Association of Clinical Symptomatic Hypoglycemia With Cardiovascular Events and Total Mortality in Type 2 Diabetes

A nationwide population-based study

Pai-Feng Hsu, MD[1,2,3,4]
Shih-Hsien Sung, MD[2,3,4]
Hao-Min Cheng, MD[2,5,6]
Jong-Shiuan Yeh, MD[7,8,9]
Wen-Ling Liu, MS[10]
Wan-Leong Chan, MD[1,4]
Chen-Huan Chen, MD[2,3]
Pesus Chou, DrPH[3]
Shao-Yuan Chuang, PhD[10]

OBJECTIVE—Hypoglycemia is associated with serious health outcomes for patients treated for diabetes. However, the outcome of outpatients with type 2 diabetes who have experienced hypoglycemia episodes is largely unknown.

RESEARCH DESIGN AND METHODS—The study population, derived from the National Health Insurance Research Database released by the Taiwan National Health Research Institutes during 1998–2009, comprised 77,611 patients with newly diagnosed type 2 diabetes. We designed a prospective study consisting of randomly selected hypoglycemic type 2 diabetic patients and matched type 2 diabetic patients without hypoglycemia. We investigated the relationships of hypoglycemia with total mortality and cardiovascular events, including stroke, coronary heart disease, cardiovascular diseases, and all-cause hospitalization.

RESULTS—There were 1,844 hypoglycemic events (500 inpatients and 1,344 outpatients) among the 77,611 patients. Both mild (outpatient) and severe (inpatient) hypoglycemia cases had a higher percentage of comorbidities, including hypertension, renal diseases, cancer, stroke, and heart disease. In multivariate Cox regression models, including diabetes treatment adjustment, diabetic patients with hypoglycemia had a significantly higher risk of cardiovascular events during clinical treatment periods. After constructing a model adjusted with propensity scores, mild and severe hypoglycemia still demonstrated higher hazard ratios (HRs) for cardiovascular diseases (HR 2.09 [95% CI 1.63–2.67]), all-cause hospitalization (2.51 [2.00–3.16]), and total mortality (2.48 [1.41–4.38]).

CONCLUSIONS—Symptomatic hypoglycemia, whether clinically mild or severe, is associated with an increased risk of cardiovascular events, all-cause hospitalization, and all-cause mortality. More attention may be needed for diabetic patients with hypoglycemic episodes.

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From the [1]Healthcare and Management Center, Taipei Veterans General Hospital, Taipei, Taiwan; the [2]Department of Medicine, National Yang-Ming University, Taipei, Taiwan; the [3]Institute of Public Health and Community Medicine Research Center, National Yang-Ming University, Taipei, Taiwan; the [4]Cardiology Division, Internal Medicine Department, Taipei Veterans General Hospital, Taipei, Taiwan; [5]The Joanna Briggs Institute, Faculty of Health Sciences, The University of Adelaide, Adelaide, Australia; the [6]Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan; the [7]Cardiology Division, Internal Medicine Department, Taipei Medical University Wan-Fang Hospital, Taipei, Taiwan; the [8]Department of Medicine, Taipei Medical University, Taipei, Taiwan; [9]The Skirball Center for Cardiovascular Research, Cardiovascular Research Foundation, Orangeburg, New York; and the [10]Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan.
Corresponding author: Shao-Yuan Chuang, chuangsy@nhri.org.tw.
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P.-F.H. and S.-H.S. contributed equally to this work.
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Hypoglycemia is a major side effect of glucose-lowering therapy in patients with type 1 or type 2 diabetes. Patients with type 2 diabetes are usually believed to have less frequent hypoglycemia episodes than type 1 diabetic patients (1). Prodromal symptoms of hypoglycemia, including tremor, diaphoresis, tachycardia, and anxiety, are sometimes noticed by the patient; consequently, severe complications can be avoided. If left untreated, however, neuroglycopenia may develop, resulting in neurologic damage (2,3).

