Association Between Stroke Risk and Metformin Use in Hemodialysis Patients With Diabetes Mellitus: A Nested Case–Control Study

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Background—Metformin use reduces the incidence and severity of stroke in patients with type 2 diabetes mellitus (DM). The benefits of metformin for stroke have not been examined in hemodialysis patients with DM.

Methods and Results—Using the National Health Insurance Research Database, we identified 17 760 patients with DM and new-onset hemodialysis between 2001 and 2013. Of these, 1898 patients hospitalized for either ischemic or hemorrhagic stroke were matched to 7592 control patients according to sex, age, and year of initial hemodialysis therapy by using incidence sampling. The association between metformin use and stroke risk was estimated using conditional logistic regression after adjustment for hemodialysis frequency, comorbidity, and prescribed medications. Metformin use was recorded before the date of stroke admission and the date of pseudostroke of the case and control patients, respectively. Results showed that hemodialysis patients with ischemic stroke were more likely to use metformin than the controls 1 year before the date of stroke admission (adjusted odds ratio: 1.64; 95% confidence interval, 1.32–2.04). The association was evident within 90 days before the index date (adjusted odds ratio: 1.81; 95% confidence interval, 1.27–2.60). The results were consistent with those of hemodialysis patients with hemorrhagic stroke. Metformin use remained a risk factor for stroke in patients treated with antihypertensive, sulfonylurea, and antiplatelet drugs.

Conclusions—This nested case–control study is the first to show that metformin use is associated with stroke risk in hemodialysis patients with DM. We suggest that metformin should not be used by hemodialysis patients with DM. (*J Am Heart Assoc.* 2017;6: e007611. DOI: 10.1161/JAHA.117.007611.)

Key Words: diabetes mellitus (kidney) • diabetes mellitus • diabetic therapy/glitazones • hemodialysis • metformin • stroke

Metformin is an oral glucose-lowering agent initially prescribed to patients with type 2 diabetes mellitus (DM). Metformin improves hyperglycemia by enhancing insulin sensitivity, reducing hepatic glucose release, and elevating muscle uptake of glucose. Many studies have reported that metformin administration to patients with DM before stroke onset may be associated with reduced neurological severity.[1–3] Moreover, metformin use in patients with DM has been shown to reduce the risk of coronary artery disease and mortality.[4,5] Consequently, because of its benefits, metformin is preferred as the initial drug for treatment of patients with DM and systemic vascular diseases.

Globally, drug regulatory agencies have issued specific cautions and restrictions related to the use of metformin in patients with DM and advanced chronic kidney disease (CKD). An increased risk of impaired lactate metabolism has been implicated in metformin-using patients with CKD; metformin use leads to severe metabolic acidosis, adverse outcomes, and mortality in such patients.[6,7] Impaired kidney function retards metformin elimination and may cause it to accumulate, raising concerns about lactic acidosis. In patients with DM and advanced CKD, metformin is cautiously prescribed because of the perceived risk of lactic acidosis or adverse effects.

Some studies, however, have shown the possible safety of metformin use in dialysis patients with type 2 DM.[8–10] Two

Clinical Perspective

What Is New?

- In the general population, metformin use in patients with type 2 diabetes mellitus (DM) and without chronic kidney disease improves neurological severity and reduces the risk of stroke.
- Although clinical recommendations have been in place in Taiwan since 2009 suggesting that metformin not be prescribed for DM patients with late-stage chronic kidney disease, several studies observed that a portion of hemodialysis patients with type 2 DM still received metformin because its use might be safe in dialysis patients with type 2 DM.
- Until now, no studies had examined the association between metformin use and stroke events in hemodialysis patients. Using the National Health Insurance Research Database, we investigated the effects of metformin use on stroke events (ischemic or hemorrhagic stroke) in hemodialysis patients with type 2 DM.

What Are the Clinical Implications?

- Our findings indicate that in hemodialysis patients with type 2 DM, metformin users had a significantly higher risk of stroke (ischemic and hemorrhagic stroke) than nonusers, regardless of antihypertensive, sulfonylurea, or antiplatelet drug use.
- Our study supports the clinical recommendations that metformin should not be prescribed to hemodialysis patients with type 2 DM, although several studies showed metformin associated with lactic acidosis could be removable and might be safe in dialysis patients with type 2 DM.

hemodialysis patients with DM were enrolled in an open-label study conducted to observe the association between lactic acidosis and metformin therapy in patients with CKD; the results showed no correlation between metformin use and lactate concentrations, and ≈14% of the daily dose of metformin was extracted during a single dialysis session (5 hours).[10] Al-Hwiesh et al reported a pilot study on metformin therapy in peritoneal dialysis; they enrolled 35 patients with type 2 DM (median age: 54 years; interquartile range: 47–59 years) who received automated peritoneal dialysis and metformin treatment. The results revealed that no patients recorded a plasma lactate level >5 mmol/L; furthermore, no correlation was observed between the plasma metformin and lactate levels ($r=0.27$).[8] Moreover, a systematic review reported that metformin is moderately dialyzable and that metformin poisoning with lactic acidosis appears to be amenable to extracorporeal treatments in hemodialysis patients.[9] Taken together, these studies have shown that metformin might be safe in dialysis patients with type 2 DM.[8–10]

