Severe Hypoglycemia and Risk of Atherosclerotic Cardiovascular Disease in Patients With Diabetes

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Meta-analyses and reviews of observational cohorts have reported a relationship between severe hypoglycemia (SH) and atherosclerotic cardiovascular disease (ASCVD) events, but estimates of effect vary widely and many studies are limited by size and diversity, ability to adjust for confounders, and inconsistent definitions of exposures and outcomes (1–4). We studied the association of SH events and risk of ASCVD in a large, diverse cohort of patients. This study was approved by the Kaiser Permanente Northern California (KPNC) Institutional Review Board.

This observational cohort study included adults (age ≥18 years) with diabetes who were members of KPNC, an integrated health care delivery system, with continuous membership during the 2 years prior to baseline. The outcomes of interest were ASCVD events, defined as a composite of nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or death due to coronary heart disease. The exposure of interest was an SH event defined by a primary diagnosis of hypoglycemia in the emergency department or principal diagnosis in the hospital. Baseline was determined by the date of the first SH event during 1 January–31 December 2013. For each individual in the reference group (no SH event), baseline was a randomly assigned date in 2013. We followed subjects from baseline until censoring due to ASCVD event, death, loss to follow-up, or the end of the study, 31 December 2017. Adjusted multivariate Cox proportional hazards models were specified to estimate time to ASCVD events by SH.

We identified 233,696 eligible individuals; their mean age was 63.6 years, 47.6% were women, and mean follow-up was 3.8 years. In 2013, there were 2,179 SH events (Table 1). Unadjusted hazard ratio (HR) of ASCVD among those with an SH event versus those without was 3.2 (95% CI 2.9–3.6). The age-, sex-, and race-adjusted HR was 2.6 (95% CI 2.3–2.9). In a fully saturated model (additional adjustments for residing in the most deprived neighborhood quartile, sulfonylurea use, diabetes type, prevalent ASCVD, last HbA_{1c}, diabetes duration, estimated glomerular filtration rate (eGFR), Charlson comorbidity score, and insulin use), the HR was 1.3 (95% CI 1.2–1.5).

In a large, diverse, and contemporary cohort of patients with diabetes, SH events were associated with a (unadjusted) tripling of ASCVD risk. Unlike previous studies, we were able to capture a wide array of clinical and socioeconomic factors in a real-world population. We found that crude estimates of the SH-ASCVD relationship were most strongly confounded by insulin use, Charlson comorbidity score, eGFR, and diabetes duration. After accounting for substantial confounding, SH was still associated with an ∼30% increase in ASCVD risk.

There are several limitations to note. These data are derived from a regionally based integrated health care delivery system and may not be representative of the U.S. Most SH events (for which the patient requires assistance) are treated outside of the health care system and are not captured in the medical record; we estimate that ∼5% of SH results in emergency department or hospital utilization (5). Although we adjusted for a wide range of potentially confounding factors, the observational nature of these data precludes causal inferences. Moreover, we cannot rule out that ASCVD also increases the risk of SH.

SH is a potential marker for heightened risk of ASCVD. Increased vigilance in care for patients with history of SH is warranted.

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Table 1—Prebaseline characteristics and ASCVD outcomes of 233,696 patients with diabetes with or without SH events

	No SH event (N = 231,517)	SH event (N = 2,179)
***A.* Characteristics**		
Sex (female)	110,173 (47.6)	1,025 (47.0)
Age, years, mean (SD)	63.57 (13.5)	67.84 (15.0)
Age category, years		
18–40	10,869 (4.7)	115 (5.3)
40–65	111,397 (48.1)	692 (31.8)
65–75	60,518 (26.1)	582 (26.7)
75–85	37,109 (16.0)	558 (25.6)
>85 years	11,624 (5.0)	232 (10.6)
Race/ethnicity		
White	103,875 (44.9)	1,018 (46.7)
African American	22,840 (9.9)	362 (16.6)
Asian	47,946 (20.7)	243 (11.2)
Latino	39,564 (17.1)	334 (15.3)
Other/unknown	17,292 (7.5)	222 (10.2)
HbA_{1c} (%), last prebaseline, mean (SD)	7.42 (1.50)	7.89 (1.89)
LDL-C (mg/dL), last, mean (SD)	87.28 (31.1)	82.57 (31.8)
BMI, kg/m^2, mean (SD)	31.38 (7.17)	30.02 (7.26)
Diabetes, type 2	221,267 (95.6)	1,872 (85.9)
Medication use		
Insulin	55,846 (24.1)	1,515 (69.5)
Sulfonylurea	90,745 (39.2)	952 (43.7)
Other OHA	129,868 (56.1)	825 (37.9)
Smoking (ever)	95,627 (41.8)	1,119 (51.5)
Hypertension	199,758 (86.3)	2,028 (93.1)
Hyperlipidemia (low HDL, high TC)	54,681 (25.6)	392 (20.7)
Prevalent ASCVD	13,699 (5.9)	332 (15.2)
SH events in previous 2 years (yes/no)	1,831 (0.8)	287 (13.2)
Charlson comorbidity score (including DM), mean (SD)	2.43 (1.95)	4.22 (2.38)
eGFR (mL/min/1.73 m^2), last prebaseline, mean (SD)	78.17 (24.0)	60.95 (29.3)
Resides in most deprived neighborhood quartile	47,932 (20.9)	529 (24.4)
***B.* ASCVD outcomes**		
Nonfatal MI	5,823 (2.5)	119 (5.5)
Nonfatal stroke	4835 (2.1)	110 (5.0)
CHD (fatal)	358 (0.2)	10 (0.5)
Stroke (fatal)	358 (0.2)	10 (0.5)

Data are n (%) unless otherwise indicated. In part *A*, all differences $P < 0.0001$ except sex, $P = 0.61$. In part B, all differences $P < 0.0001$ except stroke, $P = 0.0004$. Outcomes from baseline to end of follow-up. DM, diabetes; CHD, coronary heart disease; MI, myocardial infarction, OHA, oral hypoglycemic agent; TC, total cholesterol.

the study and drafting of the manuscript. J.Y.L. was responsible for data analysis. J.S.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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