Hypoglycemia has also been associated with adverse cardiovascular events in type 2 diabetic patients beyond hypoglycemic episodes themselves (4). The surge of sympathetic activity during hypoglycemic episodes has been suggested to be the underlying mechanism leading to destabilization of atherosclerotic plaques (5), increased arrhythmia attributable to increased corrected QT interval (6), and induction of cardiac and cerebral ischemia. Studies including epidemiological cohort studies and clinical trials (7–10) have already suggested that hypoglycemia also is a risk factor for cardiovascular outcomes. However, some patients in these studies had comorbidities on admission, such as unstable angina and acute myocardial infarction (11–14). Recently, the ADVANCE study suggested that hypoglycemia is associated with increased risks of a range of adverse clinical outcomes, and it is considered to be a marker for vulnerability to such events for type 2 diabetic patients (15).

Whether hypoglycemia is a risk factor or a marker, it is important to evaluate the possible correlates to both hypoglycemia and serious health conditions, including hepatic disease, malignancy, renal disease, and use of various medications. Furthermore, in real-world clinical practice, it is intriguing to identify hypoglycemic events based solely on symptoms or a physician's diagnosis rather than on

glucose levels, as most previous studies have. Moreover, patient selection bias, especially the Berkson bias, in hospital-based observational or case-control studies probably confounds and casts doubt on the associations between hypoglycemia and clinical outcomes. Finally, the clinical impact of mild self-reported hypoglycemic episodes is largely unknown. We therefore conducted this nationwide random-sampling cohort study of type 2 diabetic patients to characterize their comorbidities and evaluate the influences of mild and severe hypoglycemia and their outcomes.

RESEARCH DESIGN AND METHODS

Study population

In Taiwan, National Health Insurance is a single-payer program that has operated since 1995, covering 98% of the population. The database includes patient demographics, diagnosis, and prescriptions in the hospital and in outpatient claims. Currently, the National Health Research Institutes is in charge of the National Health Insurance Research Database (NHIRD) in Miaoli, Taiwan (www.nhri.org.tw/nhird/), and the complete National Health Insurance claims database along with several dozen extracted datasets are available to researchers. A nationally representative group of one million individuals was randomly selected from all insured persons in NHIRD, which also is one of the largest nationwide population-based databases in the world. All selected insured persons' medical records from 1996 to 2009 were included in the dataset. For research purposes, the information for all persons was managed with a double scrambling protocol. The original identification number was encrypted to protect privacy while maintaining consistency. Therefore, it was possible to follow-up patients by linking claims belonging to the same patient within the NHIRD datasets. Because the National Health Insurance was initiated from 1996, the claim data were not totally completed. We included data from individuals who were enrolled between January 1, 1997 and December 31, 2009.

Study design

We designed a cohort of type 2 diabetic patients from the one million patients in the nationally representative sample dataset. We excluded patients with diabetes medical records before December 31, 1997. A total of 77,611 new diabetic patients were identified as having received a diagnosis of diabetes more than three times (ICD-9-CM: 250.XXX) from 1998 to 2009. Among them, 500 diabetic patients with hypoglycemia (ICD-9-CM: 251.2×) were identified from the hospital claims dataset (defined as severe hypoglycemia), and 1,344 diabetic patients with hypoglycemia were identified from the outpatient claims dataset (defined as mild hypoglycemia).

Further, we also designed a cohort consisting of hypoglycemic type 2 diabetic patients and randomly selected and matched them with type 2 diabetic patients without hypoglycemia. To control for the confounding effects of age, sex, and diabetes duration, we constructed a matched variable containing the age at hypoglycemia onset, sex, and diabetes duration for each patient with hypoglycemia. The diabetes duration was calculated from the first diagnosis date to the date of hypoglycemia onset.

Then, we used SAS MACRO to identify hypoglycemic diabetic patients with the same matched variable and randomly selected one to four nonhypoglycemic diabetic cases from those with the same match variables. Finally, we randomly selected 7,376 diabetic patients without hypoglycemia by matching age of hypoglycemia onset, sex, and diabetes duration. Each matched pair had the same initial date (hypoglycemia onset date) signaling the commencement of follow-up (Fig. 1).