The Taiwan National Health Insurance program has provided compulsory universal health insurance since 1995, and it covers >99% of the population of Taiwan. Consequently, claims data obtained from the National Health Insurance Research Database (NHIRD) are ideal for longitudinal cohort studies.[11–18] Because many studies have shown that metformin reduces mortality and the risk of cardiovascular outcomes, metformin has been used to treat patients with CKD without exercising necessary caution. Until 2009, CKD was not considered a contraindication for metformin prescription in Taiwan. In 2009, the Taiwan Food and Drug Administration announced that metformin use was contraindicated in men and women with serum creatinine concentrations of >133 and >124 μmol/L, respectively. This change in the guidelines of the Taiwan Food and Drug Administration provides a basis to examine the safety of metformin in hemodialysis patients with DM in a national population-based cohort. Moreover, recent studies have shown that metformin use might be safe in dialysis patients with type 2 DM.[8–10] According to our review of the literature, no studies have examined the association between metformin use and stroke events in hemodialysis patients. Using the NHIRD, we investigated the effects of metformin use on stroke events (ischemic or hemorrhagic stroke) in hemodialysis patients with type 2 DM.

Methods

Data Sources

This study used the data from the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW). Researchers can access the data only in an independent operation zone in the HWDC, MOHW. Only statistical results can be brought out; therefore, the data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The Joint Institutional Review Board of Taipei Medical University approved this study (TMU-JIRB no. N201605039) and granted a waiver of informed consent. This nested case–control study was conducted using data from the NHIRD collected between 2000 and 2014. The NHIRD is a population-based claims database provided by the National Health Insurance Administration and is managed by the National Health Research Institutes; the data cover >99% of all residents of Taiwan. All dialysis patients with catastrophic illness registration certificates are enrolled in the National Health Insurance program because such patients are not required to pay deductibles for the treatment of a catastrophic illness or its related conditions during the valid period of the certificate. The NHIRD is one of the highest quality databases of its type in the world and has been widely used for longitudinal cohort studies,[11–13,15,17–22] including our previous reports.[15,17–21]

The NHIRD files contain data on all reimbursement claims of beneficiaries for most medical services in Taiwan, including inpatient and outpatient care and prescription drugs. The information on diseases is coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. In addition, encrypted patient identifiers are linked to the death records of the National Death Registry under the regulation of the HWDC, MOHW.

Study Cohort

The study cohort included new-onset hemodialysis patients with DM between 2001 and 2013. New-onset hemodialysis patients were defined as patients who received hemodialysis continuously for at least 3 months and had no dialysis record before the initial date of hemodialysis therapy. Of the patients, those who had diagnostic claims of DM and received antidiabetic medications were included. We then excluded patients whose age and sex were not recorded; who were aged <40 years; and who had a history of cancer, kidney transplant, or renal replacement therapy in addition to hemodialysis and stroke. The last exclusion criterion was used to ensure that stroke occurred only after the initial hemodialysis.

Case and Control Patient Selection

The case patients were those who were admitted to the hospital because of ischemic stroke (*ICD-9-CM* codes 433, 434, and 436) or hemorrhagic stroke (*ICD-9-CM* codes 430–432), and the date of stroke admission was defined as the index date of stroke. To reduce the overdiagnosis of stroke,[23] we further limited the cases to patients who received computed tomography or magnetic resonance imaging at same stroke admission to ensure that the diagnosis was active. Each case patient was matched to 4 control patients by sex, age ($\pm$1 year), and year of initial hemodialysis therapy by using an incidence density sampling approach, which involves matching each case to a sample of those who are at risk at the time of case occurrence.[24] Because the control patients did not experience a stroke event, they were assigned a date for a pseudostroke event, which corresponded to the index date of their matched case patients (referred to as the index date hereafter). This approach allowed us to observe both patient groups for similar periods, eliminating the bias caused by differences in time frame.

Metformin Use

Metformin use was determined using prescription claims. We examined metformin use 1 year before the index dates of the case and control patients. The patients were classified as *users* if they had metformin claims and as *nonusers* if they did not have metformin claims within the 1-year observational period before the index date. To determine the effect of time, the users were further categorized according to the time interval between the last prescription and the index date, and the intervals were coded as ≤90 and 91 to 365 days.

