Evidence Linking Hypoglycemic Events to an Increased Risk of Acute Cardiovascular Events in Patients With Type 2 Diabetes

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OBJECTIVE—This retrospective study examined the association between ICD-9-CM–coded outpatient hypoglycemic events (HEs) and acute cardiovascular events (ACVEs), i.e., acute myocardial infarction, coronary artery bypass grafting, revascularization, percutaneous coronary intervention, and incident unstable angina, in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Data were derived from healthcare claims for individuals with employer-sponsored primary or Medicare supplemental insurance. A baseline period (30 September 2006 to 30 September 2007) was used to identify eligible patients and collect information on their clinical and demographic characteristics. An evaluation period (1 October 2007 to 30 September 2008) was used to identify HEs and ACVEs. Patients aged ≥18 years with type 2 diabetes were selected for analysis by a modified Healthcare Effectiveness Data and Information Set algorithm. Data were analyzed with multiple logistic regression and backward stepwise selection (maximum $P = 0.01$) with adjustment for important confounding variables, including age, sex, geography, insurance type, comorbidity scores, cardiovascular risk factors, diabetes complications, total baseline medical expenditures, and prior ACVEs.

RESULTS—Of the 860,845 patients in the analysis set, 27,065 (3.1%) had ICD-9-CM–coded HEs during the evaluation period. The main model retained 17 significant independent variables. Patients with HEs had 79% higher regression-adjusted odds (HE odds ratio [OR] 1.79; 95% CI 1.69–1.89) of ACVEs than patients without HEs; results in patients aged ≥65 years were similar to those for the entire population (HE OR 1.78, 95% CI 1.65–1.92).

CONCLUSIONS—ICD-9-CM–coded HEs were independently associated with an increased risk of ACVEs. Further studies of the relationship between hypoglycemia and the risk of ACVEs are warranted.

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The long-term complications that result from poor glycemic control contribute substantially to the morbidity, mortality, and economic burden of diabetes. Over time, the hyperglycemia seen in patients with diabetes can increase the risk of both microvascular complications and result in a two- to fourfold increase in the risk of macrovascular complications (1–3). The relationship between macrovascular complications and glycated hemoglobin is not understood precisely; however, atherosclerosis and vascular occlusion from hypercoagulability and increased adhesion of platelets are thought to occur through various metabolic mechanisms, placing individuals with diabetes at an increased risk for cardiovascular disease (4).

Although near normoglycemic control has been demonstrated to reduce the incidence of microvascular complications such as retinopathy, nephropathy, and neuropathy, the independent effect of A1C lowering on the risk of cardiovascular events in patients with type 2 diabetes is less clear (5–7). Although observational studies have described the naturalistic association between hyperglycemia and increased cardiovascular risk in type 2 diabetes, the results of interventional randomized controlled trials in establishing the cardiovascular benefit of pharmacotherapeutic management of hyperglycemia, including intensive therapy, have been inconsistent. The UK Prospective Diabetes Study of patients with type 2 diabetes reported a substantial but statistically nonsignificant ($P = 0.052$) 16% reduction in cardiovascular complications (combined fatal or nonfatal myocardial infarction [MI] and sudden death) between patients randomized to intensive management and patients randomized to conventional management over 10 years. However, data from an additional 10-year follow-up study of this same cohort of patients did show a quantitatively similar but statistically significant long-term cardiovascular benefit of intensive control (sulfonylurea-insulin group: relative risk reduction for MI 15%, $P < 0.01$; metformin group: relative risk reduction for MI 33%, $P = 0.005$), even after an intensive strategy was abandoned (1,8).