Definition of variables

Patients with a diagnosis of diabetes were defined as those with three outpatient claims with ICD-9-CM code 250. All confounding variables were defined according to the diagnosis before the index date in hypoglycemic and nonhypoglycemic patients. Hypertension was defined as two outpatient claims with ICD-9-CM code 401–405. Dyslipidemia was defined as two outpatient claims with ICD-9-CM code 272. Atrial fibrillation was defined as two outpatient claims with ICD-9-CM 427.3X. Liver cirrhosis was defined as two outpatient visits with ICD-9-CM codes between 571.2X and 571.5X. Renal disease was defined as two outpatient visits with ICD-9-CM codes between 580 and 589. Mental diseases were defined as two outpatient visits with ICD-9-CM codes between 290 and 319. The socioeconomic status was defined according to the insured person's salary (median, 16,500 new Taiwan dollars). Compliance with diabetes treatment was measured by proportion of days covered of treatment (16). Sufficient compliance of treatment for diabetes was defined proportion of days covered as ≥80% (17).

Cancer, stroke, coronary heart disease (CHD), and cardiovascular disease (CVD) were also identified from the hospital claim dataset. Cancer diseases were defined by ICD-9-CM codes between 140 and 239. Stroke was defined by ICD-9CM codes 430–438. CVD was defined by ICD-9-CM codes 390–459.

Death status was ascertained according to the discharge reasons with death or critically ill discharge, or if the person had quit insurance with death.

Statistical methods

The different groups were compared using the unpaired Student *t* test for parametric continuous data and the χ^2 test for categorical data. We investigated the relationship between hypoglycemia and cardiovascular events. Survival time was calculated from the date of hypoglycemia diagnosis for each data pair to the onset date of the event (stroke, CHD, CVD, or any cause for hospitalization), death, or end of study (31 December 2009). The Kaplan-Meier method was used to estimate the survival curves, and the log-rank test was used to test the homogeneity between survival curves. Hazard ratio (HR) and the 95% confidence interval (CI) for the Cox proportional hazard model were used to evaluate the association between hypoglycemia and cardiovascular events. We also performed a propensity score analysis to evaluate the association between hypoglycemia and cardiovascular events, hospitalization, and total mortality. All statistical analyses were performed using Statistical Package for SAS 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Incidence of hypoglycemia

There were 1,844 hypoglycemic events (500 in inpatients and 1,344 in outpatients) among 77,611 new type 2 diabetic patients from 1998 to 2009. The incidence of hypoglycemia was 2.38% (1,844/77,611). Women had a higher risk of hypoglycemia than men (1.34% vs. 1.04%; $P < 0.0001$).

Characteristics of hypoglycemic and matched nonhypoglycemic type 2 diabetic patients

Hypertension, atrial fibrillation, liver cirrhosis, renal disease, mental disease, history

