39.29, 39.50) (21). Ascertainment for all events occurred through 31 December 2013.

Mortality was assessed via proxy, coroner reports, and the National Death Index through 2013 (17). Cause-specific mortality was classified by the underlying cause of death listed on the death certificate: cardiovascular mortality (ICD-9 codes: 390–459, ICD-10 codes: I00–I99), cancer mortality (ICD-9 codes: 140–239, ICD-10 codes: C00–D49), and all other causes of death. Cause of death was missing for 29 participants, and they were censored at time of death.

Covariates
Because we did not have the exact date of the diabetes diagnosis, we dichotomized diabetes duration as ≥ 9 years or < 9 years, based on whether a participant had reported diabetes at the first ARIC study visit. Participants were asked to bring in all medications taken within the past 2 weeks to each study visit. We classified diabetes medication use as no diabetes medication use, oral medication use only, or any insulin use. Hemoglobin A_{1c} was not available at visit 4, so we used fructosamine to characterize glycemic control.

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation from serum creatinine (22). Albuminuria was categorized based on the urinary albumin-to-creatinine ratio (ACR). The mean of two seated

blood pressure measurements was used. Fasting total cholesterol and HDL cholesterol were measured, and LDL cholesterol was calculated using the Friedewald equation. Smoking status and household income were based on self-report. Disability was based on self-report of any difficulty with activities of daily living (eating, dressing, getting out of bed, or walking between rooms).

For comparison with prior findings (2,23), we classified participants as high or low cardiovascular risk based on the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial inclusion criteria: age ≥55 years, fructosamine ≥300 μmol/L (instead of hemoglobin A_{1c} >7.5%), and a history of cardiovascular disease or at least two of the following risk factors: hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >95 mmHg, with or without treatment), BMI >32 kg/m^2, LDL cholesterol >130 mg/dL, with or without cholesterol-lowering medication, low HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women), or current smoking.

Statistical Analysis

We considered severe hypoglycemia, conceptualized as "no history of severe hypoglycemia," or "history of severe hypoglycemia," to be a time-varying exposure in all analyses.

For the main analysis, we examined the association of severe hypoglycemia with cardiovascular outcomes and mortality using Cox regression. We progressively adjusted the models for potential confounders. Model 1 included age, sex, and race-center (blacks from Jackson, blacks from Forsyth County, whites from Forsyth County, whites from Minneapolis, and whites from Washington County). Model 2 included all variables in model 1 plus shared risk factors for hypoglycemia and cardiovascular events and mortality: diabetes medication use (none, orals only, any insulin), duration of diabetes (≥9 years, <9 years), tertiles of fructosamine (<296, 296–351, ≥ 352 μmol/L), low eGFR (<60 mL/min/1.73 m^2), albuminuria (ACR <30, 30–300, ≥300 mg/g), income (<$12,000, $12,000–$23,999, $24,000–$49,999, ≥$50,000), and disability. Model 3 additionally included cardiovascular risk factors: systolic blood pressure, hypertension medication use, LDL cholesterol, HDL cholesterol, cholesterol-lowering medication use, and smoking

status (current, former, never). We verified that the proportional hazards assumption was met by inspecting negative log-log survival plots.

We examined the association of the number of hypoglycemia events (zero, one, or two or more) with cardiovascular disease and mortality. To examine the effect of time since hypoglycemia on risk of events, we used time-varying indicator variables to classify each individual's person-time into one of three categories: no hypoglycemia, hypoglycemia within the past year, or hypoglycemia more than 1 year ago. As others have observed, we expected to see the highest risk of cardiovascular events in the first year after severe hypoglycemia (2,6,11).

