

Impact of Hypoglycemia Associated With Antihyperglycemic Medications on Vascular Risks in Veterans With Type 2 Diabetes

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OBJECTIVE—Hypoglycemia is associated with failure to show cardiovascular benefit and increased mortality of intensive glycemic control in randomized clinical trials. This retrospective cohort study aimed to examine the impact of hypoglycemia on vascular events in clinical practice.

RESEARCH DESIGN AND METHODS—Patients with type 2 diabetes were identified by ICD-9-CM codes (250.xx except for 250.x1 and 250.x3) between 1 January 2004 and 1 September 2010 from the Veterans Integrated Service Network 16. Index date was defined as the first date of new antihyperglycemic medications (index treatment). Patients with 1-year preindex records of hypoglycemia, cardiovascular, and microvascular diseases were excluded. The hypoglycemia group was identified by ICD-9-CM codes (250.8, 251.0, 251.1, and 251.2) within the index treatment period. A propensity score-matched group was used as control subjects. Cardiovascular events, microvascular complications, and all-cause death were compared using Kaplan-Meier analysis and Cox proportional hazards regression model.

RESULTS—Among the unmatched sample ($N = 44,261$), the hypoglycemia incidence rate was 3.57/100 patient-years. The matched sample (hypoglycemia group: $n = 761$; control group: $n = 761$) had a median follow-up of 3.93 years, mean age of 62.6 ± 11.0 years, and preindex HbA_{1c} of $10.69 \pm 2.61\%$. The 1-year change in HbA_{1c} was similar (hypoglycemia group -0.51 vs. control group -0.32% , $P = 0.7244$). The hypoglycemia group had significantly higher risks of cardiovascular events (hazard ratio 2.00 [95% CI 1.63–2.44]) and microvascular complications (1.76 [1.46–2.11]) but no statistical mortality difference. Patients with at least two hypoglycemic episodes were at higher risks of vascular events than those with one episode (1.53 [1.10–1.66]).

CONCLUSIONS—Hypoglycemia is associated with higher risks of incident vascular events. Patients with hypoglycemia should be monitored closely for vascular events.

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Diabetes is a prevalent and costly chronic disease, often requiring close management of complicated conditions during one's whole life. According to the American Diabetes Association, the estimated total cost of diabetes in the U.S. was \$174 billion in 2007 (1). Despite recent advances in diabetes treatment, hypoglycemia emerges as an important issue in the management of diabetes. In 2005, the excess annualized cost related to hypoglycemia

among insulin users in the U.S. was reported to be \$3,241 per patient who had experienced hypoglycemia, with the risk of short-term disability increasing fivefold in the week after a hypoglycemic event (2). In addition, the risk of hospitalization and emergency room visits was increased twofold among the patients with hypoglycemia (2).

Prevention of short-term and long-term complications of diabetes has been a fundamental goal for maintaining glycemic level

as close as possible to the normal range among individuals with diabetes. Epidemiologic and meta-analysis studies clearly show a direct and strong relationship between glycemic control and all kinds of cardiovascular disease (CVD) events (3–8). However, most CVD risks have not been substantially reduced by intensive glycemic control in a series of major clinical trials (9–13).

The development of hypoglycemia as a result of intensive treatment is one of the major barriers to intensifying treatment and to preventing patients from achieving the benefits of good glycemic control. A systematic review of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT) found that hypoglycemic events were 2.5 times as common in the intensively treated group as in the control group (14). In the ACCORD trial, the increased risk of hypoglycemia with intensive therapy was threefold. Hypoglycemia related to the use of antihyperglycemic medications has been associated with the excess mortality in the ACCORD trial (14,15). However, Bonds et al. (16) reported that symptomatic, severe hypoglycemia might not account for the difference in mortality between two treatment arms in an epidemiological analysis of ACCORD data; instead, hypoglycemia was shown to be associated with an increased risk of death within each study arm. Furthermore, a post hoc analysis of ADVANCE data also found strong associations between severe hypoglycemia and greater risks of vascular and nonvascular outcomes (17). In addition, Desouza et al. (18) suggested hypoglycemia might affect CVD events by several mechanisms, following the counterregulatory responses induced by hypoglycemia.

