

Association of Hypoglycemia With Incident Chronic Kidney Disease in Patients With Type 2 Diabetes

A Nationwide Population-Based Study

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Abstract: This article aims to investigate the long-term risk of incident chronic kidney disease (CKD) in type 2 diabetes mellitus (T2DM) patients with hypoglycemia.

This nationwide, population-based, propensity score (PS)-matched cohort study involved 2 cohorts: a hypoglycemic cohort and a matched cohort without hypoglycemia. Data from 1.3 million patients with newly diagnosed T2DM between 2000 and 2010 were extracted from Taiwan's National Health Insurance Research Database. Hypoglycemic events were collected using inpatient, outpatient, and emergency department diagnoses. Patients aged <20 years and those with previous histories of CKD were excluded. The association between hypoglycemia and subsequent CKD risk in patients with T2DM was examined using Cox regression analysis after PS matching.

During the mean follow-up period of 4.2 years, a total of 15,036 (1.7%) patients experienced at least 1 episode of hypoglycemia and 15,036 matched controls without hypoglycemia were identified among 906,368 eligible patients. The incidence rates of subsequent CKD were 26.1 and 14.8 events per 1000 person-years in the hypoglycemic and matched cohorts, respectively. The hazard ratio (HR) of hypoglycemia for incident CKD was 1.77 (95% confidence interval [CI], 1.63–1.92; $P < 0.001$). Compared with those without hypoglycemia, HRs for 1 to 3 and ≥ 4 episodes of hypoglycemia for CKD were 1.65 (95% CI, 1.50–1.81) and 1.75 (95% CI, 1.34–2.29), respectively (P for trend < 0.001).

Our study supports the association of hypoglycemia with CKD development among patients with T2DM, possibly in a dose-dependent relationship.

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Abbreviations: CIs = confidence intervals, aDCSI = adapted diabetes complications severity index, CCI = Charlson Comorbidity Index, CKD = chronic kidney disease, 0 = diabetes mellitus, ESRD = end-stage renal disease, GFR = glomerular filtration rate, HR = hazard ratio, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, SD = standard deviation.

INTRODUCTION

Hypoglycemia is a major potential adverse effect of diabetes mellitus (DM) treatment with glucose-lowering drugs, such as insulin or oral medications. The presentation of hypoglycemia can be mild, involving symptoms such as dizziness, diaphoresis, and/or disorientation, or severe, involving symptoms such as neuroglycopenia, which represents a medical emergency and causes permanent brain damage if not detected and treated early. Hypoglycemia can also activate the adrenergic response, resulting in vascular hypoperfusion, cardiac arrhythmia, or even sudden death.^{1–3}

A post hoc analysis of data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study⁴ found that hypoglycemia was associated with a higher risk of subsequent mortality, which did not differ between intensive and conservative glycemic control groups. Hypoglycemia appeared to be the main barrier to achieving optimal glycemic targets and clinical benefits in patients with type 2 diabetes mellitus (T2DM). Observational studies have also found that hypoglycemic episodes may elevate the risks of adverse cardiovascular events, such as stroke and coronary artery disease.^{5–7} However, the impact of hypoglycemia on the development of diabetic kidney disease has not been thoroughly examined since T2DM diagnosis.

The prevalence of diabetic kidney disease in the United States did not markedly decrease among diabetes population between 1988 and 2008, despite the widespread use of glucose-lowering and renoprotective drugs (eg, renin-angiotensin-aldosterone system blockers).⁸ This phenomenon may be explained by the hypothesis that the harmful effects of hypoglycemia during the treatment of DM may affect kidney function. With respect to hypoglycemia, it is biologically plausible that it may induce kidney damage through its effects on sympathetic overactivity and oxidative stress.^{9,10} Thus, we conducted a propensity score (PS)-matched nationwide study that included the majority of patients with T2DM in Taiwan from 2000 to 2010 to compare the long-term risk of incident chronic kidney disease (CKD) between patients who reported

having at least 1 hypoglycemic event and those who reported no clinically evident hypoglycemic episode.

METHODS

Data Source

Taiwan's National Health Insurance (NHI) program, launched in 1995, offers comprehensive medical coverage, including coverage of ambulatory and emergent care, hospital admission, dental care, prescription drugs, examinations, laboratory tests, and interventions. The compulsory NHI currently covers 99% of Taiwan's 23 million residents. This study used data from the National Health Insurance Research Database (NHIRD), maintained by the National Health Research Institutes (NHRI). The NHIRD has been described in detail in the previous studies.^{11,12} For the current study, we used the Longitudinal Cohort of Diabetes Patients dataset, which has been validated by the NHRI for research purposes. This database consists of deidentified secondary data from a random sample of 120,000 patients with diagnosis of incident DM per year, which represent the majority (about 70%) of this population in Taiwan, from 2000 to 2010. This sampling number of patients (120,000 patients per year) was based on a regulation that allows <10% NHI enrollees' medical data extracted for research purposes. Previous studies have validated the accuracy of DM diagnoses in the NHIRD.¹³ Diseases were defined based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. Owing to the deidentified and secondary nature of data, this study was exempted from full review by the Institutional Review Board of Taipei City Hospital, Taipei, Taiwan.