Covariates

Hemodialysis itself was a risk factor for stroke[25–27]; therefore, we considered the frequency of hemodialysis in terms of sessions per week. Cardiovascular diseases have been reported to be risk factors for stroke; therefore, hypertension, dyslipidemia, and heart failure were considered in this study if they were diagnosed before the index date. Inflammation-related diseases such as osteoarthritis or rheumatism were also considered in this study. In addition, previous or coexisting medical conditions were recorded if the patients were diagnosed with chronic obstructive pulmonary disease, pneumonia, asthma, chronic liver disease, and dementia. To quantify the severity of comorbidity, we used the Charlson comorbidity index as a proxy measure after adjustment for prescribed medications, including metformin, thiazolidinedione, sulfonylureas, α-glucosidase inhibitors, insulin, dipeptidyl peptidase 4, angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, β-selective blockers, diuretics, calcium channel blockers, antiplatelet drugs, statins, nonsteroidal anti-inflammatory drugs, and steroids. Furthermore, the Charlson comorbidity index was used to measure the severity of comorbidity after adjustment for the risk of stroke in the patients who had received medications within 6 months before the index dates.

Statistical Analyses

We used standardized difference to evaluate the balance of baseline characteristics between the case and control patients' difference, which was assessed in some studies[28,29] and in our study.[19] The threshold of standardized difference can indicate an important imbalance such that a value >10% is interpreted as significant difference in the mean of a covariate between treatment groups.[30,31] Conditional logistic regression was used to estimate the crude odds ratios (ORs), adjusted ORs, and 95% confidence intervals (CIs) for the association between metformin use and the risk of stroke. We also performed a subgroup analysis to identify the association between metformin use and stroke in the patients who received medications including antihypertensive drugs, sulfonylureas, insulin, antiplatelet drugs, statins, nonsteroidal anti-inflammatory drugs, and steroids. The statistical analyses were performed using SAS/STAT version 9.3, (SAS Institute) and STATA 12 (StataCorp). A *P* value of <0.05 was set as the level of statistical significance.

Results

Baseline Characteristics

Of the 17 760 hemodialysis patients with DM, we identified 1353 patients with ischemic stroke and used an incidence sampling approach to match them with 5412 control patients who did not undergo stroke hospitalization (Figure 1). This approach was also used to identify 545 case patients with hemorrhagic stroke and 2180 matched controls. Of the case patients with ischemic stroke, the mean age was 63.4 years (SD: 9.5), and ≈50% were male. The 3 most common comorbidities were hypertension (89.9%), dyslipidemia (34.8%), and heart failure (24.6%), and 65.1% had a Charlson comorbidity index ≥5. In terms of medication use 6 months before hemodialysis initiation, the most common antidiabetic drugs used were insulin (57.4%) and sulfonylureas (53.1%); the most common antihypertension drugs used were calcium channel blockers (88.5%), diuretics (87.0%), angiotensin-

converting enzyme inhibitors and angiontensin receptor blockers (66.5%), and beta blockers (61.0%). In addition, 59.7% and 50.4% of patients used antiplatelet drugs and nonsteroidal anti-inflammtory drugs, respectively. Compared with ischemic stroke patients, the mean age of those with hemorrhagic stroke was lower, but a higher percentage was male (58.5%); the most common comorbidities and medication use were very similar between groups. After age and sex matching, most baseline characteristics did not differ significantly between the case and control patient groups except that the patients with hemorrhagic stroke had lower rates of heart failure and steroid medication use than did their matched control patients (Table 1).