No study using data from clinical practice settings has been conducted to examine the relationship between hypoglycemia and vascular disease risks. The aim of this study was to examine the effect of

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severe hypoglycemia on CVD events among patients with type 2 diabetes treated in real practice settings.

RESEARCH DESIGN AND METHODS

A retrospective cohort study was conducted using the electronic medical and pharmacy records from 1 January 2004 to 1 September 2010 in the Veterans Health Administration (VHA) Veterans Integrated Service Network 16 (VISN 16) warehouse. Approximately 1 million lives are served by the VISN 16. Data format and content were in compliance with the Health Insurance Portability and Accountability Act requirements. Approvals for this study protocol were obtained from the Tulane and VHA institutional review boards and the VHA Office of Research and Development.

Sample selection

Figure 1 presents a flowchart of sample selection based on inclusion and exclusion criteria. Adult patients (age ≥ 18 years) with a diagnosis of type 2 diabetes (identified by ICD-9-CM codes 250.xx, except for 250.x1 and 250.x3) in at least one inpatient record or in two outpatient records from 1 January 2004 to 1 September 2010 were included. A new antihyperglycemic medication, after a 6-month washout period, was defined as the index treatment, with its first dispense date defined as the index date. Since at least a 1-year baseline (preindex) period and a 2-year follow-up (post-index) period were required for the analysis, the index treatments had to be initiated between 1 January 2005 and 1 September 2008. The hypoglycemia group was identified by a diagnosis of hypoglycemia (ICD-9-CM codes 250.8, 251.0, 251.1, and 251.2) within the index treatment period, which was from the index date to the end of the last fill of the index treatment.

Other inclusion/exclusion criteria were as follows: patients with any diagnosis of CVD (ICD-9-CM 410, 412, 430–438, 428, 443.9, 785.4, and V43.4) and/or microvascular complications (ICD-9-CM 250.4–250.6) during the 1-year preindex period were excluded. Finally, patients with the first recorded hypoglycemic episode beyond the index treatment period were excluded, as well as patients whose first recorded hypoglycemia occurred within the index treatment period but beyond 1 year after the index date.

Measurements

Baseline sociodemographic characteristics, illness characteristics, the Charlson

Comorbidity Index (CCI), tobacco use, vital signs, and HbA_{1c} levels were measured during a 1-year preindex period.

Clinical events over the whole follow-up period after the index date were studied, including CVD, microvascular complications, and all-cause death. CVD was defined as any of the following conditions diagnosed: myocardial infarction (ICD-9-CM 410 and 412), stroke (ICD-9-CM 430–438), congestive heart failure (ICD-9-CM 428), and peripheral vascular disease (ICD-9-CM 441.x, 443.9, 785.4, and V43.4). Microvascular complications were defined as diabetes with renal, ophthalmic, or neurologic manifestations (ICD-9-CM 250.4–250.6). The last recorded HbA_{1c} levels were examined during 1 year after the index date.

Propensity score matching

Propensity score matching using the greedy 5 to 1 method was applied to adjust for noncomparable baseline characteristics (heterogeneity of hypoglycemia and control groups) (19). Through a logistic regression model on group membership, the best set of baseline variables predicting occurrence of hypoglycemia was used to produce the propensity score to construct a 1:1 matched sample.

Statistical analyses

Continuous variables were examined and compared using Wilcoxon rank sum tests. χ^2 tests were used to compare categorical variables. Outcomes of time to clinical events were studied by Kaplan-Meier survival analyses. Cox proportional hazards regression models were also used to compare time to clinical events, controlling for the covariates, including baseline demographic and illness characteristics, vital signs, prior medication use, and type of index drug. Two-tailed significant level was set at 0.05. All analyses were done using SAS statistical software version 9.2.

