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Severe Hypoglycemia, Cardiac Structure and Function, and Risk of Cardiovascular Events Among Older Adults With Diabetes

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OBJECTIVE

To assess the association of severe hypoglycemia measured at baseline with cardiovascular disease (CVD) among community-dwelling older individuals with diabetes, a group particularly susceptible to hypoglycemia.

RESEARCH DESIGN AND METHODS

We included older adults with diabetes from the Atherosclerosis Risk in Communities (ARIC) study who attended visit 5 (2011–2013, baseline). Severe hypoglycemia at baseline was defined with use of first position ICD-9 codes from hospitalizations, emergency department visits, and ambulance calls. We examined cross-sectional associations of severe hypoglycemia with echocardiographic indices of cardiac structure-function. We prospectively evaluated the risks of incident or recurrent CVD (coronary heart disease, stroke, or heart failure) and all-cause mortality, from baseline to 31 December 2018, using negative binomial and Cox regression models.

RESULTS

Among 2,193 participants (mean [SD] age 76 [5] years, 57% female, 32% Blacks), 79 had a history of severe hypoglycemia at baseline. Severe hypoglycemia was associated with a lower left ventricular (LV) ejection fraction (adjusted β-coefficient −3.66% [95% CI −5.54, −1.78]), higher LV end diastolic volume (14.80 mL [95% CI 8.77, 20.84]), higher E-to-A ratio (0.11 [95% CI 0.03, 0.18]), and higher septal E/e′ (2.48 [95% CI 1.13, 3.82]). In adjusted models, severe hypoglycemia was associated with incident or recurrent CVD (incidence rate ratio 2.19 (95% CI 1.24, 3.88]) and all-cause mortality (hazard ratio 1.71 [95% CI 1.10, 2.67]) among those without prevalent CVD.

CONCLUSIONS

Our findings suggest that a history of severe hypoglycemia is associated with alterations in cardiac function and is an important marker of future cardiovascular risk in older adults.

Hypoglycemia is more common among older individuals with diabetes (1), with a doubling of risk with each additional decade of life after age 60 years (2). A number of factors can contribute to the high risk of hypoglycemia in older adults including age-related decline in renal function, physiological changes in drug metabolism, a high burden of comorbidities, diminished cognitive ability, and potential overtreatment (3). Overtreatment (understood as treatment that is unlikely to result in benefit and may cause harm) is thought to be common in older adults (4), despite recommendations from

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professional bodies for higher glycemic targets in older adults with diabetes (5). Clinical recommendations for diabetes endorse glycemic targets among older adults that are largely based on extrapolation from trials and other studies conducted in middle-aged populations (6). Few community-based studies have examined the consequences of hypoglycemia in older adults (especially those aged 75 years or older). Recent work suggests that severe hypoglycemia is strongly associated with cardiovascular risk, but the pathways remain unclear (7). Emerging evidence shows that subclinical myocardial damage, as assessed by elevated levels of high-sensitivity cardiac troponin T (hs-cTnT), is related to hypoglycemia (8,9). It is unknown whether hypoglycemia independently associates with cardiac structure or function or whether hypoglycemia is associated with incident heart failure.

We used data from the Atherosclerosis Risk in Communities (ARIC) study to assess the cross-sectional associations of severe hypoglycemia with indices of cardiac structure and function and prospective associations with subsequent cardiovascular events among older adults with diabetes.

RESEARCH DESIGN AND METHODS

Study Population

The ARIC study originally recruited 15,792 participants from four U.S. communities (10). The first visit took place in 1987–1989. Since then, participants have returned for subsequent study visits and received telephone calls annually and semiannually (since 2012). Baseline for the current study was the fifth visit (visit 5), which took place from 2011 to 2013 and was attended by 6,538 individuals.

For the current investigation, participants were excluded if they did not have type 2 diabetes at baseline (visit 5). We further excluded the small number of Blacks from Minneapolis or Washington County and those without follow-up data (Supplementary Fig. 1). After these exclusions, there were 2,193 participants with diagnosed diabetes (defined by self-report of a physician diagnosis or use of glucose-lowering medication use [11]) included in our analyses (Supplementary Fig. 1). All the included participants had echocardiographic data on the indices of cardiac function and structure. In our analyses of incident cardiovascular events, we further excluded participants with prevalent disease at baseline for sample sizes of 1,699 for incident coronary heart disease (CHD), 1,986 for incident stroke, and 1,675 for incident heart failure. In a secondary analysis, we examined risk of incident atrial fibrillation in 1,822 participants with no history of atrial fibrillation at baseline.