We hypothesized that severe hypoglycemia may represent failing health caused by other illnesses, such as cancer. We looked to see whether incidence rates of severe hypoglycemia were higher among participants with high-fatality cancers compared with lower-fatality cancers, as defined by 5-year survival rates. High-fatality cancers included cancers of the pancreas, liver, lung, stomach, brain, and of unknown primary site (24,25). Cancer diagnoses were identified from ARIC hospitalization surveillance and through linkage to state or county cancer registries until 31 December 2012 (26,27). All incident cancer analyses were administratively censored at 31 December 2012 and additionally excluded participants who did not consent to research on noncardiovascular topics (n = 2).

We conducted two sensitivity analyses. First, we excluded participants with a history of severe hypoglycemia at visit 4 (n = 14) to reduce the possible influence of survival bias. Second, we replaced fructosamine with hemoglobin A_{1c} measured at visit 2 (6 years prior).

All analyses were conducted using Stata 13.1 software (StataCorp, College Station, TX).

RESULTS

Among the 1,209 participants with diagnosed diabetes, 14 had a history of hypoglycemia at baseline, and 186 experienced at least one event of severe hypoglycemia during a median follow-up time of 15.3 years (median time from baseline to severe hypoglycemic event: 7.7 years). Individuals with severe hypoglycemia at baseline were older, more likely to be black or using insulin and to have poor glycemic

control and longer duration of diabetes (Table 1). They were also more likely to have poor kidney function, kidney damage, and to be disabled. The cardiovascular risk profile was slightly worse in those with severe hypoglycemia.

Of the 195 participants with severe hypoglycemia, 118 died; the median (25th and 75th percentiles) time between severe hypoglycemia and death was 3.8 (1.2 to 7.3) years. In 3 years after severe hypoglycemia, cumulative mortality was 28.3%, and 10.8% experienced incident coronary heart disease. The median time between the severe hypoglycemic episode and the different incident cardiovascular outcomes was ~3 years, with the exception of atrial fibrillation, where the median time was 5.6 years. The crude incidence rates of cardiovascular events and mortality were two- to four-times higher after severe hypoglycemia compared to without hypoglycemia, with the exception of stroke (Table 2).

In minimally adjusted models, severe hypoglycemia was associated with a more than a two-times higher risk of each type of cardiovascular event except for stroke and atrial fibrillation (Table 2; model 1). The association with coronary heart disease was most robust and remained statistically significant even in model 3 (hazard ratio [HR] 2.02, 95% CI 1.27–3.20). For heart failure, the initially strong association in model 1 (HR 2.35, 95% CI 1.72–3.20) was substantially attenuated and not statistically significant in models 2 or 3 (model 2: HR 1.37, 95% CI 0.98–1.91). Adjustment for covariates also attenuated the association for peripheral artery disease (model 3: HR 1.55, 95% CI 0.86–2.80). For atrial fibrillation, the modest association in model 1 was no longer observed after further adjustment (model 3: HR 1.05, 95% CI 0.68–1.60). No association with hypoglycemia was found for stroke in any model.

After adjustment, severe hypoglycemia was associated with a more than two-times greater risk of all-cause mortality and cardiovascular mortality in model 1; the associations were substantially attenuated in model 2, but changed little after additional adjustment (model 3: all-cause mortality, HR 1.73, 95% CI 1.38–2.17; cardiovascular mortality, HR 1.64, 95% CI 1.15–2.34). In contrast, hypoglycemia was associated with a risk of cancer that was ~2.5-times greater, regardless of adjustment. For other causes of death,

Table 1—Baseline characteristics of ARIC participants with diagnosed diabetes at visit 4 (1996–1998) by severe hypoglycemia (n = 1,209)