Metformin Use and Stroke Risk

Table 2 presents the association between metformin use and the risk of stroke based on the timing of metformin use. The
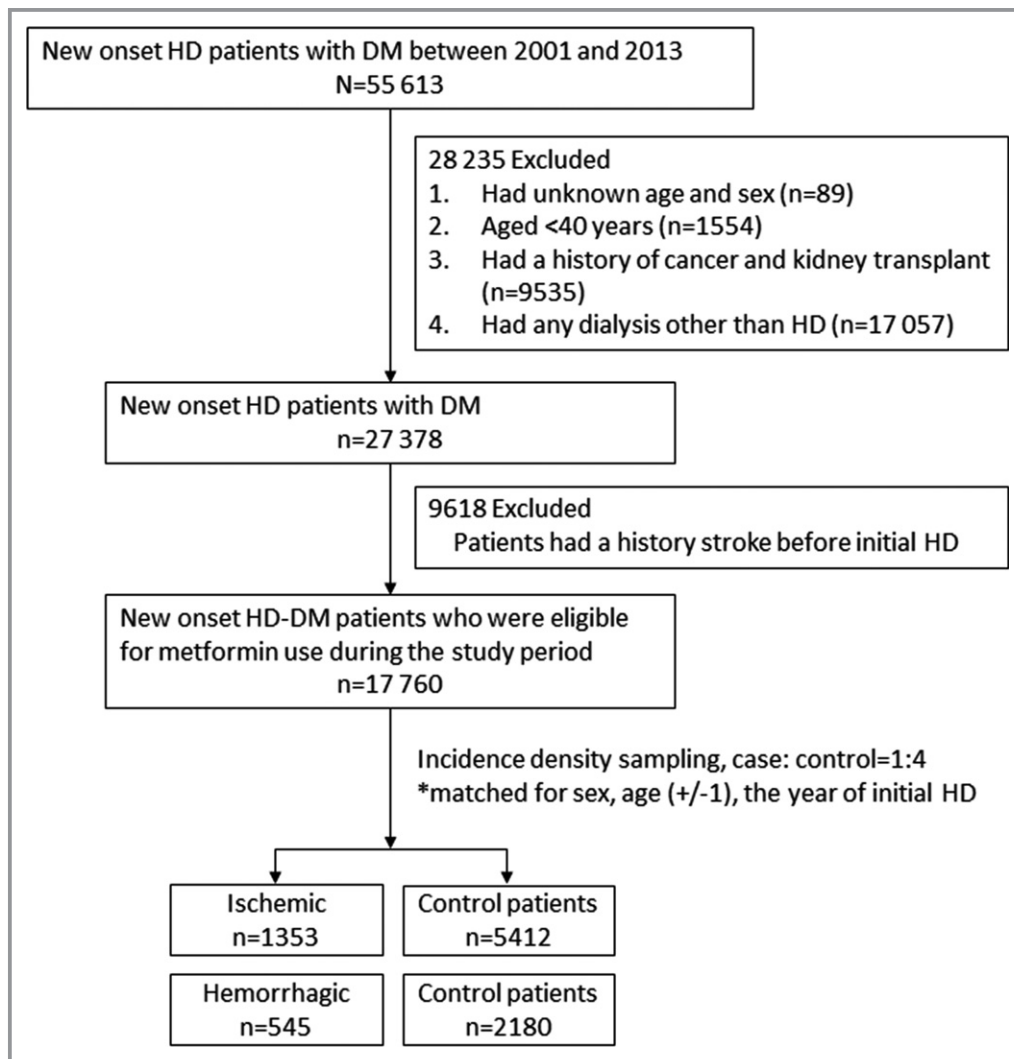

Figure 1. Cohort assembly of hemodialysis patients (metformin users and nonusers). DM indicates diabetes mellitus; HD, hemodialysis.

Table 1. Basic Characteristics of Case Patients With Ischemic or Hemorrhagic Stroke and Matched Control Patients Among New–Onset Hemodialysis Patients With Type 2 DM

	Ischemic Stroke			Hemorrhagic Stroke		
	Cases	Matched Controls	Stn Diff*	Cases	Matched Controls	Stn Diff*
Demographic characteristics						
Sample size, n	1353	5412		545	2180	
Age, y, mean (SD)	63.4 (9.5)	63.4 (9.5)	0.00	60.0 (9.1)	60.0 (9.1)	0.00
Male, n (%)	666 (49.2)	2664 (49.2)	0.00	319 (58.5)	1276 (58.5)	0.00
HD frequency per wk, n (%)						
≤1	129 (9.5)	610 (11.3)	0.06	46 (8.4)	230 (10.6)	0.07
2–3	1149 (84.9)	4498 (83.1)	0.05	471 (86.4)	1843 (84.5)	0.05
>3	75 (5.5)	304 (5.6)	0.00	28 (5.1)	107 (4.9)	0.01
Comorbidity, n (%)						
Hypertension	1216 (89.9)	4749 (87.7)	0.07	490 (89.9)	1905 (87.4)	0.08
Dyslipidemia	471 (34.8)	1702 (31.4)	0.07	174 (31.9)	679 (31.1)	0.02
Heart failure	337 (24.6)	1501 (27.7)	0.06	117 (21.5)	570 (26.1)	0.11
Osteoarthritis	93 (6.9)	383 (7.1)	0.01	32 (5.9)	127 (5.8)	0.00
Rheumatism	146 (10.8)	597 (11.0)	0.01	61 (11.2)	220 (10.1)	0.04
COPD	91 (6.7)	418 (7.7)	0.04	34 (6.2)	153 (7.0)	0.03
Pneumonia	100 (7.4)	400 (7.4)	0.00	24 (4.4)	178 (8.2)	0.16
Asthma	34 (2.5)	183 (3.4)	0.05	12 (2.2)	59 (2.7)	0.03
Chronic liver disease	76 (5.6)	405 (7.5)	0.08	57 (10.5)	200 (9.2)	0.04
Dementia	13 (1.0)	62 (1.1)	0.02	6 (1.1)	29 (1.3)	0.02
Charlson Comorbidity Index, n (%)						
1–2	124 (9.2)	489 (9.4)	0.00	46 (8.4)	202 (9.3)	0.03
3–4	348 (25.7)	1361 (25.1)	0.01	148 (27.2)	540 (24.8)	0.05
5	881 (65.1)	3562 (65.8)	0.02	351 (64.4)	1438 (66.0)	0.03
Medications 6 mo before hemodialysis initiation, n (%)						
Metformin	360 (26.6)	1379 (25.5)	0.08	113 (20.7)	544 (25.0)	0.10
TZD	159 (11.8)	603 (11.1)	0.00	57 (10.5)	255 (11.7)	0.04
Sulfonylureas	719 (53.1)	2829 (52.3)	0.03	275 (50.5)	1116 (51.2)	0.02
AGIs	159 (11.8)	603 (11.1)	0.00	57 (10.5)	255 (11.7)	0.04
Insulin	776 (57.4)	2976 (55.0)	0.04	308 (56.5)	1191 (54.6)	0.04
DPP4	18 (1.3)	88 (1.6)	0.00	10 (1.8)	45 (2.1)	0.02
ACEIs/ARBs	900 (66.5)	3555 (65.7)	0.02	378 (69.4)	1434 (65.8)	0.08
Beta blockers	825 (61.0)	3162 (58.4)	0.05	321 (58.9)	1302 (59.7)	0.02
Diuretics	1177 (87.0)	4759 (87.9)	0.00	473 (86.8)	1905 (87.4)	0.02
CCBs	1197 (88.5)	4714 (87.1)	0.05	491 (90.1)	1871 (85.8)	0.13
Antiplatelet drugs	808 (59.7)	3288 (60.8)	0.00	338 (62.0)	1303 (59.8)	0.05
Statins	446 (33.0)	1715 (31.7)	0.04	185 (33.9)	717 (32.9)	0.02
NSAIDs	682 (50.4)	2783 (51.4)	0.00	262 (48.1)	1083 (49.7)	0.03
Steroids	357 (26.4)	1449 (26.8)	0.03	129 (23.7)	620 (28.4)	0.11