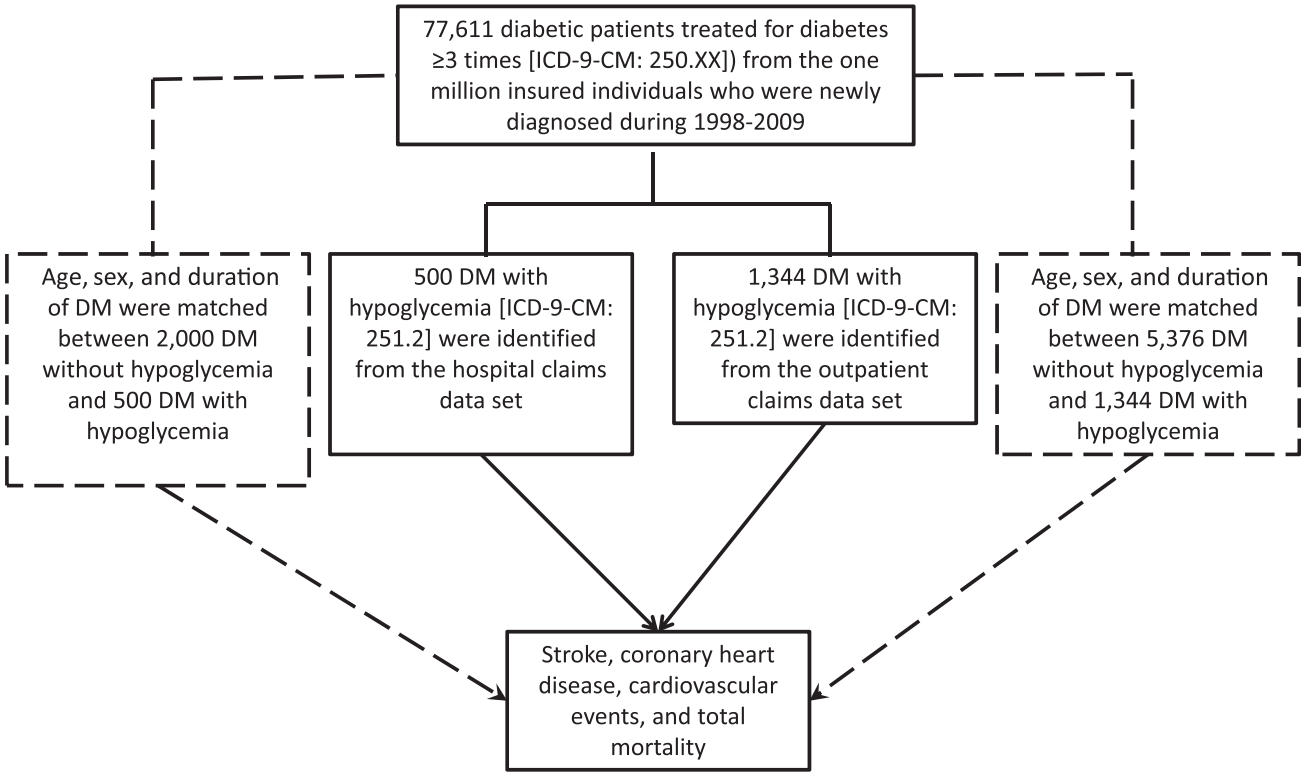

Figure 1—*Flow chart of study population. DM, diabetes or diabetic patients.*

of cancer disease, stroke, and heart disease were positively associated with hypoglycemia risk. The percentage of insulin and sulfonylureas usage and good compliance with diabetes medications also were higher in both mild and severe hypoglycemia cases. However, social economic status did not differ significantly between hypoglycemic and nonhypoglycemic cases. Because of the matched conditions, the variables age, sex, and duration of diabetes did not differ between hypoglycemic and nonhypoglycemic patients (Table 1). In both mild and severe hypoglycemia matched case-controls, comorbidities independently associated with hypoglycemia were hypertension (HR 1.75 [95% CI 1.57–1.96]); atrial fibrillation (1.96 [1.24–3.11]); liver cirrhosis (1.71 [1.17–2.48]); renal disease (3.26 [2.76–3.86]); mental disease (1.50 [1.30–1.73]); cancer (2.73 [2.12–3.50]); stroke (2.84 [2.31–3.48]); and CHD (2.04 [1.65–2.51]).

Total mortality and incidence of stroke, CHD, and cardiovascular events in hypoglycemic diabetic patients

During the follow-up period, 1,187 diabetic patients had development of stroke, 1,164 had development of CHD, 3,515 had development of cardiovascular events, and 773 died before the end of the study.

Patients with hypoglycemia had a significantly higher risk of cardiovascular events during the clinical treatment periods (Fig. 2). Compared with patients without hypoglycemia, those with hypoglycemia (both inpatient and outpatient claims datasets) had a higher hospitalization rate for stroke (27.97 vs. 69.05 and 71.73, respectively, per 1,000 person-years; both $P < 0.0001$), CHD (27.96 vs. 65.51 and 65.77, respectively, per 1,000 person-years; both $P < 0.0001$), CVD hospitalization (106.00 vs. 323.36 and 325.79, respectively, per 1,000 person-years; both $P < 0.0001$), and total mortality (14.30 vs. 41.04 and 52.28, respectively, per 1,000 person-years; all comparisons $P < 0.0001$). Both inpatients and outpatients with hypoglycemia had a more than two-fold higher relative risk of stroke (HR 2.55 [95% CI 2.24–2.90]), CHD events (HR 2.35 [95% CI 2.06–2.68]), CVD (3.19 [2.94–3.47]), and total mortality (3.49 [3.01–4.05]).

Table 2 shows the independent risk factors for stroke events, CHD events, cardiovascular events, and total mortality. In the multivariate Cox regression model, both mild and severe hypoglycemia events showed increased HRs for stroke, CHD, and all cardiovascular events after adjusting for other important comorbidities.