	No severe hypoglycemia (n = 1,014)	Severe hypoglycemia (n = 195)*	P value
Age, years	63.4 ± 5.7	64.7 ± 5.6	0.004
Female	53.7	57.9	0.28
Black	31.2	46.7	<0.001
BMI, kg/m^2	31.4 ± 5.9	32.4 ± 5.8	0.028
Diabetes medications			<0.001
None	30.2	8.2	
Oral medication(s) only	45.4	41.5	
Any insulin	24.5	50.3	
Fructosamine			<0.001
Middle tertile (296–351 μmol/L)	33.2	32.3	
Highest tertile (≥352 μmol/L)	29.4	51.8	
Diabetes duration ≥9 years	40.4	60.0	<0.001
eGFR <60 mL/min/1.73 m^2	10.7	19.0	0.001
Albuminuria			<0.001
ACR 30 to <300 mg/g	13.8	20.0	
ACR ≥300 mg/g	6.6	14.9	
Household income			<0.001
<$12,000	16.9	32.3	
$12,000–23,999	27.0	26.7	
$24,000–49,999	32.9	27.7	
≥$50,000	23.3	13.3	
Disability	23.9	37.9	<0.001
Systolic blood pressure, mmHg	131.6 ± 19.5	135.6 ± 19.5	0.009
Hypertension medication	68.3	76.4	0.03
LDL cholesterol, mg/dL	116.6 ± 35.1	122.2 ± 38.5	0.045
HDL cholesterol, mg/dL	44.1 ± 13.7	46.4 ± 15.9	0.04
Cholesterol-lowering medication	24.1	27.2	0.36
Smoking status			0.19
Current smoker	12.7	14.9	
Former smoker	48.1	41.0	
History of coronary heart disease at visit 4	17.4	21.0	0.22

Data are presented as mean ± SD or percentage. *Severe hypoglycemia occurred in 14 before visit 4, all others had hypoglycemia during follow-up.

hypoglycemia was associated with more than two-times greater risk of death from other causes in model 1 but was not significantly associated after additional adjustment (model 3: HR 1.40, 95% CI 0.95–2.03).

We examined the findings by subgroups of age, sex, race, diabetes duration at baseline, history of cardiovascular disease, and cardiovascular risk status. In model 3, there was no significant effect modification (all P values for interaction ≥0.2), and all HRs were between 1.5 and 2.0 for all-cause mortality (Fig. 1). For other outcomes, the results were similar, with a few, likely spurious, interactions for some outcomes (Supplementary Tables 2 and 3).

For most outcomes, the risk was highest in the first year after the hypoglycemic event (Fig. 2). This difference was most pronounced for cancer mortality: within 1 year of the hypoglycemic event, the HR was 5.58 (95% CI 2.53–12.28), and for more than 1 year since the hypoglycemic event, the HR was 1.89 (95% CI 1.02–3.51).

Across outcomes, the HRs for two or more severe hypoglycemic events were slightly stronger than for one severe hypoglycemic event, but there were only 59 participants with two or more events (Supplementary Fig. 1).

A sensitivity analysis excluding individuals with a history of severe hypoglycemia at visit 4 found the associations with hypoglycemia were slightly stronger for most outcomes (Supplementary Table 4). Results were similar in a second sensitivity analysis using HbA$_{1c}$ measured

6 years before baseline instead of fructosamine (Supplementary Table 5).

Incident Hypoglycemia in Participants With Cancer

Only 21 episodes of severe hypoglycemia occurred among participants with cancer diagnoses, and only 4 episodes occurred after a diagnosis of a high-fatality cancer. Although not statistically significant, the risk of severe hypoglycemia was nominally twice as high among those with more fatal cancers (HR 1.89, 95% CI 0.68–5.20) compared with those without cancer, whereas the risk of severe hypoglycemia was similar in those with less fatal cancers (HR 0.84, 95% CI 0.56–1.27).

CONCLUSIONS

Severe hypoglycemia is a high-risk state and is followed by a high rate of cardiovascular events and deaths in persons with diabetes in the community, with nearly 30% cumulative mortality after 3 years. The strong associations of severe hypoglycemia with coronary heart disease and all-cause mortality persisted after adjustment for a wide range of potential confounders, suggesting that severe hypoglycemia is a strong risk marker, independent of diabetes severity and standard cardiovascular risk factors. Further, the risk of cardiovascular outcomes and mortality was highest in the first year after severe hypoglycemia. These results suggest that clinicians should pay particular attention to the potential for morbidity and mortality in the first year after a severe hypoglycemic event.