Because the clinical trial evidence regarding the macrovascular benefit of A1C lowering to traditional A1C targets had been inconsistent, the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) sought to explore whether treatment to more intensive A1C targets (≤6.5 or <6%) might more consistently establish the macrovascular benefit that has been so elusive in studies evaluating less intensive glycemic targeting (5–7). Unfortunately, these trials did not, in general, demonstrate the macrovascular benefit of intensive glycemic control. Furthermore,

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the finding of increased all-cause mortality in the intensively managed cohort of the ACCORD trial has caused some to reevaluate intensive management entirely in light of what has been perceived by some as an unfavorable risk-to-benefit ratio (9). Since the publication of these studies, the scientific community has sought a deeper understanding of the complex relationships among glycemic control, patient comorbidity, and cardiovascular morbidity and mortality in patients with type 2 diabetes. In doing so, some have focused their attention on the role that severe hypoglycemia may play, although this does not seem to be the primary culprit in ACCORD in the intensively treated cohort.

Hypoglycemia can trigger a series of maladaptive sequelae that can alter a patient's cardiovascular risk profile and possibly contribute to increased mortality. Research has suggested that hypoglycemia may induce hematologic changes that restrict blood flow to the distal tissues and encourage thrombosis, stimulate stress responses that lead to increases in the expression of inflammatory markers associated with endothelial damage and the development of vascular disease, and promote localized vasoconstriction through hypoglycemia-induced release of epinephrine (10). Furthermore, research has suggested that hypoglycemia may impair the counter-regulatory autonomic response to subsequent episodes of hypoglycemia. In addition, autonomic impairment has been shown to be associated with an increase in the risk of mortality in patients with diabetes (11–13).

Current understanding of the adverse impact of hypoglycemia provides the theoretic framework that forms the underpinning of some of the exploratory post hoc analyses carried out by the ACCORD and VADT researchers. For example, a recently published post hoc analysis of the ACCORD study found that patients who experienced severe hypoglycemia, regardless of study arm, exhibited an increased risk of death (14). In addition, an exploratory analysis of the VADT trial data found that severe hypoglycemia within 90 days was a strong predictor of cardiovascular mortality (15).

Given the unresolved nature of this important subject, this retrospective observational study was conducted to examine the association between hypoglycemic events (HEs) and acute cardiovascular events (ACVEs) in a large cohort of U.S. patients with type 2 diabetes in the noninterventional setting of routine care.

RESEARCH DESIGN AND METHODS

Data source and patient selection

Data were derived from inpatient, outpatient, and outpatient prescription drug claims and encounter records for approximately 43 million employees and dependents with employer-sponsored primary or Medicare supplemental insurance contained in the 2006 to 2008 *Thomson Reuters MarketScan* Commercial Claims and Encounters (Commercial) database and Medicare Supplemental and Coordination of Benefits (Medicare) database. The data contained in the Commercial and Medicare databases are fully compliant with the Health Insurance Portability and Accountability Act Privacy Regulations and statistically de-identified, exempting this study from an institutional review board approval requirement.

Two consecutive years of data from 30 September 2006 to 30 September 2008 were used for this study, which represented the latest available data in the Commercial and Medicare databases at the time that the study was conducted. The first year (baseline period) was used to select a prevalence-based sample of patients with type 2 diabetes and identify their baseline demographic and clinical information. The second year (evaluation period) was used to evaluate the presence of HEs and ACVEs.

Patients meeting the following inclusion criteria during the baseline period were selected for study:

1a. Modified Healthcare Effectiveness Data and Information Set criteria for type 2 diabetes during baseline period: At least one claim with a diagnosis code for type 2 diabetes (ICD-9-CM 250. × 0 or 250. × 2) and no claims with a diagnosis code for type 1 diabetes (ICD-9-CM = 250. × 1 or 250. × 3); or if claims for type 1 diabetes, the patient must also have at least one claim for type 2 diabetes and at least one claim for an oral antidiabetic drug or the patient must have more claims for type 2 diabetes than for type 1 diabetes if no claims for an oral antidiabetic drug.

1b. Patients with at least two prescription claims for antidiabetic drugs (either a single agent or multiple agents) filled in the baseline period were also included in the study if they did not meet criterion 1a, a step that represents the aforementioned modification to the base Healthcare Effectiveness Data and Information Set criteria.