All study protocols received institutional review board approval at each study site, and all participants provided written informed consent.

History of Severe Hypoglycemia

Severe hypoglycemia events were ascertained at any point prior to baseline (up to the date of visit 5). Severe hypoglycemic events were identified from hospitalizations, emergency department visits, and ambulance calls using a validated algorithm that relies on ICD-9 codes in the primary position (12). The hospitalization records were obtained via active surveillance that captures hospitalizations of ARIC participants in local hospitals and hospitals outside the local catchment area (10) and linkage to Medicare claims for hospitalizations, emergency department visits, and ambulance calls, available for participants enrolled in Medicare fee-for-service part B.

Cardiac Structure and Function

Echocardiography was conducted at visit 5 with use of a standardized protocol across all field centers (13). We examined the following indices: left ventricular ejection fraction (LVEF), left ventricular (LV) mass indexed to body surface area, LV hypertrophy (LVH), left atrial (LA) volume, E-to-A ratio, global longitudinal strain (GLS), interventricular septal thickness, LV end-diastolic diameter (LVEDD), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), relative wall thickness (RWT), right ventricular fractional area change (RVFAC), and pulmonary artery systolic pressure.

Cardiovascular Events and Death

We examined risk of cardiovascular morbidity and mortality including CHD, stroke, and heart failure. The details of the process to define incident CHD (nonfatal or fatal CHD events), stroke (definite or probable ischemic or hemorrhagic stroke), and heart failure, using a two-step process including ICD codes from hospital records and followed by adjudication, are shown in Supplementary Table 1. An expert committee adjudicated cardiovascular events (10,14). An LVEF $\geq$50% was used to define heart failure with preserved ejection fraction and $<$50% to define heart failure with reduced ejection fraction. Atrial fibrillation was identified with ICD-9 or -10 codes for atrial fibrillation or atrial flutter (437.3 or I48) in the absence of cardiac surgery (procedure codes 35.x or 36.x) from hospital records (15). Mortality was assessed via proxy, coroner reports, and the National Death Index through 2017 (10). Follow-up was available through 31 December 2018.

Covariates

Covariates at ARIC visit 5 (2011–2013) were assessed by standardized questionnaires, physical examination, and laboratory tests. Covariates of interest were age, sex, race-center, income, smoking status, use of diabetes medications (insulin or oral medications), duration of diabetes, hemoglobin A_{1c} (HbA_{1c}), estimated glomerular filtration rate (eGFR) calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation (16), albuminuria, BMI, mean systolic and diastolic blood pressures, use of hypertension medication (including ACE inhibitors and angiotensin receptor blockers [ARBs]), LDL cholesterol, HDL cholesterol, lipid-lowering medication use, liver enzymes (ALT, AST), cardiac biomarkers (hs-cTnT and N-terminal–pro–hormone BNP [NT-proBNP]), history of cardiovascular disease (CVD) or heart failure, and frailty. Total cholesterol and HDL cholesterol were measured, and LDL cholesterol was calculated with use of the Friedewald equation. Plasma hs-cTnT was measured with a novel highly sensitive assay with a lower measurable limit of 3 ng/L (Elecsys Troponin T; Roche Diagnostics, Indianapolis, IN). NT-proBNP was measured by an electrochemiluminescent immunoassay on an automated cobas e 411 analyzer (Roche Diagnostics) with a lower measurable limit of 5 pg/mL.

Information on medical history, medication use, alcohol use, and current smoking was obtained with standardized questionnaires. The frailty phenotype was based on a combination of data on weight loss, BMI, physical activity level, waking speed, low energy, and grip strength (17). We classified diabetes medication use as none, oral medication use only, or any insulin use.

Statistical Analyses

We classified participants into categories defined by the presence or absence of

severe hypoglycemia in two groups (no history of severe hypoglycemia or history of severe hypoglycemia) and compared differences in baseline characteristics of participants' variables across these two groups using *t* test (for continuous variables) or the χ^2 test (for categorical variables).