Furthermore, we also estimated the association between hypoglycemia and cardiovascular events, hospitalization, and total mortality for patients with insulin treatment (n = 1,068) and sulfonylurea treatment (n = 4,817). The HRs for mild and severe hypoglycemia were as follows: 2.57 (95% CI 0.73–9.09) and 1.44 (0.40–5.17), respectively, for stroke; 2.06 (0.76–5.57) and 2.10 (0.45–9.77), respectively, for CHD; 2.21 (1.39–3.53) and 1.48 (0.69–3.19), respectively, for CVD; and 1.94 (0.79–4.76) and 2.67 (0.68–10.45), respectively, for total mortality for patients with insulin treatment. Hypoglycemia was significantly and positively correlated with cardiovascular events and mortality for patients receiving sulfonylurea treatment. The HRs for mild and severe hypoglycemia were as follows: 1.82 (1.41–2.34) and 1.32 (0.96–1.82), respectively, for stroke; 1.88 (1.47–2.42) and 1.35 (0.99–1.85), respectively, for CHD; 2.32 (1.98–2.70) and 1.96 (1.59–2.43), respectively, for CVD; and 2.97 (2.22–3.97) and 2.24 (1.53–3.27), respectively, for total mortality.

Table 1—*Characteristics of diabetic patients with hypoglycemia and matched diabetic patients without hypoglycemia*

	Severe hypoglycemia n = 500	No hypoglycemia n = 2,000	P	Mild hypoglycemia n = 1,344	No hypoglycemia n = 5,376	P
Age, years	65.2 ± 9.2	65.2 ± 9.2	1.0000	62.6 ± 9.6	62.6 ± 9.6	1.0000
Males	233 (46.60)	932 (46.60)	1.0000	573 (42.63)	2,292 (42.63)	1.0000
Duration, years	3.75 ± 2.8	3.75 ± 2.8	1.0000	5.41 ± 3.1	5.41 ± 3.1	1.0000
Hypertension	318 (63.60)	1,023 (51.15)	<0.0001	895 (66.59)	2,600 (48.36)	<0.0001
Atrial fibrillation	6 (1.20)	14 (0.70)	0.2616	27 (2.01)	45 (0.84)	0.0002
Dyslipidemia	85 (17.00)	433 (21.65)	0.0218	408 (30.36)	1,351 (25.13)	<0.0001
Liver cirrhosis	15 (3.00)	26 (1.30)	0.0074	32 (2.38)	78 (1.45)	0.0162
Renal disease	87 (17.40)	103 (5.15)	<0.0001	226 (16.82)	286 (5.32)	<0.0001
Mental disease	107 (21.40)	250 (12.50)	<0.0001	262 (19.49)	688 (12.80)	<0.0001
Cancer	40 (8.00)	48 (2.40)	<0.0001	84 (6.25)	130 (2.42)	<0.0001
Stroke	75 (15.00)	80 (4.00)	<0.0001	150 (11.16)	176 (3.27)	<0.0001
Heart disease	66 (13.20)	72 (3.60)	<0.0001	132 (9.82)	203 (3.78)	<0.0001
High social economic status	214 (42.80)	937 (46.85)	0.1041	700 (52.08)	2,854 (53.09)	0.5094
Good compliance	142 (28.40)	529 (26.45)	0.3788	302 (22.47)	866 (16.11)	<0.0001
Insulin	121 (24.20)	87 (4.35)	<0.0001	460 (34.23)	400 (7.44)	<0.0001
Sulfonylureas	339 (67.80)	1,099 (54.95)	<0.0001	912 (67.86)	2,467 (45.89)	<0.0001
Other drugs	307 (61.40)	940 (47.00)	<0.0001	894 (66.52)	2,404 (44.72)	<0.0001

Data are mean ± SD or *n* (%) unless otherwise indicated. Other drugs here are other orally administered diabetes medications. Good compliance of treatment here is proportion of days covered >80%. High social economic status here is salary of the insured more than the median (16,500 new Taiwan dollars).

As shown in Table 2, the results were similar for patients who had good medication compliance, as defined by proportion of days covered.