Study Design

This population-based observational cohort study aimed to assess the association between clinically evident hypoglycemia and subsequent CKD in patients with DM. It included 2 cohorts: a hypoglycemic cohort and a control cohort without hypoglycemia. We identified all patients with diagnosis of incident DM between January 2000 and December 2010. The diagnosis of DM was defined by a primary discharge diagnosis of DM (ICD-9-CM code 250.x), 2 ambulatory visits with a diagnosis of DM (ICD-9-CM code 250.x), or use of any antihyperglycemic drug. The hypoglycemic cohort comprised all patients with DM whose first episode of hypoglycemia (ICD-9-CM codes 251.0x, 251.1x, 251.2x) required medical assistance in an inpatient, outpatient, or emergency department. The index date was defined as 91 days after the occurrence of hypoglycemia to avoid immortal time bias. The matched control cohort comprised the remaining patients with DM in whom hypoglycemia had not occurred during the study period. As these patients never developed hypoglycemia, index dates were randomly assigned according to those of patients in the hypoglycemic cohort. Patients aged <20 years ($n=89,594$) and those with previous histories of CKD or end-stage renal disease (ESRD) ($n=9958$) were excluded in the hypoglycemic cohort. The same exclusion criterion was applied to the matched cohort.

For patients in both the cohorts, we extracted all data regarding demographic variables, diagnosis and procedure codes, and drug prescriptions for the period extending from January 1995 to December 2011, and ensured that all individuals had available data for at least 5 years before study inclusion. Baseline information was collected from the 5-year period before inclusion. Sociodemographic data included age,

sex, monthly income, and urbanization. Charlson Comorbidity Index (CCI) score¹⁴ adapted diabetes complications severity index (aDCSI) score,¹⁵ and other comorbidities that are known to be the risk factors for CKD were examined. In addition to antidiabetic medications, other concomitant medications that could be the potential confounding effect between hypoglycemia and CKD were also considered (Table 1).

For each patient, we calculated PSs for the likelihood of hypoglycemia occurrence using baseline covariates and a multivariate logistic regression model. We matched 1 control patient with each patient in the hypoglycemic cohort according to PS (calipers of width equal to 0.1 standard deviation [SD] of the logit of the PS) based on nearest-neighbor matching without replacement.

Outcomes

The primary study outcome was the occurrence of incident CKD, defined as 2 outpatient visits or 1 hospitalization with ICD-9-CM code 585. This definition was used in a previous study for a similar purpose.¹⁶ The reliability of ICD-9-CM coding of CKD has also been confirmed.^{17–19} The secondary outcome was all-cause mortality. Both cohorts were followed from the index date until the occurrence of CKD or death, withdrawal from the NHI program, or December 31, 2011.

Statistical Analysis

Descriptive statistics were used to describe the baseline characteristics of the study cohorts. These characteristics were compared between groups using Pearson χ^2 tests for categorical variables and independent t tests for continuous variables, respectively. Standardized mean difference was used to compare the characteristics between groups after PS matching. PSs for the likelihood of hypoglycemia occurrence were calculated by multivariate logistic regression, conditional on baseline covariates (Supplementary Table 1, <http://links.lww.com/MD/A249>). The cumulative incidence of CKD was calculated using the Kaplan–Meier method and compared between groups using the log-rank test. Poisson distribution was used to compare the incidence rate of CKD between groups. The relative risk of CKD and all-cause mortality between cohorts was calculated using the hazard ratio (HR) in a Cox regression model. The competing-risks regression was also calculated based on the model by Fine and Gray.²⁰ Subgroup Cox regression analyses were performed according to prespecified variables including age, sex, CCI score, hypertension, cerebrovascular disease, myocardial infarction, and insulin use. Interaction tests were performed using the likelihood ratio test.

As at least 3-month observation period was required to diagnose incident CKD, short follow-up period after hypoglycemia occurrence may overestimate the HR for CKD attributed to hypoglycemia. Thus, we performed a sensitivity analysis that excluded patients with follow-up periods <180 and <365 days. We also performed separate analyses dividing the hypoglycemic cohort into 3 subset according to inpatient, outpatient, or emergency department diagnosis of hypoglycemia. Additionally, to test the robustness of our results, we adjusted PS or imbalanced covariates after PS matching. Cox models before PS matching and with the hypoglycemic episode as a time-dependent covariate were also performed. Microsoft SQL Server 2012 (Microsoft Corporation, Redmond, WA) was used for data linkage, processing, and sampling. PSs were calculated using SAS version 9.3 (SAS Institute Inc., Cary, NC). All other statistical analyses were conducted using STATA statistical

