Severe Hypoglycemia and Risk of Falls in Type 2 Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

Alexandra K. Lee,[1] Stephen P. Juraschek,[2,3] B. Gwen Windham,[4] Clare J. Lee,[5] A. Richey Sharrett,[2] Josef Coresh,[2] and Elizabeth Selvin[2]

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OBJECTIVE

Hypoglycemia has been postulated to contribute to falls risk in older adults with type 2 diabetes. However, few studies have prospectively examined the association between severe hypoglycemia and falls, both important causes of morbidity and mortality.

RESEARCH DESIGN AND METHODS

We conducted a prospective cohort analysis of participants from the Atherosclerosis Risk in Communities (ARIC) study with diagnosed diabetes at visit 4 (1996–1998). Episodes of severe hypoglycemia requiring medical treatment were identified using ICD-9 codes from hospitalizations, emergency department visits, and ambulance calls; total falls were identified from medical claims using E-codes from 1996 to 2013. Secondary analyses examined hospitalized falls and falls with fracture. We calculated incidence rates and used Cox regression models to evaluate the independent association of severe hypoglycemia with falls occurring after visit 4 through 2013.

RESULTS

Among 1,162 participants with diabetes, 149 ever had a severe hypoglycemic event before baseline or during the median of 13.1 years of follow-up. The crude incidence rate of falls among persons without severe hypoglycemia was 2.17 per 100 person-years (PY) (95% CI 1.93–2.44) compared with 8.81 per 100 PY (6.73–11.53) with severe hypoglycemia. After adjustment, severe hypoglycemia was associated with a more than twofold higher risk of falls (hazard ratio 2.23, 95% CI 1.61–3.07). Associations were consistent in subgroups defined by age, sex, race, BMI, duration of diabetes, or functional difficulty.

CONCLUSIONS

Severe hypoglycemia was associated with a substantially higher risk of falls in this community-based population of adults with diabetes. Fall risk should be considered when individualizing glycemic treatment in older adults. Assessing hypoglycemia history and future hypoglycemia risk could also improve multifactorial fall prevention interventions for older adults with diabetes.

[1]Division of Geriatrics, University of California, San Francisco, San Francisco, CA
[2]Department of Epidemiology and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
[3]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA
[4]Department of Medicine/Geriatric Medicine, University of Mississippi Medical Center, Jackson, MS
[5]Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins School of Medicine, Baltimore, MD

Corresponding author: Elizabeth Selvin, eselvin@jhu.edu

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Falls and fractures have a high burden of morbidity and mortality among older adults (1,2). In the U.S., approximately one-third of adults aged ≥65 years fall each year (3), and falls are the leading cause of injury-related death among older adults (1,4). Falls can also lead to a downward spiral in health: >30% of falls result in injury (2), and related injuries or fear of future falls can lead to restriction of daily activities and loss of independence (5). Individuals with falls are also more likely to be admitted to nursing homes (6), a major change in quality of life. Given the high burden of falls in the growing aging population, it is important to identify modifiable risk factors for fall prevention to preserve the health and quality of life of older adults.

For older adults with diabetes, falls are both more common (7,8) and are more likely to result in fracture and further health consequences (9,10). However, factors contributing to this association are uncertain (11–13). Numerous studies have shown that insulin use is associated with an increased risk of falls (8,14), but it is unclear whether insulin is a marker of more severe diabetes with a greater burden of complications, such as retinopathy and peripheral neuropathy, known to increase fall risk (11–13), or whether the association is due to hypoglycemia. Hypoglycemia may directly lead to falls due to symptoms, particularly from neuroglycopenia, including confusion, blurred vision, and motor and balance incoordination (15). Additionally, recurrent hypoglycemia over time contributes to autonomic dysfunction and diminished counterregulatory responses, leading to poor hypoglycemia awareness, potentially increasing risk of falls. Previous studies examining the association of hypoglycemia and fall risk have been mixed and limited in scope and follow-up time (16–21).

We evaluated the longitudinal association of severe hypoglycemia with the risk of falls among middle-aged and older adults with type 2 diabetes in the Atherosclerosis Risk in Communities (ARIC) study cohort. We hypothesized that severe hypoglycemia would be associated with increased fall risk even after adjustment for diabetes severity and other risk factors.