Our study is one of the first epidemiologic studies to show that the association of severe hypoglycemia with incident cardiovascular events may be most pronounced for outcomes that are more strongly linked to atherosclerotic disease rather than cardiovascular conditions more broadly. In particular, we observed that after multivariable adjustment, only coronary heart disease was significantly associated with severe hypoglycemia (HR 2.02). Peripheral artery disease also appeared to be strongly associated with hypoglycemia (HR 1.55, not significant), but was limited by low statistical power (n = 89 peripheral artery disease events). In contrast, our results were essentially null for stroke and atrial fibrillation. Only two other studies have examined hypoglycemia and subtypes of cardiovascular

Table 2—Crude incidence rates and adjusted HRs (95% CI) for incident cardiovascular events and mortality by severe hypoglycemia

		Crude incidence rate per 100 PY				
	Events/N	Without hypoglycemia	After hypoglycemia	Model 1*	Model 2*	Model 3*
Incident cardiovascular events						
Coronary heart disease	173/992	1.24 (1.05–1.46)	3.87 (2.65–5.64)	2.78 (1.81–4.38)	2.23 (1.23–3.52)	2.02 (1.27–3.20)
Stroke	120/1,163	0.81 (0.67–0.98)	1.17 (0.63–2.17)	1.15 (0.59–2.23)	0.91 (0.46–1.81)	0.81 (0.40–1.63)
Heart failure	300/1,190	1.82 (1.61–2.06)	6.61 (5.04–8.67)	2.35 (1.72–3.20)	1.37 (0.98–1.91)	1.35 (0.96–1.89)
Atrial fibrillation	254/1,162	1.70 (1.49–1.94)	3.36 (2.32–4.87)	1.55 (1.03–2.32)	1.13 (0.74–1.73)	1.05 (0.68–1.60)
Peripheral artery disease	89/1,128	0.53 (0.42–0.67)	2.07 (1.30–3.29)	3.35 (1.94–5.78)	1.85 (1.04–3.30)	1.55 (0.86–2.80)
Mortality						
All-cause	586/1,209	3.20 (2.92–3.50)	11.43 (9.54–13.68)	2.56 (2.08–3.17)	1.86 (1.49–2.33)	1.73 (1.38–2.17)
Cardiovascular**	218/1,209	1.15 (0.99–1.34)	4.74 (3.59–6.28)	2.80 (2.00–3.91)	1.76 (1.23–2.51)	1.64 (1.15–2.34)
Cancer**	121/1,209	0.68 (0.56–0.83)	2.03 (1.33–3.12)	2.44 (1.49–3.99)	2.61 (1.55–4.38)	2.49 (1.46–4.24)
Other**	218/1,209	1.21 (1.04–1.40)	3.97 (2.92–5.39)	2.31 (1.62–3.30)	1.47 (1.01–2.15)	1.40 (0.95–2.03)

Severe hypoglycemia was modeled as a time-dependent exposure. PY, person-years. *Model 1 was adjusted for age, sex, and race-center. Model 2 additionally included diabetes medications, fructosamine tertiles, duration of diabetes, low eGFR, albuminuria, income, and any difficulty with activities of daily living. Model 3 additionally included systolic blood pressure, hypertension medication use, LDL cholesterol, HDL cholesterol, cholesterol-lowering medication use, and smoking status. **Cause of death was missing for 29 individuals, and they were censored at the time of death in the analyses of cause-specific death.

disease, with inconsistent results (28,29). The specificity of the association of hypoglycemia to coronary heart disease suggests that the association is less likely to be explained by reverse causation or other biases that would likely be similar across the cardiovascular conditions, such as unintentional weight loss.