TABLE 1. Baseline Characteristics of Diabetes Patients

Characteristics	Propensity Score Matched		
	Hypoglycemic Cohort	Matched Nonhypoglycemic Cohort	Standardized Mean Differences*
Patient (no.)	15,036	15,036	
Mean age (SD), y	66.3 (14.7)	66.4 (13.3)	-0.010
Male, n (%)	7116 (47.3)	7203 (47.9)	-0.012
Monthly income, NT\$, n (%)			
Dependent	5219 (34.7)	5288 (35.2)	-0.010
<19,100	3674 (24.4)	3697 (24.6)	-0.004
19,100-41,999	5790 (38.5)	5687 (37.8)	0.014
≥42,000	353 (2.3)	364 (2.4)	-0.005
Urbanization [†] , n (%)			
Level 1	4549 (30.3)	4548 (30.2)	0.000
Level 2	9449 (62.8)	9460 (62.9)	-0.002
Level 3	854 (5.7)	850 (5.7)	0.001
Level 4 (rural area)	184 (1.2)	178 (1.2)	0.004
Outpatient visits of metabolism and endocrinology, in the past 1 y, n (%)			
0-5 visits	12,857 (85.5)	12,895 (85.8)	-0.007
6-10 visits	1401 (9.3)	1397 (9.3)	0.001
11-15 visits	498 (3.3)	468 (3.1)	0.011
>15 visits	280 (1.9)	276 (1.8)	0.002
Charlson Comorbidity Index score [‡] , n (%)			
1	1191 (7.9)	1142 (7.6)	0.012
2	1854 (12.3)	1876 (12.5)	-0.004
3	2439 (16.2)	2391 (15.9)	0.009
≥4	9552 (63.5)	9627 (64.0)	-0.010
Adapted diabetes complications severity index score [§] (SD)	3.0 (2.3)	3.0 (2.4)	-0.003
Duration of diagnosis of diabetes, mo (SD)	42.5 (34.8)	42.3 (33.7)	0.007
Antidiabetic drugs			
Acarbose inhibits enzymes	957 (6.4)	932 (6.2)	0.007
Sulfonylurea	4714 (31.4)	4708 (31.3)	0.001
Insulin	1491 (9.9)	1380 (9.2)	0.025
Metformin	6929 (46.1)	7023 (46.7)	-0.013
Thiazolidinediones	1178 (7.8)	1154 (7.7)	0.006
Glinide	768 (5.1)	747 (5.0)	0.006
Dipeptidyl peptidase-4 inhibitor	209 (1.4)	207 (1.4)	0.001
Antihypertensive drug, n (%)			
α-blocker	550 (3.7)	621 (4.1)	-0.024
β-blocker	2490 (16.6)	2503 (16.6)	-0.002
Calcium channel blocker	4833 (32.1)	4973 (33.1)	-0.020
Diuretics	2912 (19.4)	2962 (19.7)	-0.008
ACE inhibitors or ARB	4961 (33.0)	5020 (33.4)	-0.008
Other antihypertensive drugs	344 (2.3)	362 (2.4)	-0.008
Other concomitant medications, n (%)			
Antiplatelet agent	3800 (25.3)	3868 (25.7)	-0.010
Steroid	1444 (9.6)	1398 (9.3)	0.010
Nitrate	1114 (7.4)	1111 (7.4)	0.001
NSAID	3539 (23.5)	3517 (23.4)	0.003
PPI	747 (5.0)	757 (5.0)	-0.003
Statin	1712 (11.4)	1793 (11.9)	-0.017
SSRI	329 (2.2)	347 (2.3)	-0.008
Comorbidities, n (%)			
Coronary artery disease	6790 (45.2)	6807 (45.3)	-0.002
Hypertension	11,776 (78.3)	11,838 (78.7)	-0.010
Heart failure	3031 (20.2)	3014 (20.0)	0.003
Peripheral vascular disease	1194 (7.9)	1165 (7.7)	0.007
Peptic ulcer disease	8004 (53.2)	8106 (53.9)	-0.014
Liver disease	5330 (35.4)	5271 (35.1)	0.008

Characteristics	Propensity Score Matched		
	Hypoglycemic Cohort	Matched Nonhypoglycemic Cohort	Standardized Mean Differences*
Atrial fibrillation	1000 (6.7)	1021 (6.8)	-0.006
Dyslipidemia	8004 (53.2)	7957 (52.9)	0.006
Cerebrovascular disease	6391 (42.5)	6505 (43.3)	-0.015
Valvular heart disease	1756 (11.7)	1673 (11.1)	0.017
Cancer	2207 (14.7)	2252 (15.0)	-0.008
Autoimmune disease	574 (3.8)	570 (3.8)	0.001
Propensity score (IQR)	0.04 (0.02–0.09)	0.04 (0.02–0.09)	0.000

All data were described as number (%), except mean age and propensity score. ACE = angiotensin-converting-enzyme, ARB = angiotensin II receptor blockers, CCI = Charlson Comorbidity Index, IQR = interquartile range, NSAIDs = nonsteroidal anti-inflammatory drugs, NT\$ = new Taiwan dollars, PPI = proton pump inhibitor, SD = standard deviation, SSRI = selective serotonin reuptake inhibitors.