RESEARCH DESIGN AND METHODS

Study Population

The ARIC study began in 1987–1989 and recruited 15,792 participants from four U.S. communities: Jackson, Mississippi; Forsyth County, North Carolina; Washington County, Maryland; and suburbs of Minneapolis, Minnesota. Details of study recruitment have been published elsewhere (22). In-person study visits occurred every 3 years from 1987 to 1989 (visit 1) through 1996–1998 (visit 4), and subsequent visits were in 2011–2013 (visit 5), 2015–2017 (visit 6), and 2018–2019 (visit 7). Visit 4 is the baseline for the present analysis, chosen to maximize the number of participants with Medicare claims at baseline and throughout follow-up.

Our study population was composed of ARIC participants at visit 4 (1996–1998) with diagnosed diabetes through self-report of diabetes diagnosis or current use of diabetes medications (n = 1,511). Participants were excluded if they self-reported race other than black or white (n = 4) or if they reported black race at the Maryland or Minnesota study sites (n = 6) to avoid small group sizes for analysis. We also excluded participants who were missing any covariates (n = 339). Our final sample size was 1,162.

Severe Hypoglycemia

Severe hypoglycemia was ascertained from ARIC hospitalization records since visit 1 and Medicare claims for hospitalizations, emergency department visits, and ambulance calls from 1991 to 2013 for Medicare beneficiaries; emergency department and ambulance claims were available only for 1,005 participants (86.5%) who were enrolled in Medicare Fee-For-Service Part B. Using a widely used algorithm, we identified events based on a primary position *International Classification of Diseases*, Ninth Revision (ICD-9) code for hypoglycemia (23). ARIC hospitalization records were available for all ARIC participants from 1987 to 2013.

Fall Outcomes

The primary outcome was any fall, captured in ARIC hospitalization records or Medicare claims from visit 4 (1996–1998) through 2013, identified by ICD-9-Clinical Modification E codes E880.x–E886.x or E888.x (Supplementary Table 1). The sensitivity and specificity of this approach have been reported previously (24). To investigate whether hypoglycemia was associated with potentially more harmful falls requiring hospitalization or treatment for fractures, we examined several secondary outcomes. First, we looked at any hospitalized fall, using the same set of codes as above. Second, we examined any fall with additional ICD-9 diagnosis codes for fracture (fractures from injury: 800.x–829.x; pathologic or stress fractures: 733.1, 733.93, 733.94, 733.95, 733.96, 733.97, and 733.98; and late effect of fractures: 905.0, 905.1, 905.2, 905.3, 905.4, and 905.5).

Statistical Analysis

We compared baseline (visit 4) characteristics of participants with and without severe hypoglycemia before baseline or anytime during follow-up by using χ^2 tests and t tests as appropriate. We calculated incidence rates and modeled incidence rate ratios using Poisson regression to adjust for age, sex, and race-center.

The primary analysis used Cox regression for the outcome of falls, with severe hypoglycemia modeled as a time-varying exposure, conceptualized as "no history of hypoglycemia" or "any history of severe hypoglycemia." Because the risk of falls increases substantially with older age, we used age as the time scale (25). To explore the effects of various sets of confounders, we progressively adjusted the Cox models. Model 1 included age, sex, and race-center. Model 2 included the variables in model 1 and diabetes characteristics: diabetes duration, fructosamine with a linear spline knot at 330 μmol/L, and diabetes medication use, categorized as none, any oral medication (90% of which were sulfonylureas), and any insulin use. Because hemoglobin A_{1c} (HbA_{1c}) was not measured at visit 4, fructosamine was used to adjust for average glycemia. Model 3 included variables from model 2 plus other shared risk factors for hypoglycemia and falls: antidepressant use, benzodiazepine use, difficulty with any activity of daily living (ADL) (eating, dressing, walking between rooms, standing from an armless chair, and getting out of bed), estimated glomerular filtration rate based on cystatin C, albuminuria (modeled as log of albumin-to-creatinine ratio), BMI (modeled using a linear spline with a knot at 25 kg/m^2), global cognitive z score (averaged z scores from the Digit Symbol Substitution Test, Delayed Word Recall Test, and Word Fluency Test), and number of comorbidities (0, 1, 2, or ≥3) of the following: coronary heart disease, stroke, heart failure, lung disease, liver cirrhosis, Parkinson disease, cancer, arthritis, pulmonary, or deep vein thrombosis. Several comorbidities were assessed