Hypoglycemia and hospitalization

The hospitalization rate was 73.1% (1,348/1,844) among hypoglycemic diabetic patients during the observation period. Hypoglycemic patients had a 3.54-fold higher risk of being hospitalized (CI, 3.27–3.82). Further, the first-year hospitalized rate was 53.1% (714/1,344) for patients with mild hypoglycemia and 63.4% (317/500) for those with severe hypoglycemia (Fig. 2*B*). Moreover, 76.5% (*n* = 1,031/1,384) of hospitalization events occurred during the first year after hypoglycemia onset. The reason for admission of these hypoglycemic patients in the first year included CVD (ICD code 390–459, 22.0%), diabetes (ICD-9-CM code 250, 18.5%), genitourinary disease (ICD-9-CM code 580–629, 10.7%), and digestive disease (ICD-9-CM code 520–527, 8.7%).

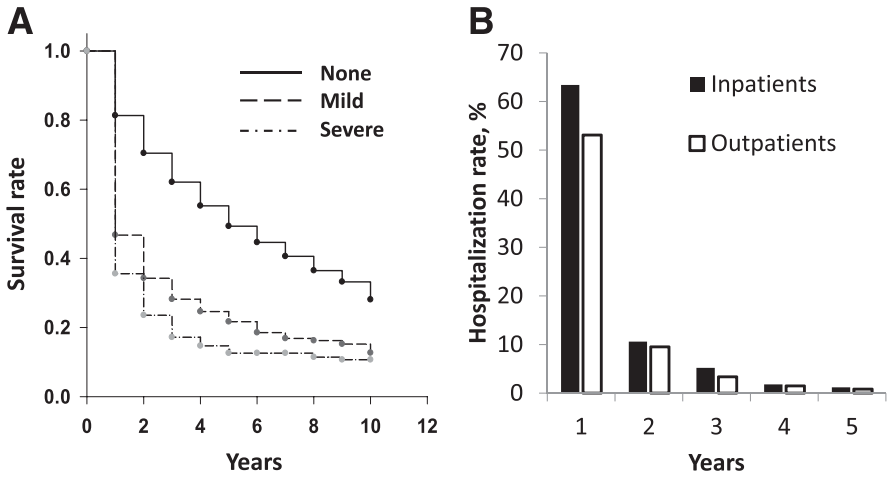

Figure 2—*Association between hypoglycemia and hospitalization.* A*: Survival curves for patients with hypoglycemia and hospitalization.* B*: The hospitalization rate* (n = *1,348) during the follow-up period was 53.1%* (n = *714/1,344) for mild hypoglycemia and 63.4%* (n = *317/500) for severe hypoglycemia, and occurred during the first year.*

Propensity score analysis

Propensity score analysis was conducted to evaluate the association between hypoglycemia, including both mild and severe cases, and hospitalization for cardiovascular events and total mortality. The distributions of potential confounding variables (Supplementary Table 1) did not differ significantly between patients with diabetes with or without hypoglycemia in the propensity score-matched data. Hypoglycemic patients had approximately a two-fold higher relative risk of cardiovascular events (HR 2.09 [95% CI 1.63–2.67]), hospitalization (2.51 [2.00–3.16]), and total death (2.48 [1.41–4.38]) in the propensity-matched dataset.

CONCLUSIONS—The major findings of this study suggest that hypoglycemia episodes, both mild and severe, are strongly associated with subsequent major cardiovascular events including stroke, CHD, and CVD hospitalization in outpatient-treated type 2 diabetic patients. Furthermore, higher all-cause mortality was associated with these hypoglycemic events. Diabetic patients who are vulnerable to hypoglycemia have more comorbidities, including hypertension, liver cirrhosis, renal disease, mental disease, cancer, and previous stroke or heart diseases. Medications, including insulin and sulfonylurea, also are important factors that impact clinical events related

Table 2—*Association between hypoglycemia and hospitalization attributable to stroke, CHD, and cardiovascular causes in the multivariate model*