* Imbalance defined as absolute value >0.023.

† Urbanization levels in Taiwan are divided into 4 strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas and level 4 designates the least urbanized areas.

‡ CCI score is used to determine overall systemic health. With each increased level of CCI score, there are stepwise increases in the cumulative mortality.

§ Adapted diabetes complications severity index is a 13-point scale from 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic, ranging from each complication. Each complication produced a numeric score ranging from 0 to 2 (0 = no abnormality, 1 = some abnormality, 2 = severe abnormality).

|| Including aspirin, clopidogrel, ticlopidine, and cilostazol.

software (version 13.0; StataCorp., College Station, TX). Statistical significance was defined as a $P < 0.05$.

RESULTS

Characteristics of the Study Population

A total of 906,368 patients with diagnosis of incident DM without CKD between January 2000 and December 2010 were enrolled in the study (Supplementary Table 2, <http://links.lww.com/MD/A249>). Among them, 15,036 hypoglycemic patients and 15,036 matched nonhypoglycemic patients who met the inclusion criteria were identified. The mean age of the study population was 66.6 (SD, 14.3) years. More than half of the patients (52.8%) were female. In the hypoglycemic cohort, the mean interval between hypoglycemia and the first day of DM diagnosis was 42.5 (SD, 34.8) months. The characteristics of the study population are shown in Table 1.

Risk of CKD and Mortality

During the follow-up period, 2419 patients developed CKD and 9776 died before the end of the study. The incidence rates of CKD were 26.14 per 1000 person-years in the hypoglycemic cohort and 14.77 per 1000 person-years in the matched control cohort. The risk of CKD was higher in the hypoglycemic than in the control cohort (HR, 1.77; 95% confidence interval [CI], 1.63–1.92; $P < 0.001$; Table 2). The HR for all-cause mortality among the hypoglycemic cohort was 1.47 (95% CI, 1.42–1.53; $P < 0.001$) compared with the matched control cohort. After considering death as a competing event, the result remained robust (HR, 1.63; 95% CI, 1.50–1.77). The cumulative incidence of CKD in patients with hypoglycemia and the matched cohort was illustrated in Figure 1. Compared with nonhypoglycemic patients, adjusted HRs (aHRs) of CKD for 1 to 3 and >4 episodes of hypoglycemia were 1.65 (95% CI, 1.50–1.81; $P < 0.001$) and 1.75 (95% CI, 1.34–2.29; $P < 0.001$), respectively (P for trend <0.001); aHRs of all-cause mortality for 1 to 3 and >4 episodes of

hypoglycemia were also statistically significant (P for trend <0.001) (Table 3). The association between hypoglycemia and CKD remained consistent in the subgroup analyses. Significant interactions between hypoglycemia and sex ($P_{\text{Interaction}} < 0.001$), CCI score ($P_{\text{Interaction}} = 0.043$), hypertension ($P_{\text{Interaction}} = 0.015$), and using antidiabetic drugs ($P_{\text{Interaction}} < 0.001$) were observed (Figure 2). The effect of hypoglycemia on risk of incident CKD was greater in women, patients with low CCI scores, those with hypertension, and those without using insulin (ie, using oral antidiabetic drugs or diet control) compared with those in male gender, high CCI scores, having no hypertension, and using insulin, respectively.

Sensitivity analyses that excluded patients with follow-up periods <180 and <365 days confirmed that hypoglycemia increased the risk of CKD in patients with DM (Table 4). The results remained consistent stratified by hypoglycemia diagnosis in inpatient, outpatient, or emergency department (Table 2). Similar results were also obtained in the Cox model with adjusting PS and imbalanced covariates in PS matching (ie, using insulin and α -blockers) (Table 2), before PS matching (Supplementary Table 3, <http://links.lww.com/MD/A249>), or in the analysis that calculated the hypoglycemia episode as a time-dependent covariate (Supplementary Table 4, <http://links.lww.com/MD/A249>).

DISCUSSION

In this nationwide cohort of about 1 million patients with T2DM and without CKD at baseline, clinically significant hypoglycemia was associated with a 1.8 and 1.5-fold greater risk of developing incident CKD and all-cause mortality than in matched control subjects without hypoglycemia during the 10-year study period. This association appeared to be dose dependent, as the risk increased with the number of hypoglycemic episodes. The impact of hypoglycemia on incident CKD remained robust after competing risk of death and consistent across subgroups stratified by age, sex, and comorbidities.