through active ARIC surveillance (coronary heart disease, stroke, and heart failure) (22,26), whereas the others were by self-report at visit 4. The proportionality assumption of the Cox model was verified with visual inspection of the negative log-log survival curves.

We examined potential effect modification by age, sex, race, obesity, duration of diabetes, diabetes medication type, and difficulty with ADLs at baseline using likelihood ratio tests.

We conducted several sensitivity analyses. First, we adjusted for retinopathy at baseline from fundus photography (27), and then we excluded individuals with peripheral artery disease at baseline and censored those who developed peripheral artery disease at the time of an amputation or revascularization procedure to eliminate the possibility that hypoglycemia was associated with falls merely due to its co-occurrence with peripheral artery disease and falls in people with advanced diabetes complications. Finally, we used HbA_{1c} measured 6 years before baseline (visit 2, 1990–1992) instead of fructosamine in all analyses.

All analysis was conducted in Stata SE 15.1 software (StataCorp LLC, College Station, TX).

RESULTS

Of the 1,162 participants with diagnosed diabetes at baseline (visit 4), 149 had severe hypoglycemia before their first fall, death, or 31 December 2013, and 334 falls occurred. Hypoglycemia was documented in 14 before baseline and in 135 during a median of 13.1 years of follow-up. Participants who ever had severe hypoglycemia were older and were more likely to be black, to have difficulty with ADLs, and to have lower cognitive function (Table 1). Participants who ever had severe hypoglycemia tended to have more advanced diabetes at baseline: they had longer duration of diabetes, had higher mean fructosamine, and were more likely to use insulin.

The crude incidence rate of falls identified via medical claims was 2.17 per 100 person-years (PY) (95% CI 1.93–2.44) among those without severe hypoglycemia and 8.81 per 100 PY (95% CI 6.73–11.53) among those with severe hypoglycemia (Fig. 1). The age-, sex-, and race-adjusted incidence rate ratio was 3.11 (95% CI 2.29–4.24). The incidence rates of hospitalized falls and falls with fracture were substantially lower than the rates of any falls but followed the same pattern as total falls. Of the 155 hospitalized falls, 95 (61%) included a code for fracture.

In the primary analysis with Cox regression, severe hypoglycemia was strongly associated with falls after adjustment. Severe hypoglycemia was associated with a threefold higher risk of any fall after adjustment for age, sex, and race-center, which was attenuated but remained more than two times higher compared with those without hypoglycemia after additional adjustment (Table 2) (model 1, hazard ratio [HR] 3.06 [95% CI 2.26–4.14]; model 2, HR 2.61 [1.90–3.57]; and model 3, HR 2.23 [1.61–3.07]). Results were similar for the other outcomes, although the increased risk for falls with fracture was no longer statistically significant but remained elevated (model 3, HR 1.61 [0.98–2.66]).

The data did not support effect modification for all falls by baseline age, sex, race, obesity, diabetes duration, diabetes medication type, or disability (all P for interaction $\geq$0.2) (Fig. 2). In sensitivity analyses, additional adjustment for retinopathy and censoring individuals at the time of peripheral artery disease did not change the results (Supplementary Table 2). Adjusting for HbA_{1c} measured 6 years before baseline instead of fructosamine did not substantially change the results (Supplementary Table 3).