We used linear and logistic regression models to characterize the cross-sectional associations of severe hypoglycemia with indices of cardiac structure and function. Logistic regression models were initially adjusted for age, sex, and race-center. In subsequent models, additional adjustments were made for diabetes duration (model 2), as well as for prevalent CVD and hs-cTnT (model 3). We examined the prospective associations of severe hypoglycemia with incident cardiovascular events and all-cause mortality using Cox regression. We used negative binomial regression to model the association of severe hypoglycemia with recurrent cardiovascular events. A negative binomial regression model accounts for the correlation of recurrent events with each other, which causes a larger variance than if the occurrences were independent because of a positive covariance term.

Model A included age, sex, and race-center. Model B included all variables in model A plus BMI, HDL cholesterol, hypertension, smoking status, and prevalent CVD. Model C included all variables in model B plus duration of diabetes and of diabetes medication use. Model D included all variables in model C plus frailty. In sensitivity analyses, we additionally adjusted for use of ACE inhibitors, ARBs, and liver enzymes (AST and ALT). We verified that the proportional hazards assumption was met by inspecting negative log-log survival plots.

Two-sided *P* values of <0.05 were considered statistically significant. All analyses were performed with Stata, version 15.

RESULTS

Among the 2,193 participants with diagnosed diabetes at visit 5 (2011–2013), 79 had a history of severe hypoglycemia (3.6%). Individuals with severe hypoglycemia at baseline were older and more likely to be Black or using insulin and to have higher HbA_{1c} and longer duration of diabetes (Table 1). A history of severe hypoglycemia was also associated with current alcohol use, elevated diastolic blood pressure, poor kidney function, history of CVD, and higher levels of hs-cTnT and NT-proBNP.

Cross-sectional Association With Cardiac Function and Structure

The echocardiographic characteristics of the participants who experienced a hypoglycemic episode and those who did not are shown in the Supplementary Table 2. There were significant differences between the two groups in terms of LVEDD, interventricular septal thickness, mean wall thickness, LV mass, LVEF, LVEDV, LVESV, GLS, RVFAC, LA volume, and E-to-A ratio. Among the 2,193 participants with diagnosed diabetes, those who experienced a severe hypoglycemia event had a lower LVEF (adjusted β-coefficient −3.66 [95% CI −5.54, −1.78]) and RVFAC (−0.03 [95% CI −0.05, −0.01]) and septal e′ (−0.39 [95% CI −0.77, −0.01]) (model 1) (Table 2). A history of severe hypoglycemia was also associated with a higher LVEDD (0.17 [95% CI 0.04, 0.30]), LVEDV (14.80 [95% CI 8.77, 20.84]), and LVESV (12.02 [95% CI 8.10, 5.93]) and LV mass (21.03 [95% CI 9.22, 32.84]), GLS (0.85 (95% CI 0.13, 1.57]), LA volume (5.61 [95% CI 0.69, 10.53]), E-to-A ratio (0.11 [95% CI: 0.03, 0.18]), and septal E/e′ (2.48 [95% CI 1.13, 3.82]) (Table 2). Additionally accounting for duration of diabetes (model 2) did not substantially affect the magnitude or significance of the associations, whereas further accounting for the history of CVD and hs-cTnT levels (potentially on the pathway from hypoglycemia to cardiac alterations) attenuated these findings, with only the differences in LVEDV, LVESV, and RVFAC remaining statistically significant (model 3) (Table 2).

Incident Cardiovascular Events and Overall Mortality

Of the 2,193 participants, 559 died and 136 experienced an incident or recurrent CVD event. The median follow-up time for CVD events was 5.53 years (range 0.07–7.57) and was 6.1 years (0.07–7.57) for death. The severe hypoglycemic events occurred a median of 5.8 years prior to baseline.

The crude incidence rates of cardiovascular events and mortality were two or more times higher among those older adults with diabetes who had experienced a severe hypoglycemic episode compared with those who had not (Table 3).

A history of severe hypoglycemia was significantly associated with a more than twofold higher risk of incident or recurrent cardiovascular events and all-cause mortality (Table 3) (models A and B). These associations persisted after additional adjustment for diabetes duration and medication use (model C), for incident or recurrent CVD (incidence rate ratio [IRR] 2.19 [95% CI 1.24, 3.88]), and for all-cause mortality (hazard ratio [HR] 1.71 [95% CI 1.10, 2.67]) but were not significant in model 3 for incident CVD (HR 1.85 [95% CI 0.84, 4.07]).