TABLE 2. Incidence and Risk of Chronic Kidney Disease and All-Cause Mortality Among Diabetes Patients With and Without Hypoglycemia

	Propensity Score Matched											
	Model 1			Model 2 [†]			Model 3 [‡]			Model 4 [§]		
	No. of Event	Person-Years	Incidence Rate*	Crude Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	
All-cause mortality												
Nonhypoglycemic cohort	4077	64,167	63.54	As reference		As reference		As reference		As reference		
Hypoglycemic cohort	5699	60,534	94.15	1.47 (1.42–1.53)	<0.001	1.47 (1.41–1.53)	<0.001	1.47 (1.41–1.53)	<0.001	1.47 (1.41–1.53)	<0.001	
Outpatient	1795	26,633	67.40	1.13 (1.07–1.20)	<0.001	1.16 (1.09–1.22)	<0.001	1.13 (1.07–1.20)	<0.001	1.13 (1.07–1.20)	<0.001	
Inpatient	1495	11,664	128.17	2.17 (2.04–2.30)	<0.001	2.17 (2.04–2.30)	<0.001	2.17 (2.04–2.30)	<0.001	2.17 (2.04–2.30)	<0.001	
Emergency department	2409	25,942	92.86	1.51 (1.44–1.59)	<0.001	1.47 (1.40–1.55)	<0.001	1.51 (1.43–1.58)	<0.001	1.51 (1.43–1.58)	<0.001	
Chronic kidney disease												
Nonhypoglycemic cohort	922	62,427	14.77	As reference		As reference		As reference		As reference		
Hypoglycemic cohort	1497	57,265	26.14	1.77 (1.63–1.92)	<0.001	1.76 (1.62–1.91)	<0.001	1.76 (1.62–1.91)	<0.001	1.63 (1.50–1.77)	<0.001	
Outpatient	463	25,485	18.17	1.30 (1.16–1.46)	<0.001	1.30 (1.17–1.46)	<0.001	1.34 (1.20–1.50)	<0.001	1.30 (1.16–1.45)	<0.001	
Inpatient	309	11,003	28.08	2.02 (1.78–2.30)	<0.001	2.02 (1.78–2.30)	<0.001	2.03 (1.78–2.31)	<0.001	1.74 (1.53–1.99)	<0.001	
Emergency department	725	24,481	29.61	2.14 (1.94–2.36)	<0.001	2.13 (1.93–2.34)	<0.001	2.06 (1.87–2.27)	<0.001	1.89 (1.71–2.08)	<0.001	

CI = confidence interval.
 * Per 10³ person-years.
 † Adjusted for propensity score.
 ‡ Adjusted for using insulin and α-blocker.
 § Death as a competing risk.

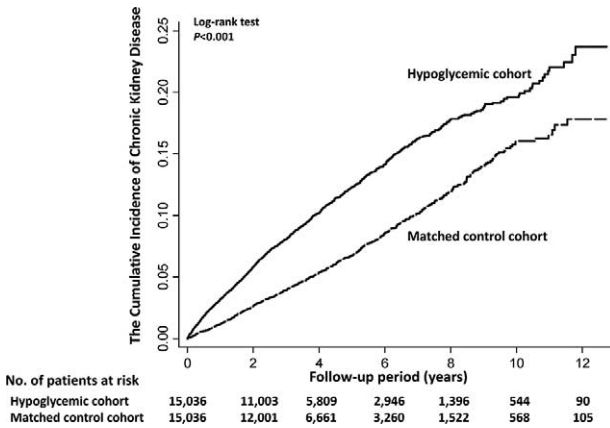


FIGURE 1. Cumulative incidence of chronic kidney disease compared between diabetes patients with hypoglycemia and individuals without hypoglycemia.

Most previous studies^{21–23} have observed increased risks of hypoglycemia and subsequent adverse cardiovascular outcomes in patients with DM and established CKD, possibly due to the prolonged half-life of antidiabetic drugs, which are mainly excreted renally. However, hypoglycemia was also found to be a common complication among patients with DM and preserved kidney function in a cohort of US veterans.²¹ A community-based study found that the risk of severe hypoglycemia was similar across patients with all levels of glyemic control (ie, those with glycosylated hemoglobin [HbA1c] concentrations of <6%, 6% to 6.9%, 7% to 7.9%, 8% to 8.9%, and ≥9%).²⁴ The emerging threat of hospital admission for hypoglycemia has also exceeded that for hyperglycemia among older US Medicare beneficiaries susceptible to CKD development or progression.²⁵ Intriguingly, small physiological studies have documented acute and transient decline in glomerular filtration rate (GFR) and renal plasma flow during hypoglycemic episodes in healthy humans and patients with T1DM.^{26,27} However, the long-term risk of incident CKD in patients with T2DM who experience hypoglycemia is not completely understood.