We found some evidence of a dose-response association for a few cardiovascular outcomes. However, these results are tentative given the small number of people with two or more severe hypoglycemic events (*n* = 59). It is worth considering that the lack of many people with repeated severe hypoglycemic events may be indicative of the strong competing risk of all-cause mortality rather than the absence of a dose-response per se.

The strong observed associations with cardiovascular outcomes are supported by potential biological mechanisms. The strong association with coronary heart disease is supported by human experimental studies showing that hypoglycemia leads to an atherogenic state caused by the release of inflammatory cytokines and increase in platelet aggregation (15). It is possible that the long-term cardiovascular effects of hypoglycemia result more from the endothelial dysfunction and a proinflammatory state rather than from temporary arrhythmic effects. An alternate potential mechanism connecting hypoglycemia to heart failure (HR 1.35, not significant) is subclinical myocardial damage, because low glucose levels during hypoglycemia may directly damage the myocardium (30).

Although others have suggested that severe hypoglycemia may be associated with cardiovascular events only in individuals with existing high cardiovascular risk (2,5), we did not fully replicate this finding. We found that an episode of severe hypoglycemia may have deleterious consequences for all adults with type 2 diabetes. Nonetheless, there was a quantitative nonsignificant difference in the HR for coronary heart disease for those at low compared with high cardiovascular risk (HR 1.60 vs. 2.54, respectively), suggesting the effect may possibly be worse for those with high cardiovascular risk.

Our analysis of cause-specific mortality extends the literature on this topic (4,6,31,32). Hypoglycemia was associated with an increased risk of cardiovascular and cancer mortality and was marginally associated with noncardiovascular and noncancer ("other") mortality (HR 1.40, 95% CI 0.95–2.03). The lack of specificity to any particular cause of death suggests that there could be a shared underlying cause of both hypoglycemia and mortality,
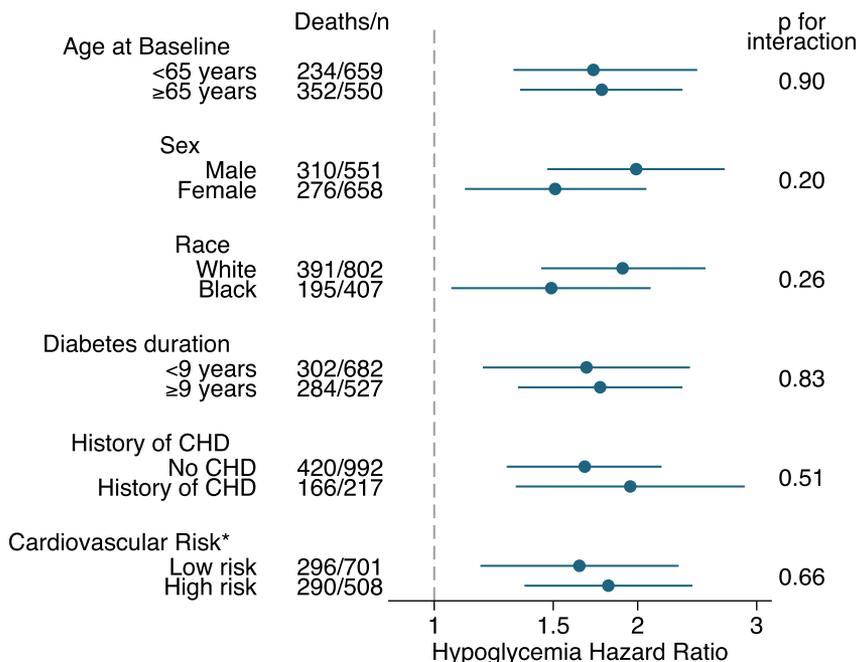