RESULTS—From the VISN 16 data warehouse, 63,003 patients (96.5%) who had not experienced any hypoglycemia episode during the 2-year postindex period after the index date were identified as the control group and 2,187 patients (3.5%) who had experienced at least one hypoglycemic episode within the index treatment period were identified as the hypoglycemia group. Patients ($n = 20,929$) who had preindex records of hypoglycemia, CVD, or microvascular complications were excluded. The analytical population consisted of 44,261 patients, including

761 patients in the hypoglycemia group and 43,500 in the control group. The incidence rate of hypoglycemia events was calculated as 3.57/100 patient-years. The matched study sample of 1,522 patients consisted of 761 patients in the hypoglycemia group and 761 patients in the control group. The median follow-up time was 3.93 years. Mean time from the index date to the occurrence of the first hypoglycemic episode was 143 days, and the median time was 123 days.

Before matching, more patients had poor glycemic control in the hypoglycemia group (91.4%) compared with the patients in the control group (87.8%) ($P = 0.0043$). The hypoglycemia group was generally sicker than the control group in terms of higher CCI (2.44 ± 1.37 vs. 2.18 ± 1.24), higher percentages of patients with renal disease (6.2 vs. 2.5%), and higher percentages of mental disorder (25.4 vs. 17.9%), substance abuse (23.7 vs. 16.2%), and tobacco use (18.7 vs. 13.6%). A significantly higher percentage of African Americans (25.8 vs. 19.6%) was found in the hypoglycemia group compared with the control group. There were fewer patients in the hypoglycemia group who had been married (52.8 vs. 62.3%, $P < 0.0001$). The proportion of patients who were on antihyperglycemic agents during the 1-year preindex period was significantly higher in the hypoglycemia group (62.5%) than in the control group (35.6%), with more patients on insulin at baseline in the hypoglycemia group (8.9%) than in the control group (2.9%).

Table 1 presents baseline characteristics for the matched sample. The observed baseline characteristics were all comparable between the groups after matching. The mean (SD) age was 62.58 (10.99) years and the CCI was 2.44 (1.37) in the matched sample. The baseline HbA_{1c} was 10.69% (2.61%) in the total sample, 10.70% (2.57%) in the hypoglycemia group, and 10.68% (2.66%) in the control group. In the total matched sample, 61.6% of patients had been taking oral antihyperglycemic agents and 9.6% had been taking insulin before the index date. In the total sample, 66.5% had used antihypertensive medications, including β -blockers (27.5%), before the index date. Use of statins did not statistically differ across groups (53.9 in the control group vs. 57.2 in the hypoglycemia group, $P = 0.1972$).

The type of index drug used was also similar between groups after matching. Overall, 31.3% of patients were initiated with biguanides on the index date, 32.3%