A post hoc analysis of Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation (ADVANCE) study²⁸ data showed that severe hypoglycemia was associated with increased risks of microvascular and macrovascular events. However, because of marked attenuation of the association by adjustment for confounding factors and the lack of a dose-dependent relationship in this analysis, the authors suggested that hypoglycemia tended to be a marker of vulnerability to CKD. The influence that patients had untraceable hypoglycemia condition before study entry and the infrequent occurrence of repeated hypoglycemia during the follow-up period may have limited the statistical power to detect the exact effects of hypoglycemia on CKD occurrence in that analysis.²⁸ In contrast, the results of our nationwide cohort study suggest that hypoglycemia is a novel risk factor for CKD and a marker presenting with similar severity to that of CKD, as the association between these conditions was dose dependent. This study produced robust and reliable findings because patients received medical attention for hypoglycemia under Taiwan full-coverage NHI program; thus, all significant episodes of hypoglycemia following T2DM diagnosis during the 10-year study period were recorded in the NHIRD. In addition, patients with antecedent hypoglycemia are likely to

TABLE 3. Episodes of Hypoglycemia and Risk of Chronic Kidney Disease and All-Cause Mortality Among Diabetes Patients

	Chronic Kidney Disease			All-Cause Mortality		
	Crude	Adjusted*	P for Trend	Crude	Adjusted*	P for Trend
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	P Value
Episode of hypoglycemia [†]						
0	Reference	Reference		Reference	Reference	
1–3	1.58 (1.44–1.73)	1.65 (1.50–1.81)	<0.001	1.47 (1.41–1.53)	1.49 (1.43–1.55)	<0.001
≥4	1.63 (1.25–2.14)	1.75 (1.34–2.29)	<0.001	1.58 (1.40–1.77)	1.60 (1.42–1.80)	<0.001

CI = confidence interval.

* Adjusted for all covariate listed in Table 1.

[†] All episodes of hypoglycemia within 1 y after enrolment. We further excluded patients without follow-up period for >1 y and redefined index date as the day of 366d after enrolment to avoid immortal time bias.

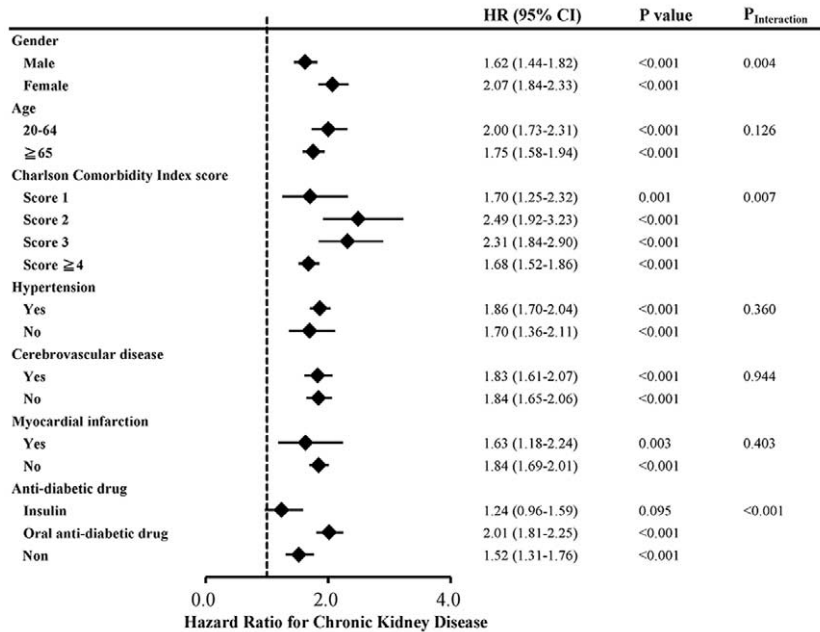


FIGURE 2. Forest plot of the effect of hypoglycemia on the risk for chronic kidney disease by subgroups.

have attenuated awareness of this condition⁴ because of impaired autonomic function.²⁹ Thus, the effect of hypoglycemia in a real-world setting may be underestimated, further supporting our findings.

The Kidney Disease: Improving Global Outcomes guidelines encourage the achievement of an optimal glycemic target to prevent or retard the progression of diabetic kidney disease.³⁰ However, evidence for the renoprotective effect of glycemic control has been confined almost entirely to the reduction or prevention of albuminuria. Its benefit in terms of clinically meaningful outcomes, such as reduction of GFR decline or ESRD rate, has been examined in only a few studies targeting patients with newly diagnosed DM and no significant cardiovascular risk.^{31,32} Most recent randomized controlled studies,

including the ACCORD⁴ study, ADVANCE³³ study, and Veterans Affairs Diabetes Trial,³⁴ have failed to demonstrate remarkably improved outcomes in terms of macrovascular or microvascular complications in patients with T2DM and established cardiovascular risk who received intensive glycemic control. The strategy of intensive control may have exposed patients to increased risks of hypoglycemia and elevated all-cause mortality. Thus, the potential renoprotective benefits of better glycemic control may be attenuated by hypoglycemia during treatment. Although the exact mechanism is not well understood, a preclinical study demonstrated that hypoglycemia can induce nonesterified fatty acid elevation in adipose tissue, which is subsequently associated with kidney damage.³⁵ In addition, hypoglycemia could induce sympathetic surges,