ACEI indicates angiotensin-converting enzyme inhibitor; AGI, α-glucosidase inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DDP4, dipeptidyl peptidase 4; DM, diabetes mellitus; NSAID, nonsteroidal anti-inflammatory drug; Stn Diff, standard difference; TZD, thiazolidinediones.
*Difference in means or proportions divided by SE; an imbalance was defined as absolute value >0.1.

Table 2. Association Between Metformin Use and the Risk of Stroke (Ischemic and Hemorrhagic Stroke) Hospitalization

Outcome	Control n (%)	Case n (%)	Unadjusted OR	P Value	Adjusted* OR	P Value
Ischemic stroke						
Metformin nonusers	4913 (90.8)	1178 (87.1)	1.00 (Ref.)		1.00 (Ref.)	
Metformin users	499 (9.2)	175 (12.9)	1.59 (1.29–1.95)	<0.001	1.64 (1.32–2.04)	<0.001
By number of days						
≤90	123 (2.3)	48 (3.5)	1.74 (1.23–2.47)	0.002	1.81 (1.27–2.60)	0.001
91–365	376 (6.9)	127 (9.4)	1.53 (1.21–1.93)	<0.001	1.58 (1.23–2.02)	<0.001
Hemorrhagic stroke						
Metformin nonuser	1994 (91.5)	477 (87.5)	1.00 (Ref.)		1.00 (Ref.)	
Metformin users	186 (8.5)	68 (12.5)	1.65 (1.19–2.29)	0.003	2.15 (1.51–3.07)	<0.001
By number of days						
≤90	49 (2.2)	16 (2.9)	1.48 (0.83–2.64)	0.189	1.97 (1.08–3.61)	0.028
91–365	137 (6.3)	52 (9.5)	1.72 (1.20–2.46)	0.003	2.22 (1.50–3.29)	<0.001

User referred to any metformin use within in 1 year before the index date. OR indicates odds ratio; Ref., reference group.

*Adjustment for covariates including hemodialysis frequency, previous and existing medical conditions (including hypertension, dyslipidemia, heart failure, chronic obstructive pulmonary disease, pneumonia, asthma, chronic liver diseases, osteoarthritis, and rheumatism) and prescribed medications before hemodialysis including metformin, thiazolidinediones, sulfonylureas, α-glucosidase inhibitors, insulin, DPP4 (dipeptidyl peptidase 4), angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, beta blockers, diuretics, calcium channel blockers, antiplatelet drugs, statins, nonsteroidal anti-inflammatory drugs, and steroids.

patients with ischemic stroke were more likely to be exposed to metformin use 1 year before their index dates compared with their matched controls. The percentages of patients with ischemic stroke (case) and control patients using metformin 1 year before the index date were 12.9% and 9.2%, respectively (adjusted OR: 1.64; 95% CI, 1.32–2.04; $P<0.001$). The association was more evident when the duration of observation was limited to 90 days before the index date (adjusted OR: 1.81; 95% CI, 1.27–2.60; $P=0.001$). Similar results were observed in the patients with hemorrhagic stroke and their matched controls. Patients with hemorrhagic stroke had higher odds of exposure to metformin than their matched controls (adjusted OR: 2.15; 95% CI, 1.51–3.07; $P<0.001$).