	Deaths/n		p for interaction
Age at Baseline			
<65 years	234/659		0.90
≥65 years	352/550		
Sex			
Male	310/551		0.20
Female	276/658		
Race			
White	391/802		0.26
Black	195/407		
Diabetes duration			
<9 years	302/682		0.83
≥9 years	284/527		
History of CHD			
No CHD	420/992		0.51
History of CHD	166/217		
Cardiovascular Risk*			
Low risk	296/701		0.66
High risk	290/508		

Hypoglycemia Hazard Ratio

Figure 1—Severe hypoglycemia HRs and 95% CIs for all-cause mortality by subgroups of the study population. CHD, coronary heart disease. *Cardiovascular risk defined by inclusion criteria for the ACCORD trial.
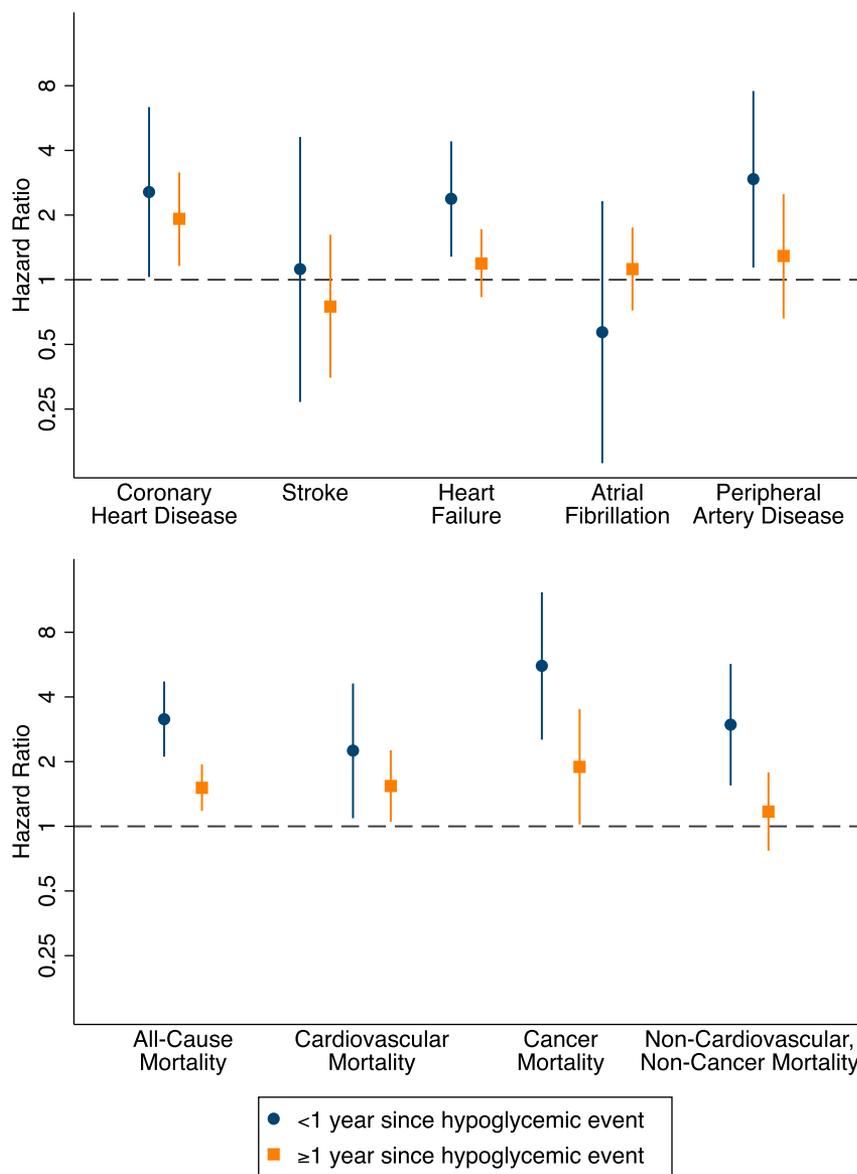
Figure 2—Hypoglycemia HRs and 95% CIs for cardiovascular disease and mortality outcomes by time since severe hypoglycemic event. All HRs are adjusted for covariates in model 3.

actions may prevent future hypoglycemia and also reduce the risk of cardiovascular disease. In particular, severe hypoglycemia may be underused as a cardiovascular risk marker, and intensification of antihypertensive or cholesterol-lowering medications could be beneficial in some individuals.