When looking at cardiovascular subtypes, we found that there were associations with incident or recurrent CHD (IRR 2.61 (95% CI 1.11, 6.14) (Table 3) (model C). The results for incident CHD (HR 2.10 [95% CI 0.81, 5.40]), heart failure (HR 1.62 [95% CI 0.65, 4.05]), stroke (HR 1.32 [95% CI 0.39, 4.50]), and atrial fibrillation (HR 1.22 [95% CI 0.49, 3.07]) were not statistically significant. When we examined subtypes of heart failure, there was only one case of heart failure with reduced ejection fraction (data not shown due to imprecision). For heart failure with preserved ejection fraction, the HR was 3.17 (95% CI 1.10, 9.08). For all outcomes, additional adjustment for frailty did not substantially affect the magnitude or the significance of the estimates (Table 3) (model D).

CONCLUSIONS

We observed associations of severe hypoglycemia with measures of cardiac structure and function, cardiovascular events, and all-cause mortality in a community-based population of older adults (including a significant proportion aged ≥75 years) with diagnosed diabetes. Specifically, a history of severe hypoglycemia was related to a lower ejection fraction, greater LV mass and chamber size, and impaired LV filling. Severe hypoglycemia was also associated with an increased risk of future cardiovascular events (including recurrent events) and overall mortality. These results suggest that clinicians should pay particular attention to the potential deleterious cardiovascular effects of hypoglycemia among older individuals with diabetes.

To our knowledge, our study is one of the first studies to assess the relation of hypoglycemia to echocardiographic measures of cardiac function. Prior studies have found associations of severe

Table 1—Baseline characteristics of study participants with diagnosed diabetes, according to history of severe hypoglycemia at baseline: the ARIC study (2011–2013)

	No prior episodes of severe hypoglycemia	Prior episode of severe hypoglycemia	*P*
N (%)	2,114 (96.4)	79 (3.6)	
Age, years	75.8 (5.2)	77.1 (5.5)	0.035
Female sex, *N* (%)	1,206 (57.0)	50 (63.3)	0.27
Race, *N* (%)			<0.001
Whites	1,450 (68.6)	38 (48.1)	
Blacks	664 (31.4)	41 (51.9)	
Systolic blood pressure, mmHg	131.0 (19.6)	133.2 (20.3)	0.35
Diastolic blood pressure, mmHg	65.4 (10.9)	62.2 (11.1)	0.014
Hypertension, *N* (%)	1,781 (85.7)	67 (89.3)	0.37
Current cigarette smoking, *N* (%)	115 (6.4)	1 (1.8)	0.36
Current alcohol use, *N* (%)	756 (38.8)	15 (22.4)	0.019
BMI, kg/m^2	30.6 (6.1)	31.0 (7.4)	0.63
eGFR, mL/min per 1.73 m^2	67.5 (19.2)	54.5 (23.3)	<0.001
eGFR <60 mL/min per 1.73 m^2, *N* (%)	717 (34.6)	38 (52.1)	0.002
HDL cholesterol, mg/dL	48.2 (12.5)	48.0 (12.8)	0.86
LDL cholesterol, mg/dL	93.8 (34.2)	96.6 (36.1)	0.49
Lipid-lowering medications, *N* (%)	1,477 (70.4)	58 (73.4)	0.56
Diabetes medications, *N* (%)			<0.001
No medication use	946 (45.0)	13 (16.5)	
Any insulin use	309 (14.7)	44 (55.7)	
Oral medications only	848 (40.3)	22 (27.8)	
HbA_{1c}, %	6.6 (1.1)	7.1 (1.1)	<0.001
Diabetes duration, years	10.0 (6.6)	18.3 (6.1)	<0.001
Prevalent CVD, *N* (%)	711 (33.6)	46 (58.2)	<0.001
hs-cTnT, ng/L	17.0 (23.0)	32.7 (41.3)	<0.001
NT-proBNP, pg/mL	135.4 (66.5–306.3)	346.7 (145.3–1,236)	<0.001
C-reactive protein, mg/L	5.0 (9.4)	4.6 (4.8)	0.71
ALT, units/L	20.2 (18.6)	17.3 (11.7)	0.18
AST, units/L	22.9 (13.1)	22.2 (9.4)	0.65
ACE inhibitors, *N* (%)	917 (43.4)	41 (51.9)	0.13
ARBs, *N* (%)	249 (11.8)	6 (7.6)	0.25