Subgroup Analysis of the Association Between Metformin Use and Risk of Stroke in Hemodialysis Patients With Other Prescribed Medication

Of patients who used angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (Figure 2), patients with ischemic stroke were more likely to be exposed to metformin 1 year before the index date compared with their matched controls (adjusted OR: 1.59; 95% CI, 1.19–2.13). Similar results were obtained for patients who used β-selective blockers, calcium channel blockers, and diuretics. Because we focused on hemorrhagic stroke, the findings were consistent across the prescribed medications. The adjusted OR of cases to matched controls, for example, was

1.96 (95% CI, 1.23–3.13) among users of angiotensin-converting enzyme inhibitors and angiontensin receptor blockers.

As depicted in Figure 3, when we focused on patients who used sulfonylureas, the risk of stroke was associated with metformin use. Among insulin users, metformin use was not associated with the risk of both ischemic and hemorrhagic stroke. Regarding other medication users (Figure 4), metformin use was related to ischemic stroke in patients who used antiplatelet and nonsteroidal anti-inflammatory drug. Furthermore, a positive association was observed between metformin use and hemorrhagic stroke in patients who took antiplatelet drugs, statins, and steroids.

Discussion

This study is the first to examine the outcome of metformin use on stroke events in hemodialysis patients with DM. After multivariate adjustment and subgroup analysis, the major findings of our study are outlined as follows: (1) The risk of stroke (ischemic and hemorrhagic) was significantly higher in hemodialysis patients with type 2 DM who were metformin users than in those who were not metformin users; (2) the association between metformin use and stroke was significant when we limited the duration of observation to 90 days before the index date; and (3) subgroup analyses revealed a hazardous association between metformin use and stroke among patients who used antihypertensive drugs, sulfonylureas, and antiplatelet drugs.
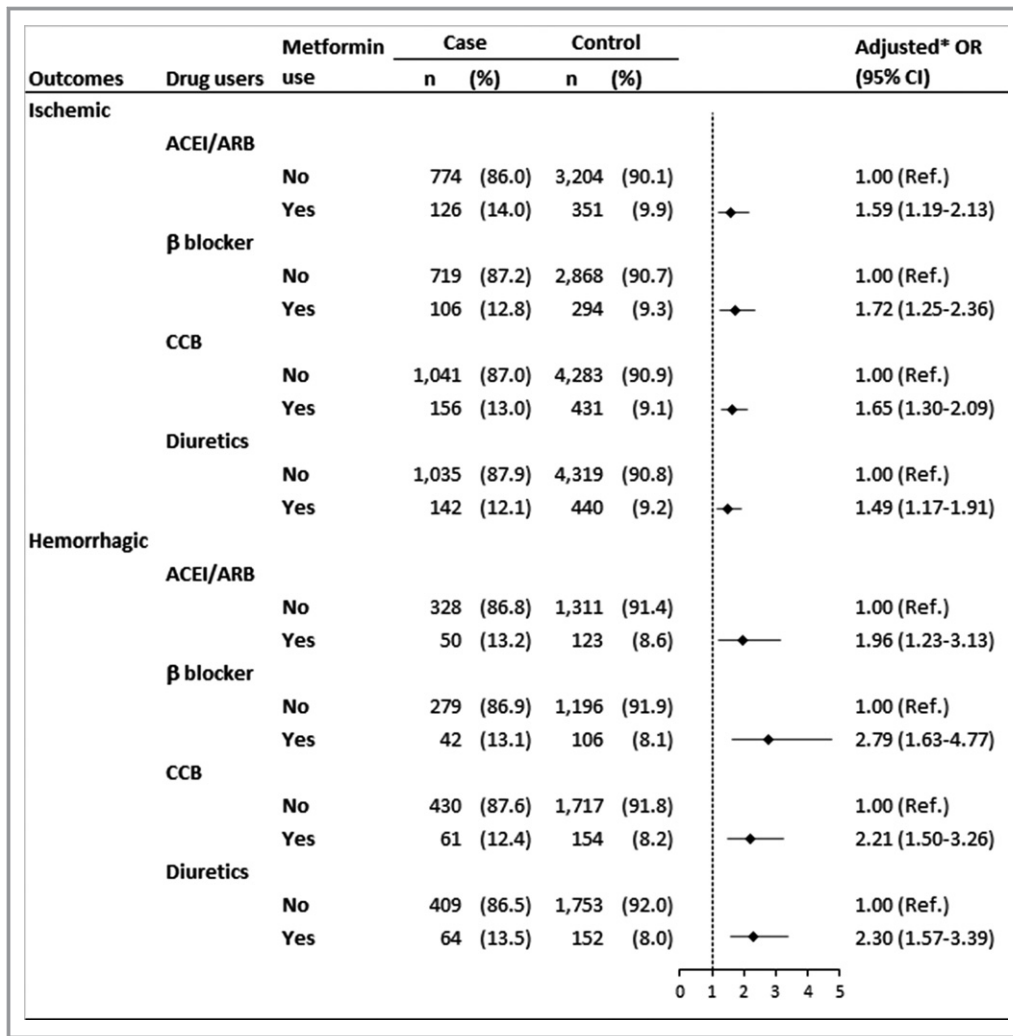
Outcomes	Drug users	Metformin use	Case n	Case (%)	Control n	Control (%)		Adjusted* OR (95% CI)
Ischemic								
	ACEI/ARB							
		No	774	(86.0)	3,204	(90.1)		1.00 (Ref.)
		Yes	126	(14.0)	351	(9.9)		1.59 (1.19-2.13)
	β blocker							
		No	719	(87.2)	2,868	(90.7)		1.00 (Ref.)
		Yes	106	(12.8)	294	(9.3)		1.72 (1.25-2.36)
	CCB							
		No	1,041	(87.0)	4,283	(90.9)		1.00 (Ref.)
		Yes	156	(13.0)	431	(9.1)		1.65 (1.30-2.09)
	Diuretics							
		No	1,035	(87.9)	4,319	(90.8)		1.00 (Ref.)
		Yes	142	(12.1)	440	(9.2)		1.49 (1.17-1.91)
Hemorrhagic								
	ACEI/ARB							
		No	328	(86.8)	1,311	(91.4)		1.00 (Ref.)
		Yes	50	(13.2)	123	(8.6)		1.96 (1.23-3.13)
	β blocker							
		No	279	(86.9)	1,196	(91.9)		1.00 (Ref.)
		Yes	42	(13.1)	106	(8.1)		2.79 (1.63-4.77)
	CCB							
		No	430	(87.6)	1,717	(91.8)		1.00 (Ref.)
		Yes	61	(12.4)	154	(8.2)		2.21 (1.50-3.26)
	Diuretics							
		No	409	(86.5)	1,753	(92.0)		1.00 (Ref.)
		Yes	64	(13.5)	152	(8.0)		2.30 (1.57-3.39)