2. At least 18 years of age at start of baseline period.

3. Continuous enrollment and pharmacy benefits throughout the 24-month study period, except in the case of inpatient death due to an acute cardiovascular cause in the evaluation period.

Study variables

The dependent variable was a dichotomous composite indicator for the occurrence of any of the following ACVEs during the evaluation period: coronary artery bypass graft, revascularization, percutaneous coronary intervention, acute myocardial infarction (AMI), or incident unstable angina (UA). Coronary artery bypass graft, revascularization, and percutaneous coronary intervention were identified by the presence of at least one inpatient or one outpatient claim with an ICD-9-CM or Current Procedural Terminology code for the specific procedure. AMI and incident UA were identified by the presence of at least one inpatient claim with an ICD-9-CM diagnosis code in any position for AMI (410.xx) or UA (411.1×), respectively; patients who had any inpatient or outpatient nondiagnostic claims with a diagnosis code for UA during the baseline period were precluded from being flagged as having incident UA during the evaluation period.

The primary independent variable was a dichotomous indicator for the occurrence of HEs during the evaluation period, identified by the presence of at least one outpatient claim with an ICD-9-CM diagnosis code for hypoglycemia in any position (251.0×, 251.1×, 251.2×, 250.8×) (16).

Although the service date of an outpatient claim with a diagnosis of hypoglycemia will accurately represent the time at which a patient sought medical attention for hypoglycemic symptoms, it is possible that the true onset of HEs may have occurred days or weeks before the patient was actually compelled to seek care in response (17,18). Therefore, to allow for the possibility of such situations, for the primary models a flexible approach was adopted in which recorded HEs were not strictly required to temporally precede recorded ACVEs; that is, HEs were allowed to occur at any time during the evaluation period, including after ACVEs. This flexible approach was also subjected to sensitivity analyses as described below.

Several other important covariates that might confound the relationship between HEs and ACVEs were measured during the baseline period: patient demographics (age, sex, insurance plan type, U.S. Census Bureau geographic region), baseline risk factors for coronary artery disease as suggested by the American College of Cardiology and American Heart Association (19) (hypercholesterolemia, hypertension, peripheral vascular disease, chronic kidney disease), baseline microvascular diabetes complications (diabetic peripheral neuropathy, diabetic retinopathy, leg and foot amputation), indices of baseline health status and healthcare resource use (Deyo–Charlson comorbidity index [20], Agency for Healthcare and Research Quality comorbidity index [21], count of medical encounters with a diagnosis of diabetes, total baseline healthcare expenditures), and baseline occurrence of ACVEs.

Other descriptive information collected during the baseline period included diabetes treatment regimens and the use of cardiovascular medications (antiplatelet agents, ACE inhibitors, β-blockers, calcium channel blockers, antihyperlipidemic drugs, other antihypertensive agents, and anticoagulants).

Statistical analysis

Bivariate descriptive statistics were used to test for statistically significant differences in all study variables between patients who did and did not experience HEs during the evaluation period. χ^2 tests for homogeneity were used to test for differences in categoric variables; two-tailed Student *t* tests were used to test for differences in continuous variables. A *P* value of 0.05 was the maximum *P* value for which differences were considered statistically significant.

Multiple logistic regression was used to examine the association between HEs occurring during the evaluation period and any ACVE occurring during the evaluation period. The models were fitted to the data using backward stepwise selection applied to an a priori model specification that expressed the probability of any ACVE as a function of the dichotomous variable for HEs in the evaluation period and covariates for patients' baseline demographics, baseline risk factors for coronary artery disease, baseline microvascular diabetes complications, baseline indices of health status and healthcare resource use, and baseline occurrence of ACVEs. Variables were retained in the models if they had a *P* value