TABLE 4. Sensitivity Analysis for the Risk of Chronic Kidney Disease Among Diabetes Patients

	Hypoglycemic Cohort		Nonhypoglycemic Cohort		Propensity Score Matched					
	No. of Events	Person-Years	Incidence Rate*	No. of Events	Person-Years	Incidence Rate*	Crude		Adjusted†	
							Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Excluding patients with follow-up period <180 d	1350	53,663	25.16	877	58,783	14.92	1.68 (1.55–1.83)	<0.001	1.68 (1.54–1.83)	<0.001
Excluding patients with follow-up period <365 d	1135	46,709	24.30	793	51,596	15.37	1.58 (1.44–1.73)	<0.001	1.58 (1.44–1.73)	<0.001

CI = confidence interval.
 * Per 10³ person-years.
 † Adjusted for propensity score.

altering renal hemodynamics¹⁰; acute fluctuations in blood glucose levels also trigger oxidative stress, which may be responsible for renal function impairment.⁹

Our study has several strengths. First, it examined 1 of the largest cohorts of patients with T2DM worldwide, which consisted of 1.3 million patients representing the majority of T2DM population in Taiwan from 2000 to 2010, and thus minimized referral bias. Second, although the incidence of CKD among patients with T2DM was typically low,³⁶ the investigation of a large sample of patients with T2DM and without CKD and comprehensive recording of subsequent hypoglycemic events during an extended follow-up period provided sufficient power to examine the temporal association between hypoglycemia and incident CKD. Additionally, as previous studies have suggested that patients who are prone to hypoglycemia tend to be older and have longer DM durations and more comorbid conditions, such as heart, renal, and/or liver disease,^{37,38} we used PS analysis to reduce confounding effects typical of analyses using observational data.

However, some limitations of this study should be addressed. First, the coded diagnosis of hypoglycemia and CKD may introduce misclassification bias in both the cohorts. Given the sample size is large, we believe that the misclassification bias would be nondifferential and biased the results toward the null hypothesis. Second, the administrative claims data allowed the identification of only clinically significant hypoglycemia; the effect of mild hypoglycemia without medical attention was not analyzed. Third, there were significant interactions between covariates (ie, women, CCI scores, hypertension, and using antidiabetic drugs) and CKD, implying that these covariates may affect the HR. Nevertheless, in separate analyses of the populations with and without these covariates, the effects of hypoglycemia for the HR were in the same direction. Fourth, although the diagnosis of hypoglycemia was based on the clinical assessments of physicians in charge and recorded using the ICD-9-CM code, actual glucose levels during hypoglycemia were not recorded in the NHIRD. Fifth, the database did not contain individual-level information such as body mass index, smoking and alcohol habits, family history of kidney disease, and indicators of glycemic control status, such as HbA1c level. A meta-analysis, however, failed to show the renoprotective effect of lower HbA1c level achieved by intensive glucose control.³⁹ In addition, we matched cohorts according to aDCSI scores and the use of glucose-lowering medication, including insulin and oral antidiabetic drugs, which may partly reflect glycemic control and lessen the impact of antidiabetic drugs on risk of CKD.^{40,41} Besides, as other registry-based databases, biochemistry data such as serum creatinine or urinalysis were unavailable in the present database, and therefore different CKD stages were not determined. However, the result of validated diagnosis of coded diagnosis of CKD was similar with that of clinical diagnosis based on estimated GFR.⁴² Finally, detection bias may be introduced in ascertainment of CKD outcomes, and consequently hypoglycemia may be simply a marker for preexisting or kidney disease. However, through implementation of nationwide Diabetes Share Care Network established by the government since 2003, annual serum creatinine measurement was included to early detect renal complications. Therefore, the bias derived from CKD surveillance was less likely to influence our results.

In conclusion, this nationwide cohort study indicated that hypoglycemia is associated with an increased risk of CKD in addition to all-cause mortality, which is strengthened by temporality and a dose-dependent relationship. As patients with

T2DM and CKD impose a devastating burden in terms of medical costs and reduced quality and length of life, clinicians must weigh the risks and benefits of T2DM treatment to reduce hypoglycemia for further prevention of kidney disease in patients with preserved kidney function.