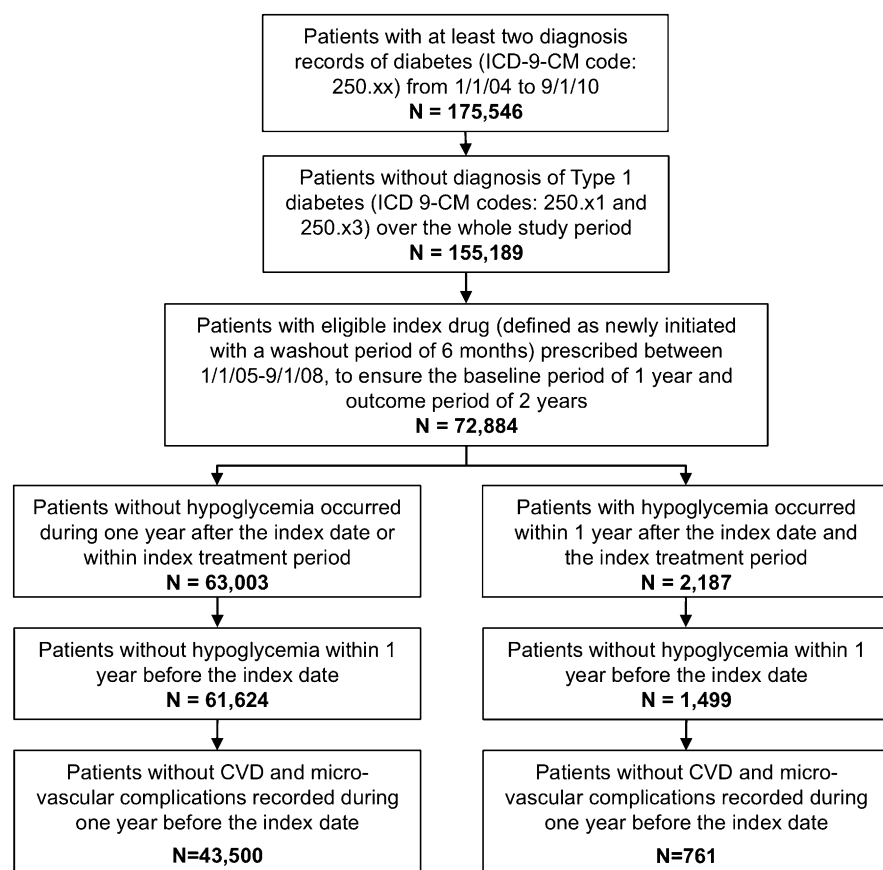


Figure 1—Sample selection flowchart.

with sulfonylureas, 11.6% with thiazolidinediones, and 21.7% with insulin. The other class of index drugs contributed only ~3%. The corresponding percentages were 31.0 vs. 31.7%, 31.4 vs. 33.2%, and 22.1 vs. 21.3% between the hypoglycemia and control groups, respectively. There was no significant difference in treatment between patients with one episode and those with more than one episode. All *P* values were >0.05.

Figure 2A presents the Kaplan-Meier survival curve for the CVD events. The cumulative incidence rate of CVD events was 30.65/100 patients during 3 years in the hypoglycemia group compared with 17.48/100 patients in the control group. Patients in the hypoglycemia group were more likely to develop CVD than those in the control group (*P* < 0.0001). The other Kaplan-Meier survival analyses on subcategories of CVD events found that patients in the hypoglycemia group were at higher risks of having stroke, congestive heart failure, and peripheral vascular disease (all *P* < 0.05). The cumulative incidence rates during 3 years were 12.99 vs. 6.28, 9.99 vs. 6.15, and 13.42 vs. 5.12 per

100 patients for stroke, congestive heart failure, and peripheral vascular disease, respectively. However, the risk of myocardial infarction was not significantly different between the hypoglycemia and control groups (log-rank test *P* = 0.4612; cumulative incidence rate = 4.47 vs. 4.52 per 100 patients during 3 years).

In a similar manner, patients in the hypoglycemia group were more likely to develop microvascular complications (*P* < 0.0001) (Fig. 2B). The cumulative incidence rate of microvascular complications was 34.46/100 patients during 3 years in the hypoglycemia group and 22.03 in the control group. Furthermore, the cumulative incidence rate of any CVD events and microvascular complications was 50.38 during 3 years in the hypoglycemia group, which was significantly higher than the control group (cumulative incidence rate = 36.12/100 patients in 3 years). The mortality rates were not significantly different between these two groups (*P* = 0.1593; cumulative incidence rate = 9.37 vs. 7.22 per 100 patients in 3 years).

Controlling for confounding variables, patients in the hypoglycemia group had higher risk of CVD events than patients in the control group (hazard ratio [HR] 2.00 [95% CI 1.63–2.44]). Increased risks of subcategories of CVD events, except myocardial infarction, also were found among the hypoglycemia group, with the HRs varying from 1.81 to 2.58 (Table 2). Specifically, patients in the hypoglycemia group were 2.58 times more likely to have peripheral vascular disease (2.58 [1.81–3.67]) and 2.25 times more likely to have a stroke (2.25 [1.62–3.13]) than patients in the control group. The risk of congestive heart failure was 81% higher for the hypoglycemia group than the control group (1.81 [1.27–2.56]). Compared with the control group, an increased risk of microvascular complications was shown in the hypoglycemia group (1.76 [1.46–2.11]). Patients in the hypoglycemia group were 1.73 times as likely to have a vascular event (any CVD and microvascular complication) as those in the control group (1.73 [1.49–2.02]). It is notable that no significant effect of group membership on all-cause mortality was shown (1.29 [0.94–1.77]).