Data are mean (SD) or median (range) unless otherwise indicated.

hypoglycemia with coronary artery calcification (18) and elevated carotid intima media thickness (19). Our results are consistent with prior findings showing a higher prevalence of subclinical myocardial damage, as assessed by hs-cTnT, in adults with a history of severe hypoglycemia, including among those with existing coronary artery disease (8,9). Our findings suggest that hypoglycemia could contribute to first and recurrent cardiovascular events and that the role of alterations in cardiac structure and function merits further investigation.

Prior studies of hypoglycemia have not examined echocardiographic measures in relation to hypoglycemia, have seldom included heart failure as an outcome (20), and have rarely included many older participants (21–28), and few have examined recurrent cardiovascular events (29). The recurrence of cardiovascular events is an important outcome, as after an initial nonfatal event, there is a high likelihood of a recurrent cardiovascular event (30), especially among individuals with diabetes and older individuals. Our findings of the mortality associated with hypoglycemia also extend the literature on this topic (2,31,32) by providing additional evidence of the adverse impact of hypoglycemia among individuals aged 75 years and above. Our results suggesting a potential association of hypoglycemia with heart failure are in line with recent results from a clinical trial of individuals with diabetes showing a higher risk of hospitalization in relation to severe hypoglycemia (20). Indeed, our overall findings provide a strong foundation to inform glycemic targets in the diabetes treatment guidelines among individuals aged 75 years and above, especially as there is currently a lack of evidence on the extent of treatment intensification in this subpopulation of patients with diabetes (5).

Severe hypoglycemia was uncommon. Less than 4% of the baseline population of adults with diagnosed diabetes in our community-based cohort was identified as having a past episode of severe hypoglycemia. These cases were likely only a very small fraction of true hypoglycemia and likely represent a subset of the most severe episodes, as they involved contact with the health care system (emergency department visit, ambulance call, or hospitalization). Older adults are more likely to have hypoglycemia unawareness compared with younger individuals with diabetes as a result of blunted counterregulatory

Table 2—Adjusted measures of association for severe hypoglycemia with indices of cardiac structure and function: ARIC visit 5 adults with diagnosed diabetes (2011–2013)

	β-Coefficient or odds ratio (95% CI)		
Indices of cardiac structure and function	Model 1	Model 2	Model 3
LV structure measures			
LVEDD, cm	0.17 (0.04, 0.30)	0.15 (0.02, 0.29)	0.10 (−0.03, 0.24)
Interventricular septum, cm	0.04 (−0.01, 0.08)	0.03 (−0.02, 0.07)	0.01 (−0.03, 0.06)
Mean wall thickness, cm	0.04 (−0.01, 0.08)	0.02 (−0.01, 0.06)	0.01 (−0.03, 0.05)
LV mass, g	21.03 (9.22, 32.84)	17.65 (5.63, 29.66)	10.94 (−1.19, 23.08)
Relative wall thickness	0.00 (−0.02, 0.02)	−0.00 (−0.03, 0.02)	−0.01 (−0.03, 0.02)
LVH*	0.99 (0.40, 2.47)	0.79 (0.31, 2.02)	0.73 (0.28, 1.91)
Ventricular systolic function			
LVEF, %	−3.66 (−5.54, −1.78)	−3.31 (−5.22, −1.39)	−2.93 (−4.86, −1.01)
LVEDV, mL	14.80 (8.77, 20.84)	12.76 (6.62, 18.90)	11.75 (5.49, 18.01)
LVESV, mL	12.02 (8.10, 15.93)	10.78 (6.79, 14.76)	9.79 (5.76, 13.83)
GLS, %	0.85 (0.13, 1.57)	0.77 (0.04, 1.50)	0.63 (−0.11, 1.36)
RVFAC	−0.03 (−0.05, −0.01)	−0.03 (−0.05, −0.01)	−0.03 (−0.05, −0.01)
PASP, mmHg	1.72 (−0.68, 4.12)	1.01 (−1.44, 3.46)	−0.03 (−2.54, 2.47)
LV diastolic function measures			
LA volume, mL	5.61 (0.69, 10.53)	4.83 (−0.18, 9.85)	2.98 (−2.08, 8.05)
E wave, cm/s	2.83 (−2.41, 8.07)	0.74 (−4.58, 6.06)	−0.85 (−6.30, 4.60)
E-to-A ratio	0.11 (0.03, 0.18)	0.10 (0.03, 0.18)	0.07 (−0.01, 0.15)
e′ septal, cm/s	−0.39 (−0.77, −0.01)	−0.30 (−0.68, 0.09)	−0.28 (−0.68, 0.12)
E/e′ septal	2.48 (1.13, 3.82)	1.82 (0.46, 3.18)	1.37 (−0.01, 2.75)