CONCLUSIONS

In this community-based prospective cohort study, severe hypoglycemia was associated with a substantially increased risk of any fall, hospitalized fall, and fall with fracture. These associations were consistent in various subgroups and remained significant in analyses adjusting for chronic diabetes complications. Among adults aged $\geq$75 years with severe hypoglycemia, the annual risk of a fall requiring medical attention was >10%. Although our findings cannot decisively support causality, it is clear that severe hypoglycemia is a strong marker of fall risk. It is plausible that severe hypoglycemia may

Table 1—Baseline (1996–1998) characteristics of participants by hypoglycemia before or during follow-up (N = 1,162)

	No hypoglycemia, n = 1,013	Ever hypoglycemia,* n = 149	P value
Age (years)	63.5 (5.7)	64.8 (5.5)	0.008
Female sex	53.8	55.7	0.66
Black race	30.4	44.3	0.001
BMI (kg/m^2)	31.4 (5.9)	32.3 (5.7)	0.08
Fructosamine (μmol/L)**	328.7 (69.1)	366.5 (76.7)	<0.001
$eGFR_{cystatin\ C}$	69.8 (20.8)	64.3 (21.9)	0.003
Albumin-to-creatinine ratio	5.6 (1.8, 20.7)	12.5 (3.6, 87.3)	<0.001
Diabetes medication use			<0.001
None	29.4	9.4	
Oral only	45.5	43.6	
Any insulin	25.1	47.0	
Diabetes duration (years)	5.1 (3.7)	6.5 (3.2)	<0.001
Antidepressant use	8.3	13.4	0.04
Benzodiazepine use	5.9	8.7	0.19
Number of comorbidities***			0.78
0	34.6	30.9	
1	41.1	43.6	
2	17.6	17.5	
≥3	6.7	8.0	
Any ADL difficulty****	34.2	47.7	0.001
Global cognitive z score	−0.36 (1.0)	−0.84 (1.0)	<0.001

Data are presented as percentage, mean (SD), or median (25th, 75th percentiles). $eGFR_{cystatin\ C}$, estimated glomerular filtration rate based on cystatin C. *14 had severe hypoglycemia before baseline, and 135 had severe hypoglycemia during follow-up. **Fructosamine of 275 μmol/L corresponds to an HbA_{1c} of 7.0%; 335 μmol/L corresponds to an HbA_{1c} of 8.2% (36). ***Comorbidities: coronary heart disease, stroke, heart failure, lung disease, liver cirrhosis, Parkinson disease, cancer, arthritis, pulmonary or deep vein thrombosis. ****ADL defined as eating, dressing, getting out of bed, standing from an armless chair, and walking between rooms. P values were calculated with χ^2 or t tests, as appropriate.

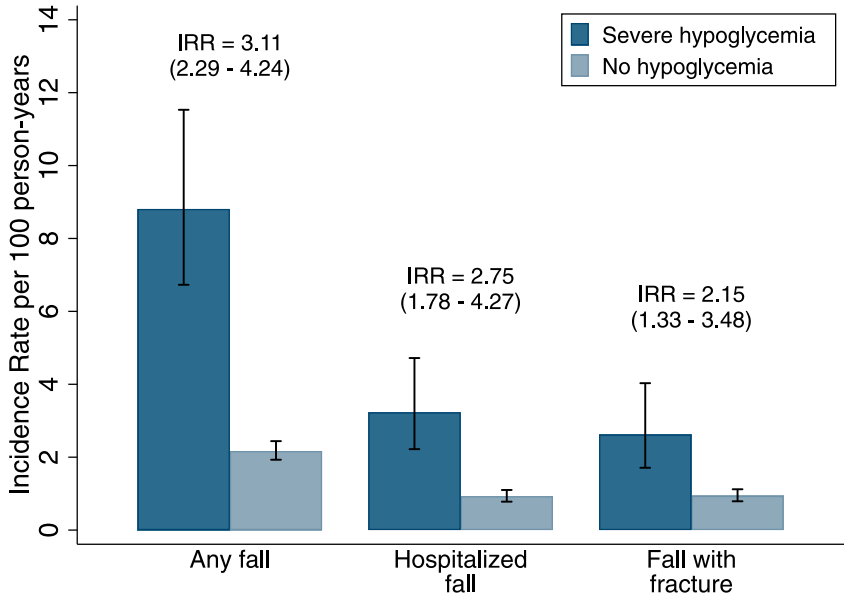

Figure 1—Incidence rates and adjusted incident rate ratios (IRRs) (adjusted for age, sex, and race-center) with 95% CIs for falls by hypoglycemia (n = 1,162).

be an important modifiable risk factor for falls among older adults with diabetes. These findings highlight the importance of avoiding hypoglycemia in older adults and support current American Diabetes Association guidelines that suggest less intensive glycemic treatment for individuals with notable fall risk (28).