Furthermore, compared with patients with only one episode of hypoglycemia, those who experienced more than one episode were more likely to have vascular events. The adjusted HRs for vascular events in general were 1.53 (95% CI 1.10–1.66); for microvascular complications, 1.58 (1.24–2.02); and for peripheral vascular disease, 1.72 (1.16–2.56).

No significant effects on glycemic control were found in the analyses. HbA_{1c} levels during the 1-year postindex period remained similar in both the control group and the hypoglycemia group, at 10.35% (SD 2.79%) and 10.17% (2.66%), respectively. This difference was not statistically significant (*P* = 0.1758). Postindex HbA_{1c} levels decreased from baseline in both groups (by 0.42% in the total sample, with a decrease of 0.51 and 0.32% in the hypoglycemia and control groups, respectively). The decrease was not significantly different across groups (*P* = 0.7244).

CONCLUSIONS

Vascular risk of hypoglycemia

In this study, we found that patients who experienced hypoglycemia during the index treatment period after the administration of a new antihyperglycemic drug were at approximately twofold risk to

Table 1—Baseline characteristics of the population by group*

Baseline characteristic	Sample (n)†	Total sample (N = 1,522)	Hypoglycemia group (n = 761)	Control group (n = 761)	P value
Sociodemographic characteristics					
Age on index date (years), mean (SD)	1,522	62.58 (10.99)	62.62 (10.69)	62.53 (11.30)	0.91
Male, n (%)	1,522	1,462 (96.1)	731 (96.1)	731 (96.1)	1.00
Race, n (%)	1,522				0.40
White		888 (58.3)	438 (57.6)	450 (59.1)	
African American		369 (24.2)	196 (25.8)	173 (22.7)	
Other		39 (2.6)	16 (2.1)	23 (3.0)	
Unknown		226 (14.8)	111 (14.6)	115 (15.1)	
Married, n (%)	1,522	775 (50.9)	402 (52.8)	373 (49.0)	0.14
BMI (kg/m ²), mean (SD)	1,455	31.39 (6.53)	31.46 (6.71)	31.32 (6.34)	0.67
Non-VA insurance coverage, n (%)	1,522	971 (63.8)	489 (64.3)	482 (63.3)	0.71
Prior drug use, n (%)					
Antihyperglycemic	1,522	938 (61.6)	476 (62.5)	462 (60.7)	0.46
Insulin	1,522	146 (9.6)	68 (8.9)	78 (10.2)	0.38
Antihypertensive	1,522	1,012 (66.5)	499 (65.6)	513 (67.4)	0.45
Statins	1,522	845 (55.5)	410 (53.9)	435 (57.2)	0.20
β -Blockers	1,522	419 (27.5)	208 (27.3)	211 (27.7)	0.86
Illness characteristics					
Renal disease, n (%)	1,522	91 (6.0)	47 (6.2)	44 (5.8)	0.75
Mental disorder, n (%)	1,522	414 (27.2)	193 (25.4)	221 (29.0)	0.11
Substance abuse, n (%)	1,522	354 (23.3)	180 (23.7)	174 (22.9)	0.72
Tobacco use, n (%)	1,522	285 (18.7)	142 (18.7)	143 (18.8)	0.95
CCI, mean (SD)	1,522	2.44 (1.37)	2.44 (1.37)	2.45 (1.38)	0.88
Metabolic laboratory test results‡					
HbA _{1c} (%), mean (SD)	1,430	10.69 (2.61)	10.70 (2.57)	10.68 (2.66)	0.98
HbA _{1c} ($\geq 7\%$), n (%)	1,430	1,298 (90.8)	655 (91.4)	643 (90.2)	0.44
LDL (> 130 mg/dL), n (%)	1,318	258 (19.6)	130 (19.6)	128 (19.6)	1.00
HDL (< 40 mg/dL male, < 50 mg/dL female), n (%)	1,313	832 (63.4)	420 (63.8)	412 (62.9)	0.73
Triglyceride (> 150 mg/dL), n (%)	1,314	704 (53.6)	353 (53.4)	351 (53.8)	0.90