Model 1, adjustment for age, sex, and race/center; model 2, adjustment for variables in model 1 + diabetes duration; model 3, adjustment for variables in model 2 + prevalent CVD and hs-cTnT (categorized as ≥90th percentile and below). PASP, pulmonary artery systolic pressure. *Estimates are odds ratios for the presence vs. absence of LVH as the reference group (null value = 1).

response, which is more common in those with long disease duration and/or cognitive impairment (33). Despite the small number of cases identified in our study, hypoglycemia was associated with substantial concurrent and future cardiovascular morbidity and mortality. The nonsignificant associations observed with some of the cardiovascular outcomes were likely due to limited power.

Clinical practice guidelines recommend avoiding tight glycemic control in older (especially those aged ≥75 years) individuals with diabetes (5), who generally have a high burden of comorbidities including prior CVD, frailty, and cognitive disorders. Despite these recommendations, putative overtreatment is common in such patients, particularly with insulin or sulfonylureas (34). Our study supports a de-escalation of therapy in some individuals in this age-group and/or the primary use of diabetes medications with a lower hypoglycemic potential, especially among those with a history of hypoglycemia, in whom the benefits of tight glycemic control may not outweigh the benefits. Our results also highlight the vulnerability of older adults and major comorbidity and mortality associated with severe hypoglycemia.

The mechanisms linking severe hypoglycemia to cardiovascular events and death are uncertain. Putative mechanisms include cardiac arrhythmias (mainly bradycardia and a prolongation of the QT interval, with the latter possibly causing sudden cardiac death) and myocardial ischemia (7,35). The diabetes-related processes that favor myocardial ischemia include a poor coronary arterial perfusion due to arterial stiffness and a proinflammatory state with prothrombotic (increased platelet activation, impaired fibrinolysis, and elevated hemostasis) effects related to endothelial dysfunction (due to high levels of endothelin) (7,35). Endothelial function is altered during hypoglycemia because of inflammation and the mobilization and activation of neutrophils and platelet activation (7,35). All these changes may promote intravascular coagulation and thrombosis and encourage the development of tissue ischemia. The observed alteration in cardiac structure and function linked to hypoglycemia may be a reflection of the ischemic remodeling associated with myocardial damage as suggested by studies linking hypoglycemia to elevated hs-cTnT (8,9). Finally, it is possible that hypoglycemia is a primary marker for cardiovascular risk and not a direct causal factor.

There are limitations to our study. First, we were not able to establish the temporality of the observed associations with abnormal cardiac structure and function. Second, there is a possibility of selection or survival bias, as healthier individuals were more likely to attend the study visit (and some individuals may have died of hypoglycemia or related complications prior to the study visit). Third, due to the limited number of severe hypoglycemia cases, we had limited power to explore some outcomes and subgroups. The latter limitation also affected our ability to account for multiple testing in investigating cardiac function and geometry, which was primarily a proof-of-concept exploration. Fourth, our reliance on hospitalizations and claims data resulted in a definition of hypoglycemia that was highly specific but likely reflects substantial under-ascertainment (12). We also did not assess hypoglycemia during the period extending from the baseline visit to the occurrence of events. Finally, we did not have data on arrhythmias other than atrial fibrillation.