Table 1—*Characteristics and outcomes of patients with type 2 diabetes*

	Type 2 diabetic patients with coded HEs	Type 2 diabetic patients without coded HEs	
	N = 27,065 (3.1%)	*N* = 833,780 (96.9%)	*P* value
Age (years), mean (SD)	64.0 (13.2)	60.6 (13.0)	<0.001
Female (%)	47.7	48.7	
Insurance plan type (%)			<0.001
Capitated payment arrangements	18.2	16.4	
Fee-for-service	80.7	82.2	
Unknown	1.1	1.4	
Geographic region (%)			<0.001
Northeast	7.5	8.8	
North Central	37.2	32.8	
South	35.6	41.8	
West	19.4	16.2	
Unknown	0.3	0.4	
Risk factors for coronary artery disease (%)			
Hypercholesterolemia	1.8	2.1	<0.001
Hypertension	28.1	23.0	<0.001
Peripheral vascular disease	6.4	1.9	<0.001
Chronic kidney disease	9.0	2.6	<0.001
Diabetes complications (%)			
Diabetic peripheral neuropathy	9.8	2.7	<0.001
Diabetic retinopathy	5.6	1.7	<0.001
Leg and foot amputation	1.1	0.1	<0.001
Medical encounters with a diagnosis of diabetes, mean (SD)	6.2 (8.3)	2.9 (3.7)	<0.001
Median	4	2	
Deyo–Charlson comorbidity index, mean (SD)	2.5 (2.0)	1.6 (1.4)	<0.001
Median	2	1	
AHRQ comorbidity index, mean (SD)	0.8 (1.3)	0.5 (0.9)	<0.001
Median	0	0	
Cardiovascular medication (%)			
Antiplatelet agents	17.1	9.3	<0.001
ACE inhibitors	47.0	40.6	<0.001
β-Blockers	43.4	32.5	<0.001
Calcium channel blockers	29.1	23.3	<0.001
Antihyperlipidemic drugs	69.3	64.2	<0.001
Hypotensive agents	12.0	6.9	<0.001
Anticoagulants	10.4	6.2	<0.001
Total expenditures, mean (SD)	$21,408 ($40,081)	$11,660 ($24,048)	<0.001
Median	$10,560	$5,919	
Diabetes treatment allowing for 15-day gap (%)			
Monotherapy with oral antidiabetic agent	22.0	34.0	
≥2 oral antidiabetic agents	14.8	16.5	
Oral antidiabetic agent(s) + one insulin type	15.0	5.7	
Oral antidiabetic agent(s) + two or more insulin type(s)	5.7	1.6	
One insulin type only	11.0	3.0	

Table 1—*Continued*

	Type 2 diabetic patients with coded HEs	Type 2 diabetic patients without coded HEs	
	N = 27,065 (3.1%)	*N* = 833,780 (96.9%)	*P* value
≥2 insulin types only	7.4	1.8	
<45 days oral antidiabetic agent(s)	4.1	6.1	
No oral antidiabetic agent(s) and no insulin use	20.1	31.2	
ACVE evaluation period (%)			
Coronary artery bypass graft	0.30	0.10	<0.001
Revascularization	0.40	0.20	<0.001
Percutaneous coronary intervention	2.30	1.20	<0.001
Incident UA	1.50	0.70	<0.001
AMI	2.60	0.80	<0.001
Any ACVE	5.30	2.20	<0.001
Inpatient death related to ACVE	0.20	0.10	<0.001
ACVE baseline period (%)			
Coronary artery bypass graft	0.30	0.20	0.001
Revascularization	0.40	0.20	<0.001
Percutaneous coronary intervention	2.30	1.30	<0.001
UA	1.80	0.90	<0.001
AMI	1.70	0.80	<0.001
Any ACVE	4.60	2.30	<0.001

AHRQ, Agency for Healthcare Research and Quality.

that was less than or equal to the maximum *P* value selection criterion of 0.01, a conservative criterion chosen because of the study's very large sample size, reported below. Model results are presented as odds ratios with 95% CIs. All analyses were conducted using SAS 9.1 and 9.2 (SAS Institute Inc., Cary, NC).