	Stroke		CHD		CVD		Death	
Variables	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Hypertension, yes versus no	1.61	1.39–1.86	1.53	1.31–1.78	1.95	1.78–2.13	1.28	1.07–1.54
Atrial fibrillation, yes versus no	1.26	0.63–2.52	1.49	0.79–2.82	1.67	1.12–2.48	0.93	0.43–2.01
Dyslipidemia, yes versus no	0.88	0.75–1.05	1.33	1.12–1.57	1.01	0.91–1.11	0.73	0.59–0.91
Liver cirrhosis, yes versus no	0.60	0.31–1.16	0.60	0.30–1.19	1.49	1.09–2.05	2.28	1.32–3.93
Renal disease, yes versus no	1.26	0.97–1.63	1.49	1.17–1.91	1.79	1.54–2.08	2.01	1.52–2.65
Mental disease, yes versus no	1.12	0.93–1.35	1.04	0.86–1.26	1.03	0.92–1.16	1.12	0.83–1.43
Previous cancer, yes versus no	0.66	0.43–1.01	0.58	0.36–0.92	1.03	0.81–1.31	2.03	1.36–3.02
Previous stroke, yes versus no	4.26	3.35–5.42	0.76	0.56–1.03	1.42	1.19–1.69	1.26	0.91–1.74
Heart disease, yes versus no	1.13	0.85–1.52	4.73	3.68–6.08	1.96	1.64–2.34	1.30	0.94–1.79
High social economic status	0.94	0.81–1.09	0.91	0.78–1.05	0.96	0.87–1.04	0.58	0.48–0.71
Good compliance	1.15	0.97–1.36	1.06	0.90–1.25	1.14	1.03–1.26	1.21	0.98–1.49
Insulin	1.63	1.29–2.07	1.54	1.21–1.95	1.74	1.51–2.01	1.74	1.34–2.27
Sulfonylureas	1.17	1.00–1.37	1.30	1.11–1.53	1.34	1.22–1.47	1.38	1.14–1.67
Mild hypoglycemia	1.92	1.60–2.31	1.76	1.46–2.13	2.21	1.98–2.47	2.70	2.19–3.33
Severe hypoglycemia	1.64	1.29–2.07	1.63	1.28–2.08	2.26	1.93–2.65	2.18	1.66–2.88

Good compliance of treatment here is proportion of days covered >80%. High social economic status here is salary of the insured more than the median (16,500 new Taiwan dollars).

to hypoglycemia. Once outpatient-treated diabetic patients have hypoglycemic episodes, cardiovascular and hospitalization events occur most frequently in the first year after the hypoglycemic event regardless of whether the hypoglycemia was mild or severe.

The incidence of clinical hypoglycemic events, including both mild and severe types, was lower in our study than in previous clinical trials such as ACCORD (12) and community epidemiological studies in other countries such as the United Kingdom (18,19). A lower proportion of patients with hypoglycemia has been reported in Asian Pacific countries and Taiwan (20), which may be explained by more conservative treatment strategies in Taiwanese clinical diabetes control (21).

In recent years, intensive glucose control strategies for long-duration type 2 diabetic patients have been intensively studied, including in the VADT (13), ADVANCE (14), and ACCORD trials (12). These trials did not consistently support strategies to improve reductions in cardiovascular events or mortality. Excessive mortality in intensive glucose control groups has led to debate regarding hypoglycemia-related adverse outcomes. However, a post hoc analysis of the data from the ACCORD trial suggests that the excess mortality in the intensively treated group cannot be directly explained by the more frequent episodes of hypoglycemia in this group of patients (22). The post hoc analysis of the data from the ADVANCE study also suggested recently that severe hypoglycemia is strongly associated with increased risk of adverse clinical outcomes, including macrovascular and microvascular changes and death from cardiovascular events. Because there is no relationship between repeated hypoglycemia episodes and adverse outcomes, the authors conclude that hypoglycemia is a likely marker of vulnerability to such events (15).

Although some previous studies have shown that hypoglycemia is a risk factor for future cardiovascular events, these analyses were almost all based on patients recruited during hospitalization (7,8). Most of the epidemiological analyses were from clinical trials related to acute myocardial infarction, including the DIGAMI-2 and OASIS-6 trials (9,10). In contrast, our study population was recruited from real-world outpatient clinical practice, and our results suggest that clinically driven hypoglycemia in diabetes may increase adverse cardiovascular outcomes and hospitalization from any cause by approximately two-fold. Even after propensity score–adjusted analysis, hypoglycemia still has ~2.0-times to 2.5-times the risk for CVD events, all-cause hospitalization, and all-cause mortality. Our result was similar to a retrospective epidemiological analysis of the ACCORD study, which showed HR of ~2.87 for all-cause mortality with severe versus not severe episodes of hypoglycemia in a standard treatment group (22). These observations suggest that hypoglycemia occurs as a consequence of intensive therapeutic intervention and has a different relationship with serious cardiovascular outcomes or death than spontaneous hypoglycemia or episodes that occur as part of routine diabetes management (4).