*Baseline characteristics were measured during the 1-year preindex period. †Valid sample size used for each baseline variable. ‡Latest test result observed during the baseline period was used.

have CVD compared with patients in the control group. A post hoc study using the ADVANCE data examined the association between severe hypoglycemia and the risks of macro- and microvascular events and death and found adjusted HRs of 3.45 (95% CI 2.34–5.08) for macrovascular events, 2.07 (1.32–3.26) for microvascular events, and 3.30 (2.31–4.72) for all-cause death (17). These findings are consistent with what was observed in our study, except that we did not find a significant increased risk of all-cause mortality.

The post hoc analysis of the ADVANCE study also found higher risks of nonvascular events associated with hypoglycemia. Furthermore, no dose-response relationship was found between repeated episodes of hypoglycemia and vascular events or death. Therefore, the ADVANCE investigators concluded that hypoglycemia was likely to be a marker of vulnerability

to these clinical events but argued that a direct causal relationship was still possible (17,18). Although the causal relationship between hypoglycemia and CVD events cannot be established from our study, it is plausible because of the dose response observed. Future large prospective trials and mechanistic studies are needed to confirm the causal link between hypoglycemia and these vascular events.

Several plausible pathophysiological mechanisms may explain our findings. Hypoglycemia induces several counter-regulatory responses, including indirect changes such as inflammation, increased platelet and neutrophil activation, and epinephrine secretion (18). All these responses may increase CVD risks and/or lead to CVD events. More important, it is also possible that the first hypoglycemic episode leads to further episodes that are

asymptomatic (20) and associated with cardiovascular ischemic and proarrhythmic changes (21,22). Moreover, hypoglycemia may not only precipitate ischemia but also induce changes in autonomic function that can lead to silent ischemia and arrhythmias (18). This may explain the observed difference in heart failure but not myocardial infarction between the groups in our study. In addition, myocardial infarction is a single event that is likely to be multifactorial, whereas heart failure is the end stage of multiple processes, some of which may be triggered by hypoglycemia.

Microvascular disease, on the other hand, has been shown to behave differently and may worsen in the short-term after improvement in glycemic control but improve in the long run (23,24). Possible mechanistic reasons have been discussed (25,26). Patients with long-standing poor