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REFERENCES

- Hoffman RP. Sympathetic mechanisms of hypoglycemic counter-regulation. *Curr Diabetes Rev*. 2007;3:185–193.
- Nordin C. The proarrhythmic effect of hypoglycemia: evidence for increased risk from ischemia and bradycardia. *Acta Diabetol*. 2014;51:5–14.
- Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes*. 2014;63:1738–1747.
- Gerstein HC, Miller ME, Byington RP, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559.
- Svensson AM, McGuire DK, Abrahamsson P, et al. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J*. 2005;26:1255–1261.
- Hsu PF, Sung SH, Cheng HM, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. *Diabetes Care*. 2013;36:894–900.
- Goyal A, Mehta SR, Diaz R, et al. Differential clinical outcomes associated with hypoglycemia and hyperglycemia in acute myocardial infarction. *Circulation*. 2009;120:2429–2437.
- de Boer IH, Rue TC, Hall YN, et al. Temporal trends in the prevalence of diabetic kidney disease in the United States. *J Am Med Assoc*. 2011;305:2532–2539.
- Monnier L, Mas E, Ginnet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *J Am Med Assoc*. 2006;295:1681–1687.
- Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? *Diabetes Metab Res Rev*. 2008;24:353–363.
- Shih CJ, Chu H, Chao PW, et al. Long-term clinical outcome of major adverse cardiac events in survivors of infectious endocarditis: a nationwide population-based study. *Circulation*. 2014;130:1684–1691.
- Chao PW, Shih CJ, Lee YJ, et al. Association of post-discharge rehabilitation with mortality in intensive care unit survivors of sepsis. *Am J Respir Crit Care Med*. 2014;190:1003–1011.
- Lin CC, Lai MS, Syu CY, et al. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. *J Formos Med Assoc*. 2005;104:157–163.
- Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.

15. Chang HY, Weiner JP, Richards TM, et al. Validating the adapted Diabetes Complications Severity Index in claims data. *Am J Manag Care*. 2012;18:721–726.
16. Ou SY, Chu H, Chao PW, et al. Effect of the use of low and high potency statins and sepsis outcomes. *Intensive Care Med*. 2014;40:1509–1517.
17. Wu IW, Wang SY, Hsu KH, et al. Multidisciplinary predialysis education decreases the incidence of dialysis and reduces mortality: a controlled cohort study based on the NKF/DOQI guidelines. *Nephrol Dial Transplant*. 2009;24:3426–3433.
18. Chen YR, Yang Y, Wang SC, et al. Effectiveness of multidisciplinary care for chronic kidney disease in Taiwan: a 3-year prospective cohort study. *Nephrol Dial Transplant*. 2013;28:671–682.
19. Hwang SJ, Tsai JC, Chen HC. Epidemiology, impact and preventive care of chronic kidney disease in Taiwan. *Nephrology (Carlton)*. 2010;15 (suppl 2):3–9.
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Statist Assoc*. 1999;94:496–509.
21. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:1121–1127.
22. Yu TM, Lin CL, Chang SN, et al. Increased risk of stroke in patients with chronic kidney disease after recurrent hypoglycemia. *Neurology*. 2014;83:686–694.
23. Kong AP, Yang X, Luk A, et al. Severe hypoglycemia identifies vulnerable patients with type 2 diabetes at risk for premature death and all-site cancer: the Hong Kong diabetes registry. *Diabetes Care*. 2014;37:1024–1031.
24. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. *Diabetes Care*. 2013;36:3535–3542.
25. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med*. 2014;174:1116–1124.
26. Hilsted J, Bonde-Petersen F, Norgaard MB, et al. Haemodynamic changes in insulin-induced hypoglycaemia in normal man. *Diabetologia*. 1984;26:328–332.
27. Patrick AW, Hepburn DA, Swainson CP, et al. Changes in renal function during acute insulin-induced hypoglycaemia in patients with type 1 diabetes. *Diabet Med*. 1992;9:150–155.
28. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363:1410–1418.
29. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes*. 2005;54:3592–3601.
30. Molitch ME, Adler AI, Flyvbjerg A, et al. Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes. *Kidney Int*. 2015;87:20–30.
31. Group DER, de Boer IH, Sun W, et al. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med*. 2011;365:2366–2376.
32. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837–853.
33. Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–2572.
34. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129–139.
35. Enslin M, Steinmann W, Whaley-Connell A. Hypoglycemia: a possible link between insulin resistance, metabolic dyslipidemia, and heart and kidney disease (the cardiorenal syndrome). *Cardiorenal Med*. 2011;1:67–74.
36. Bruno G, Biggeri A, Merletti F, et al. Low incidence of end-stage renal disease and chronic renal failure in type 2 diabetes: a 10-year prospective study. *Diabetes Care*. 2003;26:2353–2358.
37. Yakubovich N, Gerstein HC. Serious cardiovascular outcomes in diabetes: the role of hypoglycemia. *Circulation*. 2011;123:342–348.
38. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b5444.
39. Coca SG, Ismail-Beigi F, Haq N, et al. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch Intern Med*. 2012;172:761–769.
40. Hung AM, Roumie CL, Greevy RA, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. *Kidney Int*. 2012;81:698–706.
41. Masica AL, Ewen E, Daoud YA, et al. Comparative effectiveness research using electronic health records: impacts of oral antidiabetic drugs on the development of chronic kidney disease. *Pharmacoeconomol Drug Saf*. 2013;22:413–422.
42. Kuo HW, Tsai SS, Tiao MM, et al. Epidemiological features of CKD in Taiwan. *Am J Kidney Dis*. 2007;49:46–55.