Furthermore, many previous studies have suggested that hypoglycemia is a risk factor for serious health outcomes. Combined with evidence that therapies promoting hypoglycemia do not increase these outcomes, hypoglycemia is more likely to be associated with other risk factors for these outcomes rather than being causally related to them (22). However, studies have demonstrated that hypoglycemia events in general ward patients have a dose-dependent relationship with the length of hospital stay and in-hospital mortality (23). Hypoglycemia may result in poor outcomes for diabetic patients by leading to falls, seizures, or nonmedical death. This was not found in our study, because the most frequent causes of hospitalization were for CVD, diabetes, genitourinary disease, and digestive disease. Our results also suggest that hypoglycemia may be a marker for disease severity in these routinely treated diabetic patients. Diabetic patients who experienced hypoglycemic episodes were more likely to be using insulin and

sulfonylurea and have better treatment compliance. This may indirectly indicate a greater severity of diabetes for patients prone to hypoglycemic events. However, data for blood glucose or HbA_{1c} levels are not present in this type of administration database, and so these parameters could not be considered.

Some articles have studied the possible mechanics of symptomatic hypoglycemia and suggested that hypoglycemia may predispose patients to adverse cardiovascular outcomes. Hypoglycemia may be associated with elevated sympathetic activity and release of catecholamines, thereby promoting destabilization of atherosclerotic plaques (24). Hemodynamic changes with increased myocardial work, hypoglycemia-induced increase in platelet aggregation, and platelet activity also may precipitate cardiac or cerebral ischemic insults in high-risk type 2 diabetic patients (25,26). Additionally, one study revealed a higher frequency of ischemic electrocardiogram changes or a nocturnal increase in the corrected QT interval accompanied by rhythm disturbance when hypoglycemia develops (27).

In this nationwide cohort study, we also found that diabetic patients who are prone to hypoglycemia episodes are more likely to have comorbidities such as hypertension, renal disease, heart disease, stroke, and cancer history, with borderline atrial fibrillation and liver disease. Previous studies also support this association of severe hypoglycemia with older age, longer duration of diabetes, higher creatinine level, use of two or more oral glucose-lowering agents, and assignment to intensive glucose control (28). Although our study patients were matched for age, sex, and diabetes duration, this trend of associations was still evident. Our study does have some limitations. First, neither the educational status of individuals nor information about personal habits such as smoking, extent of physical activity, BMI, or the exact condition of glycemic control was available from the NHIRD. Second, this study was conducted with data from NHIRD, and the diagnosis was assumed to have been confirmed clinically by the individual physician in charge. The occurrence of mild or severe hypoglycemia was only confirmed by the outpatient or inpatient record of clinical hypoglycemia, and patient glucose levels were not recorded. By using a case-control study design, we hoped to minimize the impact of selection, misclassification, and diagnostic bias. Third, the study population consisted of Taiwanese patients who were of Chinese descent and, thus, the results may not be easily generalized to other populations.

In conclusion, symptomatic hypoglycemia, both clinically mild and severe, is associated with an increased risk for cardiovascular events, all-cause hospitalization, and all-cause mortality. Adverse events after hypoglycemia occurred most frequently in the first year. Clinically, more attention may be needed for diabetic patients with hypoglycemic episodes.

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P.-F.H., S.-H.S., and S.-Y.C. designed the study. P.-F.H. and S.-Y.C. acquired data. P.-F.H., S.-H.S., H.-M.C., J.-S.Y., W.-L.C., C.-H.C., P.C., and S.-Y.C. interpreted results. W.-L.L. and S.-Y.C. analyzed data. P.-F.H., S.-H.S., and S.-Y.C. drafted the manuscript. S.-Y.C. 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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