Sensitivity analysis

To test the sensitivity of study findings to the more conservative approach that requires an HE to occur before an ACVE when establishing an association between the two events, a secondary independent variable was created. This secondary independent variable was a dichotomous indicator for the occurrence of HEs in the period from 1 to 365 days immediately preceding the date of an ACVE; that is, such HEs were required to be temporally precedent to the ACVE.

The sensitivity analysis used a modeling approach, specification, and variable selection criteria that were otherwise identical to those used in the primary models.

RESULTS—A total of 1,852,285 patients met the patient selection criteria between 30 September 2006 and 30 September 2007. A total of 984,671 patients were excluded because they did not have continuous enrollment and pharmacy benefits throughout the 24-month study period; this is exclusive of 505 patients who experienced inpatient death resulting from an acute cardiovascular cause during the evaluation period. These patients were exempted from the continuous enrollment criteria. A further 6,769 patients were excluded because they were less than 18 years of age. The final study cohort comprised 860,845 patients with type 2 diabetes.

Table 1 presents the demographic and clinical characteristics of the study sample. A total of 27,065 patients (3.1%) experienced HEs in the evaluation period. Patients with HEs in the evaluation period were significantly older than patients without such HEs (average age of 64.0 years vs. 60.6 years; $P < 0.001$). Patients with HEs in the evaluation period tended to be sicker than patients without such HEs, as indicated by higher proportions of patients having evidence of each of the risk factors for coronary artery disease ($P < 0.001$), comorbid conditions ($P < 0.001$), and higher mean baseline total expenditures ($21,408 vs. $11,660; $P < 0.001$).

Table 1 also presents rates of ACVEs during the baseline and evaluation periods for the study sample. The rate of any ACVEs was more than twice as high in patients with HEs in the evaluation period compared with patients without such HEs (5.3 vs. 2.2%; $P < 0.001$).

Table 2 presents the results of the logistic regression of the probability of any ACVEs during the evaluation period, fitted on two different samples: *1*) patients of all ages and 2) patients aged ≥65 years. Patients of all ages with HEs during the evaluation period had 78.8% higher regression-adjusted odds of experiencing any ACVE during the evaluation period than patients without such HEs. Patients aged 65 years or older with HEs during the evaluation period had 77.8% higher regression-adjusted odds of experiencing any ACVE during the evaluation period than patients without such HEs.

The results for the sensitivity analysis in which the HEs were required to be temporally precedent to ACVEs indicate that patients of all ages with HEs that were temporally precedent to ACVEs had 26.7% higher regression-adjusted odds of experiencing any ACVE during the evaluation period than patients without such HEs (data not shown); patients aged ≥65 years with temporally precedent HEs had 21.4% higher regression-adjusted odds of experiencing any ACVE during the evaluation period than patients without such HEs (data not shown).

CONCLUSIONS—To our knowledge, this is the first retrospective observational study to quantify the association between HEs and ACVEs in U.S. patients with type 2 diabetes.

Our study results contribute uniquely to the body of recent findings related to the complex relationship between hypoglycemia and adverse outcomes. The ACCORD trial compared the effect of intensive glycemic control (target A1C <6.0%) with standard glycemic control (target A1C 7.0–7.9%) on the risk of cardiovascular events in patients with type 2 diabetes. Over a mean of 3.5 years of follow-up, all-cause mortality was significantly greater in the intensive-therapy group than in the standard-therapy group (hazard ratio 1.22; 95% CI 1.01–1.46; $P = 0.04$), which led to an early discontinuation of intensive therapy. Hypoglycemia was found to be more common among the patients in the intensive-therapy

Table 2—*Results of multiple logistic regression of acute cardiovascular events as a function of hypoglycemic events