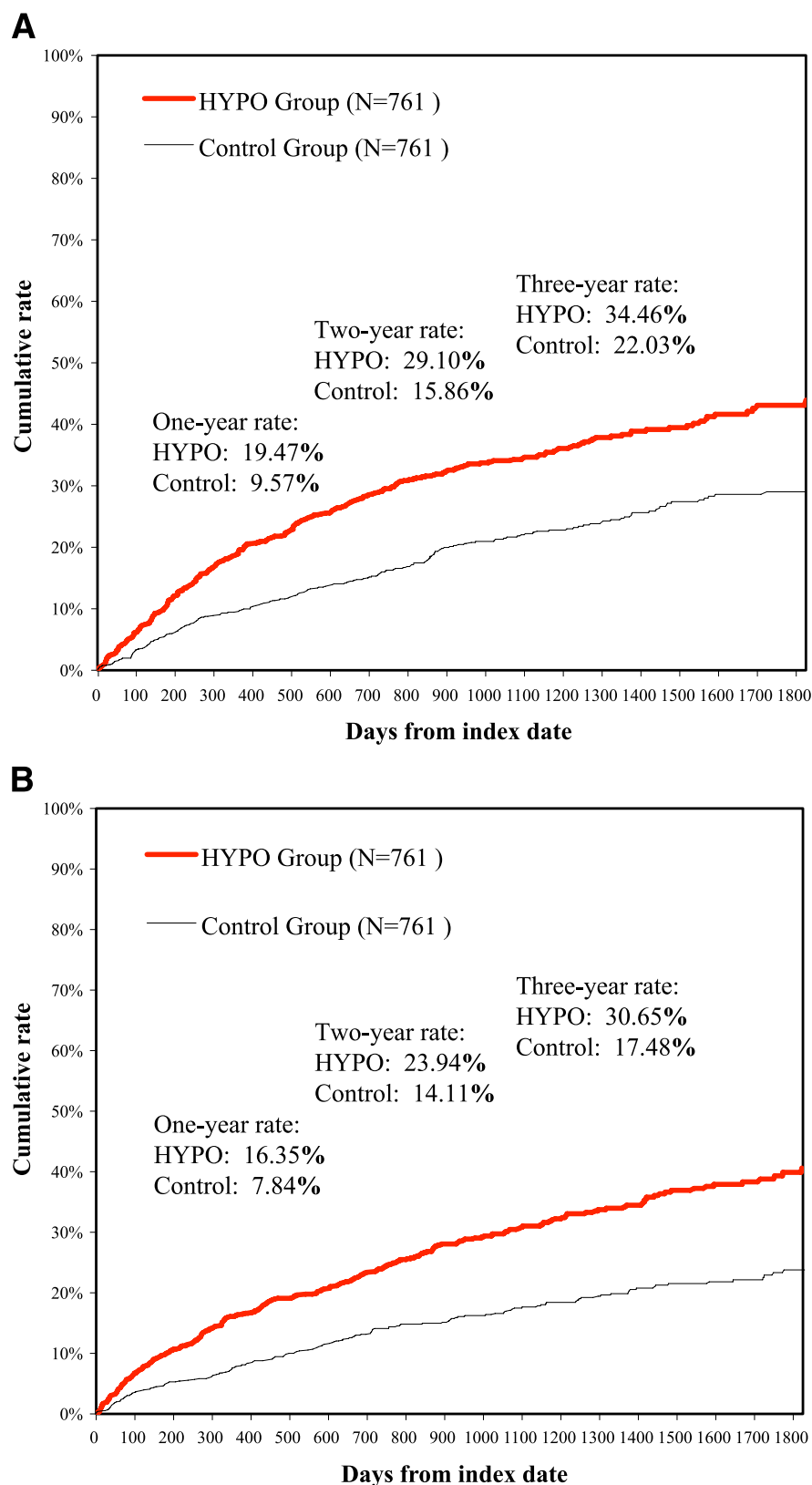


Figure 2—A: Cumulative incidence rate of CVD events by group. B: Cumulative incidence rate of microvascular complications by group. HYPO, hypoglycemia. Log-rank test showed significance (both $P < 0.0001$) in risks of CVD events and microvascular complications between groups. (A high-quality color representation of this figure is available in the online issue.)

antecedent control, as in our study, may be particularly susceptible. It is difficult to determine what role hypoglycemia plays in exacerbating these mechanisms.

In the Bonds et al. (16) analysis on ACCORD data, more deaths among the patients who had experienced hypoglycemia were observed (HR 1.41 within the intensive glucose control arm and 2.30 within the standard glucose control arm), whereas in our study, a significantly different all-cause mortality rate was not found in the hypoglycemia group after controlling for the covariates. The lack of statistical significance may relate to the lack of a sufficient power of the sample. The numerical difference observed in this study can be interpreted into the number needed to harm for one additional death, which was estimated to be 108 patients.

It is notable that some differences exist between the study populations of the clinical trials (ADVANCE and ACCORD) and our retrospective study, in addition to the differences in study design. Approximately one-third of the participants in both clinical trials had CVD history. Of import, our study population was required to have no record of CVD and microvascular disease during the 1-year preindex period. Both trials targeted lower HbA_{1c} levels, while in our study, the HbA_{1c} levels were much higher at either baseline or after the index date.