Figure 2. Subgroup analysis of metformin use and the risk of stroke among hemodialysis patients with type 2 diabetes mellitus who received antihypertensive drugs. *Adjustment for covariates including hemodialysis frequency, previous and existing medical conditions (including hypertension, dyslipidemia, heart failure, chronic obstructive pulmonary disease, pneumonia, asthma, chronic liver diseases, osteoarthritis, and rheumatism), and prescribed medications before hemodialysis (including metformin, thiazolidinediones, sulfonylureas, α-glucosidase inhibitors, insulin, DPP4 [dipeptidyl peptidase 4], ACEIs/ARBs, beta-blockers, diuretics, CCBs, antiplatelet drugs, statins, nonsteroidal anti-inflammatory drugs, and steroids). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio; Ref., reference group.

DM is a risk factor for cerebrovascular disease. In the general population, studies have reported that metformin use in patients with DM and without CKD reduces neurological severity[1] and the risk of stroke.[2] In contrast, in our study, the patients with DM and CKD stage 5D (ie, hemodialysis patients with DM) who were metformin users had a significantly higher risk of stroke than did metformin nonusers. In addition, among patients who used antihypertensive drugs, sulfonylureas, and antiplatelet drugs, our results support a hazardous association between metformin use and stroke. Although the results of this observational study should be interpreted with caution, the nested case–control analysis of the time of drug use strongly suggested an association between metformin use and stroke in hemodialysis patients with type 2 DM because of the perceived risk of its adverse effects.