	Patients of all ages† with type 2 diabetes		Patients aged ≥65 years‡ with type 2 diabetes	
Independent variables	Odds ratio	95% CI	Odds ratio	95% CI
Coded HE in evaluation period	1.79	1.69–1.89	1.78	1.65–1.92
Age 65+ vs. 18–34 years	13.26	9.64–18.25	—	—
Age 55–64 vs. 18–34 years	9.79	7.11–13.47	—	—
Age 45–54 vs. 18–34 years	6.79	4.92–9.35	—	—
Age 35–44 vs. 18–34 years	3.54	2.54–4.94	—	—
Male vs. female	1.56	1.52–1.61	1.39	1.34–1.45
West vs. Northeast	0.82	0.77–0.88	0.86	0.79–0.93
Unknown vs. Northeast	0.97	0.73–1.29	0.80	0.42–1.50
South vs. Northeast	1.09	1.03–1.15	1.05	0.97–1.13
North Central vs. Northeast	1.19	1.13–1.26	1.16	1.08–1.24
Peripheral vascular disease	1.29	1.20–1.38	1.21	1.11–1.32
Chronic kidney disease	1.17	1.10–1.25	1.16	1.07–1.26
Diabetic peripheral neuropathy	1.10	1.03–1.18	—	—
Diabetic retinopathy	1.33	1.23–1.44	1.24	1.11–1.38
Deyo–Charlson comorbidity index	1.05	1.04–1.06	1.05	1.04–1.07
Total baseline expenditures	1.76	1.70–1.83	1.56	1.48–1.64
Prior cardiovascular events	2.87	2.73–3.02	2.39	2.22–2.56

*Dependent variable = ACVEs in the evaluation period; models fit using backward stepwise selection of variables with $P < 0.01$. †Observations = 860,583; max-rescaled $R^2 = 0.0651$. ‡Observations = 316,695; max-rescaled $R^2 = 0.0322$.

group and was initially suggested as a potential explanation for the excess mortality. Further analysis, however, suggested that severe hypoglycemia did not explain the excess mortality in the intensively treated patients, but instead was associated with an increased risk of death within each study arm (14). The VADT examined the effects of intensive glucose control on cardiovascular events in patients with long-standing type 2 diabetes. VADT investigators found that intensive glucose control did not lead to a significant effect on the rates of major cardiovascular events, death, or microvascular complications. However, a significant increase in the relative risk of sudden death was observed in patients with more than one episode of severe hypoglycemia (15). The data source for this study could not identify mortality with a high level of sensitivity and therefore focused on ICD-9-CM–coded ACVEs. Despite the difference in outcomes between this and the aforementioned studies, the findings of this study add information that is suggestive of an association between hypoglycemia and cardiovascular morbidity. More large-scale retrospective studies of real-world data such as this one would be useful to further explore the association between hypoglycemia and cardiovascular and all-cause mortality.

These results neither suggest nor address any role of glycemic control in the relationship between hypoglycemic episodes and the risk of ACVEs and thus do not negate the importance of good glycemic control. The evidence base supporting a reduction in microvascular complications with tight glycemic control in both type 1 and type 2 diabetes is unequivocal. In fact, a joint statement by the American Diabetes Association, American College of Cardiology Foundation, and American Heart Association suggested no need for major changes in glycemic control targets (15). Furthermore, a recent post hoc analysis of ACCORD data examining the epidemiologic relationships between A1C and all-cause mortality verified the expected positive correlation between these factors; the risk of death in intensively treated patients was explained by factors associated with A1C persisting at >7% as opposed to decreased A1C (22).