Our results extend the epidemiologic literature on the link between hypoglycemia and falls. Two previous studies recruited small clinical samples, relying on self-reported hypoglycemia and self-reported falls within the past year. One study found a nonsignificant 66% greater odds of falls with hypoglycemia (16), while the other study showed a significant graded association between the frequency of hypoglycemia and the risk of falls (21). Three other studies used claims databases and ICD-9 codes to identify hypoglycemia and falls (with one study restricted to noninsulin users only), and each found that hypoglycemia was associated with an increased risk of falls (17–19). Many of these studies had incomplete adjustment for potential confounders such as functional status and glycemic control. We found a stronger association than in other studies even after adjustment for baseline cognitive and functional abilities as well as glycemic control and comorbidities. Thus, our study adds to the existing literature by demonstrating that the observed association between hypoglycemia and falls is more likely to be independent of confounding factors.

Our study showed that while the absolute rates of falls were higher in older adults, the association of hypoglycemia with falls did not significantly differ by age. Other studies have shown differences by age: one study found a stronger association of hypoglycemia with falls in adults aged ≥65 years compared with those aged <65 (19), whereas another study found a higher risk among adults aged <65 years (18). Our study suggests that the risk of falls with hypoglycemia should be taken just as seriously in middle-aged adults as in older adults. Similarly, we found no interaction by sex or BMI—known risk factors for falls—suggesting that hypoglycemia appears to be associated with similar fall risk regardless of these risk factors.

From these data we cannot determine whether an episode of hypoglycemia directly contributed to the fall itself, making causal inference difficult. There were five instances in which severe hypoglycemia and a fall occurred on the same day, suggesting a likely contributing role of hypoglycemia. Like others, we believe that a single episode of severe hypoglycemia may be a marker of recurrent hypoglycemia (19), because hypoglycemia is consistently underascertained, with events captured by the medical system potentially representing as few as 5% of all hypoglycemic events (29). A single episode of severe hypoglycemia is also indicative of substantial glycemic variability, representing frequent drops and spikes in blood glucose (30). Few existing data sources have measured blood glucose during hypoglycemia that may have precipitated a fall. Future studies with continuous glucose monitoring and active ascertainment of falls could provide important information on the relative timing of hypoglycemia and falls that would strengthen the case for a causal association.

It is important to note the limitations of our study. First, we relied on claims-based definitions of hypoglycemia and falls, which are highly specific but likely only moderately sensitive for the true incidence of these events (23,24,31). This could introduce bias into our results if the likelihood of hospitalization for falls was correlated with the risk of hypoglycemia.

Table 2—Adjusted HRs and 95% CIs for severe hypoglycemia with falls (N = 1,162)

	Number of events without hypoglycemia	Number of events with hypoglycemia	HR (95% CI)		
			Model 1	Model 2	Model 3
Any fall	281	53	3.06 (2.26–4.14)	2.61 (1.90–3.57)	2.23 (1.61–3.07)
Hospitalized fall	128	27	2.61 (1.69–4.02)	2.32 (1.49–3.63)	2.27 (1.43–3.59)
Fall with fracture	129	21	2.06 (1.28–3.31)	1.68 (1.03–2.74)	1.61 (0.98–2.66)

Model 1: age, sex, race-center. Model 2: model 1 plus fructosamine (linear spline knot at 330 μmol/L), diabetes medications, diabetes duration. Model 3: model 2 plus any ADL difficulty, antidepressant use, benzodiazepine use, estimated glomerular filtration rate, albumin-to-creatinine ratio, number of comorbidities (0, 1, 2, ≥3), BMI (linear spline knot at 25 kg/m^2), and global cognitive z score.