Our study has strengths that include the assessment of a community-based sample of older individuals (aged ≥75 years) with diabetes, a group with limited data. We also examined a wide range of cardiac outcomes including measures cardiac

Table 3—Event rates and estimate of relative risk (95% CI) for the associations of history of severe hypoglycemia with cardiovascular outcomes and mortality

	No hypoglycemia		Hypoglycemia		HR or IRR (95% CI)*			
Outcomes	Number of events/*N*	Crude incidence rate per 1,000 person-years (95% CI)	Number of events/*N*	Crude incidence rate per 1,000 person-years (95% CI)	Model A	Model B	Model C	Model D
Incident cardiovascular events	207/1,402	26.7 (23.3, 30.6)	8/33	51.9 (26.0, 103.8)	1.75 (0.86, 3.56)	2.50 (1.16, 5.39)*	1.85 (0.84, 4.07)	1.64 (0.74, 3.62)
Incident or recurrent cardiovascular events	1,216/2,114	159.0 (136.5, 181.5)	135/79	717.9 (398.4, 1,037.4)	4.61 (2.74, 7.74)*	3.20 (1.95, 5.25)	2.19 (1.24, 3.88)	2.24 (1.28, 3.93)
All-cause mortality	521/2,114	44.2 (40.6, 48.2)	38/79	110.9 (80.7, 152.4)	2.33 (1.67, 3.26)	2.44 (1.60, 3.72)	1.71 (1.10, 2.67)*	1.62 (1.04, 2.52)
Incident CHD	89/1,699	9.4 (7.7, 11.6)	5/51	21.2 (8.8, 51.0)	1.91 (0.77, 4.74)	2.96 (1.18, 7.40)	2.10 (0.81, 5.40)	1.74 (0.67, 4.51)
Incident/recurrent CHD	230/2,114	21.9 (18.2, 25.6)	28/79	178.7 (40.4, 317.1)	8.10 (3.56, 18.44)	4.09 (1.79, 9.34)*	2.61 (1.11, 6.14)	2.47 (1.08, 5.66)
Incident stroke	93/1,986	8.5 (7.0, 10.4)	4/69	13.1 (4.9, 34.9)	1.35 (0.49, 3.70)	1.54 (0.48, 4.91)	1.32 (0.39, 4.50)	1.30 (0.38, 4.42)
Incident or recurrent stroke	109/2,114	9.4 (7.5, 11.2)	4/79	11.6 (0.7, 22.4)	1.15 (0.40, 3.25)	1.21 (0.36, 4.08)	0.92 (0.26, 3.22)	0.88 (0.26, 2.97)
Incident heart failure	182/1,675	2.1 (1.8, 2.4)	7/40	3.6 (1.7, 7.6)	1.67 (0.78, 3.58)	2.03 (0.82, 5.02)	1.62 (0.65, 4.05)	1.51 (0.60, 3.79)
Atrial fibrillation	208/1,822	23.1 (20.2, 26.5)	8/61	33.6 (16.8, 67.2)	1.38 (0.67, 2.81)	1.30 (0.53, 3.18)	1.22 (0.49, 3.07)	1.16 (0.46, 2.90)

N, number of individuals at risk for the examined event. Cardiovascular events are myocardial infarction, fatal CHD, definite/probable stroke, and heart failure. Model A, estimate adjusted for age, sex, and race-center; model B, estimate adjusted for age, sex, race-center, BMI, HDL cholesterol, hypertension, and smoking status; model C, estimate adjusted for age, sex, race-center, BMI, HDL cholesterol, hypertension, smoking status, diabetes duration, and use of diabetes medication; model D, estimate adjusted for age, sex, race-center, BMI, HDL cholesterol, hypertension, smoking status, diabetes duration, use of diabetes medication; and frailty. Models B, C, and D are additionally adjusted for prevalent CVD for the analysis of recurrent events. Incident cardiovascular events (or heart failure) analyses exclude those with prevalent cardiovascular events (heart failure).

structure and function and incident events. The study also benefited from rigorous assessment and standardized adjustment for known cardiovascular risk factors.

Conclusion

In conclusion, our findings reinforce the concerns about hypoglycemia among older adults. Our study demonstrates that a history of severe hypoglycemia is an important marker of concurrent and future cardiovascular risk. Prevention of severe hypoglycemia and mitigation of cardiovascular risk among older adults with diabetes should be a priority.

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