HEs were identified by the presence of an outpatient medical claim with an ICD-9-CM diagnosis code that is indicative of hypoglycemia. Current ICD-9-CM diagnosis coding for hypoglycemia lacks specificity regarding clinical factors such as plasma glucose levels and therefore may reflect a wide continuum of severity. The set of ICD-9-CM diagnosis codes was chosen on the basis of their inclusion in prior peer-reviewed publications in which HEs had been identified within administrative claims data (23,24). Findings from these prior studies suggest that because all HEs were identified through ICD-9-CM diagnosis coding, these events are likely to have been sufficiently severe as to require a patient to seek medical care or to require intervention. Consequently, there likely were many more episodes of hypoglycemia, particularly those that are mild in nature, that were not captured in this study. A validation study of the ICD-9-CM code set used in this analysis indicates that these codes possessed relatively high sensitivity for medically attended HEs (16). Nevertheless, some coded instances of hypoglycemia within this study may be false positives, and the true sensitivity of the codes could not be determined in the validation study. The potential impact of misclassification depends on the nature of the error and the cardiovascular risk profile and outcomes of the misclassified subjects. If the false negatives had an elevated risk and incidence of ACVEs compared with true negatives, misclassification would have resulted in a bias toward the null hypothesis and would have weakened the association that we detected. In the opposite case, misclassification would suggest that the risk is actually highest in patients with events that require a patient to seek medical care or to require intervention. If false positives did not have an elevated risk and incidence of ACVEs compared with true negatives, then misclassification would again have resulted in a bias toward the null hypothesis and would have weakened the association that we detected. In the opposite case, misclassification would have resulted in a bias toward rejecting the null hypothesis and erroneously strengthened the association that we detected. However, many of the false positives noted in the validation study were those individuals who were coded with 250.8× and had a codiagnosis of secondary diabetic glycogenosis, ulcers of the lower extremity, cellulitis, diabetic lipidosis, Oppenheim–Urbach syndrome, or osteomyelitis. Thus, the bias of such false positives would be of concern if such individuals had an increased risk of ACVEs beyond what was adjusted for in the multivariate analyses.

The date of an outpatient diagnosis for a medically attended HE may not be a good approximation of the time at which patients actually began experiencing such

events (16–18). To address the unclear nature of actual timing of the onset hypoglycemia, this study used two approaches, one that did not require HEs to be temporally precedent to the ACVEs and one that required the HEs to occur within 1 to 365 days before the ACVEs. Although exploratory analyses of the VADT trial data found that severe hypoglycemia within 90 days was a strong predictor of cardiovascular mortality, retrospective epidemiologic analysis of the ACCORD study data found no temporal relationship between hypoglycemia and death. Thus, our 365-day timeframe for temporally precedent HEs may be appropriate.

This study was subject to limitations. The adjusted R^2 of the logistic regressions was low; however, models in previous research have demonstrated similar explanatory ability, highlighting the difficulty of specifying a model that takes into account a large proportion of the factors that explain the variance in the occurrence of ACVEs (25). Because it is not feasible to randomize diabetic patients to hypoglycemia case and noncase groups, this study used a retrospective observational study design. In the absence of randomization, however, the possibility of residual confounding may never be ruled out. The association between HEs and ACVEs may be partially driven by an independently higher baseline cardiovascular risk profile, duration of disease, and other confounding factors that are present in patients who experience HEs. To account for such baseline differences and identify the desired ceteris paribus association between HEs and ACVEs, we adjusted for multiple potential demographic and clinical confounders. In administrative claims data, however, clinical information is extracted from ICD-9-CM diagnosis and various procedure coding systems that are used by physicians to support claims for reimbursement. Such coding may result in misclassification error if the codes are incorrectly recorded, misused, or not recorded at all. A limitation of this study that is shared by all administrative claims-based retrospective observational investigations is that the true validity of the measured variables is not known with certainty. Thus, the study results must be interpreted appropriately as not representing proof of causal associations.

This study's real-world results complement recent findings from more restricted interventional or smaller observational settings and provide evidence linking ICD-9-CM–coded outpatient HEs to an increased risk of ACVEs in patients with type 2 diabetes. This is the first large-scale retrospective observational study addressing this association, so the findings should be considered an initial groundwork on which future research and understanding can be built and improved. Further studies of this relationship are needed to inform clinicians on the amount of care that should be afforded to reducing the incidence of hypoglycemia in the treatment of patients with type 2 diabetes.

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