It is important to consider our study limitations. First, similar to other epidemiologic investigations relying on claims data to identify episodes of severe hypoglycemia, we only captured episodes that resulted in immediate, professional medical treatment. This measure of severe hypoglycemia likely has moderate sensitivity but high specificity (18). The incidence rate of severe hypoglycemia in our study was 1.21 per 100 diabetic person-years (95% CI 1.05–1.39), similar to that reported by other studies (8,33–41) (Supplementary Table 6). How any under-ascertainment may have affected our results is unclear. Second, we did not have the exact date of the diabetes diagnoses because diabetes was ascertained only at the study visits. Third, we were not able to account for factors that likely changed over time, such as diabetes medications and kidney function. Finally, the number of events for some outcomes limited the precision of our estimates.

Our study also has important strengths. First, we were able to adjust for numerous rigorously measured covariates, including aspects of diabetes severity and disability. Second, our study includes primarily incident cases of severe hypoglycemia, avoiding "prevalent case bias." Given the high rate of death after severe hypoglycemia, studies using only individuals with prior hypoglycemia likely underestimate the risk of cardiovascular events and mortality associated with severe hypoglycemia (2,32). Indeed, we saw stronger associations with most outcomes after excluding individuals with a history of hypoglycemia at baseline from our analysis. Third, >90% of participants had health insurance and a regular source of care, and we adjusted for income in our models, thus reducing but not eliminating the influence of socioeconomic factors in our analysis. Fourth, we had a long duration of follow-up (~15 years) and a relatively large number of hypoglycemic events, total cardiovascular events, and deaths.

In conclusion, whether severe hypoglycemia is a marker or a cause, our findings reinforce the concern about severe

such as diminished physiologic reserve. Given that we were not able to control for changes in health status over time, it is plausible that development of frailty after baseline could partly explain the observed association between hypoglycemia and mortality. Adjustment for covariates had almost no effect for cancer mortality, suggesting that the elevated risk of cancer death might have been caused by other factors. We also found a higher incidence rate of hypoglycemia among those individuals with more fatal cancers, implying that the observed association of hypoglycemia with cancer mortality may be partly explained by reverse causality: individuals with more fatal cancers may have been more

likely to experience severe hypoglycemia and also have higher risk of death. Alternatively, individuals with reduced physiologic reserve may be more likely to experience severe hypoglycemia and also to die of their cancer. The mechanisms directly linking severe hypoglycemia to noncardiovascular deaths are unclear (31,32).

In clinical settings, severe hypoglycemia could be considered a trigger for increased monitoring by providers. Severe hypoglycemia may be a sign of rapidly declining health, and it may be timely for providers to comprehensively evaluate a patient's physical and mental status to determine whether any adjustments to treatment may be necessary. Such

hypoglycemia and its sequelae. In both middle-aged and older adults, severe hypoglycemia is followed by a high absolute risk of mortality and cardiovascular events, suggesting the need to identify those at high risk for hypoglycemia and to increase monitoring of those with a recent episode of severe hypoglycemia. Greater provider awareness of severe hypoglycemia and the associated morbidity and mortality is needed (42). Hypoglycemia risk stratification tools have recently been developed (43), and although there have been some large-scale efforts to adjust glucose-lowering medications in high-risk individuals (44), the best approaches to reducing insulin dosage and hypoglycemia are still unknown (45). Further studies are needed to determine whether interventions to prevent hypoglycemia also reduce the risk of cardiovascular outcomes.

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