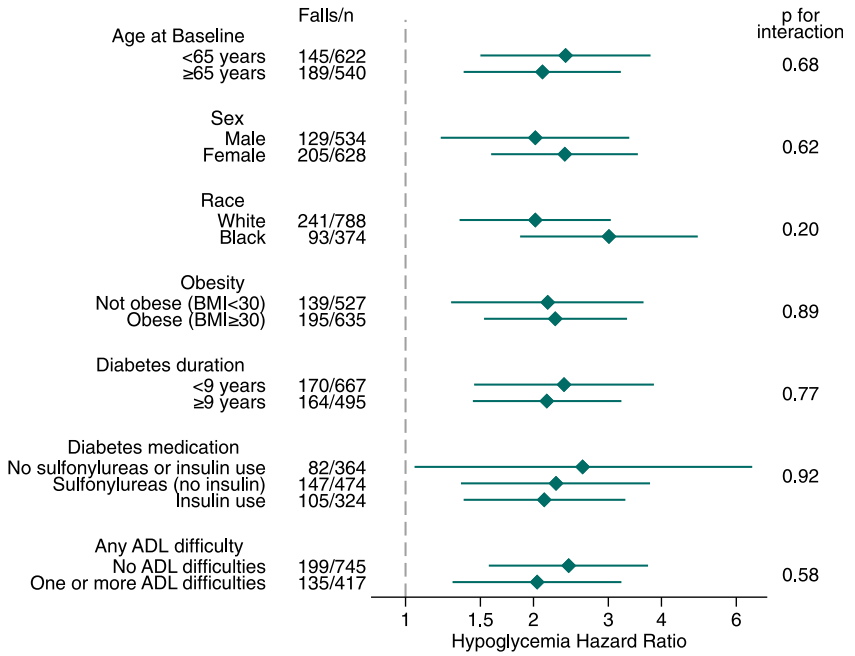

Figure 2—Adjusted HRs and 95% CIs for severe hypoglycemia with falls by subgroups ($n = 1,162$). All models include the covariates in model 3.

Second, we were unable to account for factors that likely changed over time such as diabetes medication use or retinopathy and peripheral neuropathy, both of which affect more than one-quarter of older adults (32,33). However, we did account for the development of peripheral artery disease diagnosis during follow-up in a sensitivity analysis. Third, our definition of severe hypoglycemia is insensitive because we were not able to detect hypoglycemia resulting in emergency department and ambulance services if ARIC participants did not have Medicare Fee-for-Service Part B. Finally, we were unable to determine whether hypoglycemia contributed directly to the fall.

Our study also has several strengths. First, we were able to conduct a prospective analysis of rigorously collected data on >1,100 adults with type 2 diabetes in a community-based setting, with hypoglycemia modeled as a time-varying variable. Second, we were able to control for diabetes characteristics, including glycemic control, duration of diabetes, and baseline diabetes medication use, which prior prospective studies of hypoglycemia and falls have not (17–19). Third, we were able to examine and compare associations for different types of fall events.

Our study has several clinical implications. First, it is important to consider fall risk when determining the appropriate glycemic treatment for older adults. Current American Diabetes Association guidelines consider falls a comorbidity to be incorporated into the overall assessment of an individual's health status (28), and Endocrine Society guidelines note falls as part of the general health assessment (34). In addition to hypoglycemia risk, fall risk and fear of falling should be part of diabetes treatment discussions between providers, patients, and caregivers.

A second clinical implication is that after an episode of severe hypoglycemia, action should be taken to reduce risk of future hypoglycemia, which may help reduce risk of falls. Hypoglycemia should be a triggering event to reevaluate the potential risks and benefits of glycemic treatment.

Finally, multifactorial fall assessments and interventions should consider hypoglycemia risk a potential modifiable risk factor among older adults with diabetes. Existing guidelines for fall prevention have focused on psychotropic medications and polypharmacy (35), but our results suggest that glycemic medications should also be prioritized because reducing hypoglycemic risk may help reduce fall risk.

In summary, severe hypoglycemia was associated with a more than two times greater risk of falls and a high absolute risk of falls. Given the increasing numbers of older adults with diabetes and the importance of avoiding falls for independent living and maintaining quality of life, it is important to understand whether interventions to prevent hypoglycemia will also reduce the rate of falls among older adults with type 2 diabetes.

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