Glycemic control and hypoglycemia

In this study, hypoglycemia was not associated with subsequent poor glycemic control. Indeed, it is likely that poor glycemic control was the reason why patients were started on a new antihyperglycemic medication. The degree of improvement is compatible with the degree of effectiveness reported in clinical antihyperglycemic interventions. While there was a larger decrease in 1-year HbA_{1c} levels from baseline in the hypoglycemia group, the difference from the control group was not statistically significant. Although a correlation between aggressive glycemic control (i.e., lower HbA_{1c} levels to 6.0–6.5% for type 2 diabetic patients) and higher risk of hypoglycemia has been found, HbA_{1c} itself may not be a good indicator of optimal glycemic management. In a post hoc epidemiological analysis of the ACCORD study, a greater risk of hypoglycemia was found among patients with poorer glycemic control (27). Indeed, tight glycemic control may not be the best predictor of severe hypoglycemia, with several

Table 2—Cox proportional hazards regression models for vascular events and mortality: hypoglycemia group vs. control group

Outcome	Coefficient	SE	HR	95% CI	P value
Vascular events					
All vascular event end points	0.5496	0.0770	1.73	1.49–2.02	<0.001
CVD	0.6910	0.1029	2.00	1.63–2.44	<0.001
Congestive heart failure	0.5911	0.1789	1.81	1.27–2.56	0.001
Myocardial infarction	0.1906	0.2231	1.21	0.78–1.87	0.39
Peripheral vascular disease	0.9468	0.1803	2.58	1.81–3.67	<0.001
Stroke	0.8118	0.1683	2.25	1.62–3.13	<0.001
Microvascular complications	0.5623	0.0949	1.76	1.46–2.11	<0.001
All-cause death	0.2563	0.1600	1.29	0.94–1.77	0.11

Cox proportional hazards regression models were used to control for confounding factors, including sociodemographics, illness characteristics, prior drug use, and index drug type. Best predicting model was selected for each outcome measure. Only the statistics of group membership are presented.

other factors, such as glucose variability, being more important (28,29).

Moreover, responses to intensive treatment targeting euglycemia may vary across patients with the underlying illness. Two studies find increased risks of CVD and mortality among patients with either low or high HbA_{1c} (30,31). In our study, the mean HbA_{1c} was ~10%, suggesting a group of patients with poor antecedent control. Comparison of vascular outcomes among higher HbA_{1c} and lower HbA_{1c} groups is warranted for future studies.

Limitations

The results of this study should be interpreted in light of the limitations of the study design and the VHA population. First, it is a retrospective study using existing VHA electronic medical records data where clinical information is still limited. We can access only the information on medical records that have been processed through the VHA. Therefore, we could capture only severe episodes of hypoglycemia that were reported and recorded by the physicians or had required medical assistance from a clinical facility. Underreporting is a commonly accepted problem of hypoglycemia (20,32). Moreover, the propensity score approach can match patients from the two groups on observed variables only. Important factors related to hypoglycemia and health outcomes may be unobserved, unavailable, or inadequately captured in the data and, therefore, are not subject to control in the analysis. For example, duration of diabetes, duration and dose of insulin use, and timely self-monitored glucose levels were not available in the data warehouse. Other limitations of this study include a lack of formal diagnostic testing for hypoglycemia. Second, VHA patients (predominantly male and elderly)

are not representative of the U.S. population, nor does the VHA system operate like other health care delivery systems.

From this retrospective cohort study with an average follow-up period of ~4 years, we identified a high-risk group of veterans with type 2 diabetes who developed hypoglycemia after the initiation of a new antihyperglycemic medication and were found to be at higher risks of CVD events and microvascular complications. However, hypoglycemia did not lead to subsequent poorer glycemic control. Physicians and patients in clinical practices should work together to prevent hypoglycemia after new medication initiation. Identification of patients who develop hypoglycemia in such a clinical situation may help us develop strategies to prevent CVD events in such patients.

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Y.Z. researched data and wrote the manuscript. C.R.C. and V.F. contributed to discussion and reviewed and edited the manuscript. L.S. researched data, contributed to discussion, and reviewed and edited the manuscript. Y.Z. 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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