Metformin is generally recommended as the initial pharmacological treatment for patients with type 2 DM. Metformin is mostly excreted unchanged by the kidney; therefore, this drug can accumulate and cause adverse effects in patients with advanced CKD.[32] Evidence suggests the cautious use of metformin in patients with advanced CKD.[6] A recent population-based observational cohort study revealed that metformin use is associated with a 35% increase in the risk of all-cause mortality in patients with type 2 DM and advanced
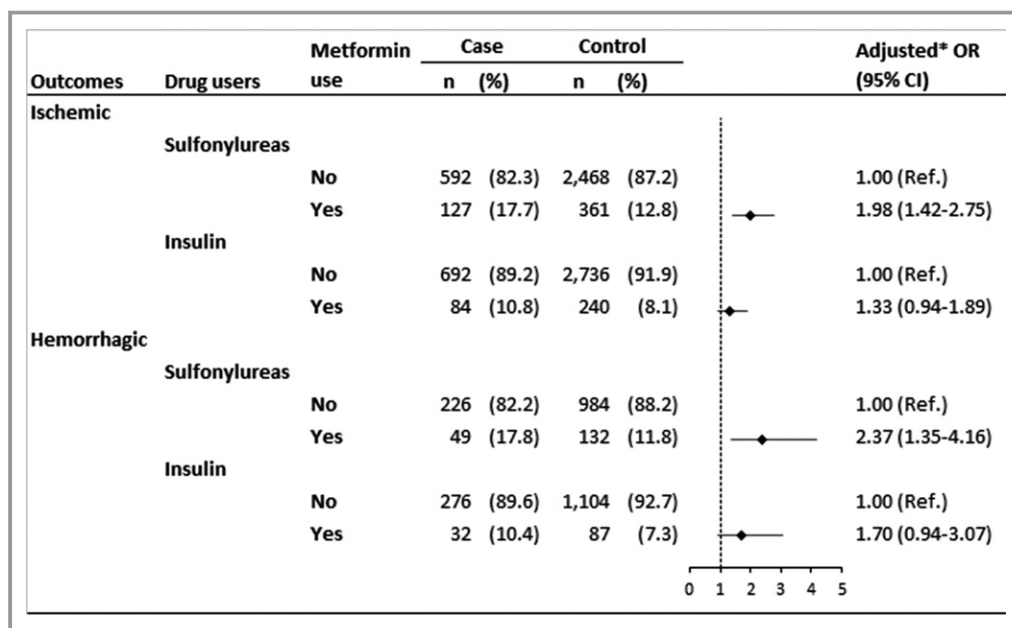
Figure 3. Subgroup analysis of metformin use and risk of stroke among hemodialysis patients with type 2 diabetes mellitus who received sulfonylureas and insulin. *Adjustment for covariates including hemodialysis frequency, previous and existing medical conditions (including hypertension, dyslipidemia, heart failure, chronic obstructive pulmonary disease, pneumonia, asthma, chronic liver diseases, osteoarthritis, and rheumatism), and prescribed medications before hemodialysis (including metformin, thiazolidinediones, sulfonylureas, α-glucosidase inhibitors, insulin, DPP4 [dipeptidyl peptidase 4], angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, beta blockers, diuretics, calcium channel blockers, antiplatelet drugs, statins, nonsteroidal anti-inflammatory drugs, and steroids). CI indicates confidence interval; OR, odds ratio; Ref., reference group.

CKD (approximately stage 5).[33] The molecular mechanism of adverse outcomes associated with the action of metformin is not completely understood. Some studies have suggested that accumulated concentrations of metformin act as an inhibitor of complex I, a component of the mitochondrial electron transport chain, further causing mitochondrial dysfunction.[34,35] The degree of mitochondrial dysfunction is associated with the severity of adverse outcomes.[36,37]

Although clinical recommendations have been in place in Taiwan since 2009 suggesting that metformin not be prescribed for DM patients with late stage of CKD, this current study observed that a portion of hemodialysis patients with DM had received metformin. A possible reason for this observation is that several studies have shown that metformin poisoning with lactic acidosis can be removed by extracorporeal dialysis treatment and might be safe in dialysis patients with type 2 DM.[8–10] Nevertheless, the trend of hemodialysis patients with DM receiving metformin decreased in Taiwan after 2009 (Table S1).

Because this study found that metformin use was associated with an increased risk of both ischemic and hemorrhagic stroke, a disease-management team with care managers, physicians, and specialists is needed for hemodialysis

patients with DM to improve overall health. This approach has been applied successfully for patients with heart failure and DM.[38]

Two systematic reviews and meta-analyses have shown that different classes of antihypertensive drugs (angiotensin-converting enzyme inhibitors and angiontensin receptor blockers, beta blockers, calcium channel blockers, and diuretics) did not significantly affect the risk of stroke in patients with hypertension and DM.[39,40] The subgroup analysis of antihypertensive drugs in our study revealed a hazardous association between metformin use and the risk of stroke in hemodialysis patients with DM, regardless of the class of antihypertensive drugs used.

A meta-analysis of randomized controlled trials comparing insulin with oral hypoglycemic agents revealed that insulin did not reduce the risk of stroke events in patients with DM.[41] However, a systematic review and meta-analysis revealed that sulfonylurea use was associated with a significantly higher risk of cardiovascular events (including stroke, myocardial infarction, cardiovascular-related hospitalizations, or cardiovascular death), compared with oral hypoglycemic agents.[42] Our subgroup analysis also indicated a similar result, showing that metformin use was associated with the risk of stroke in

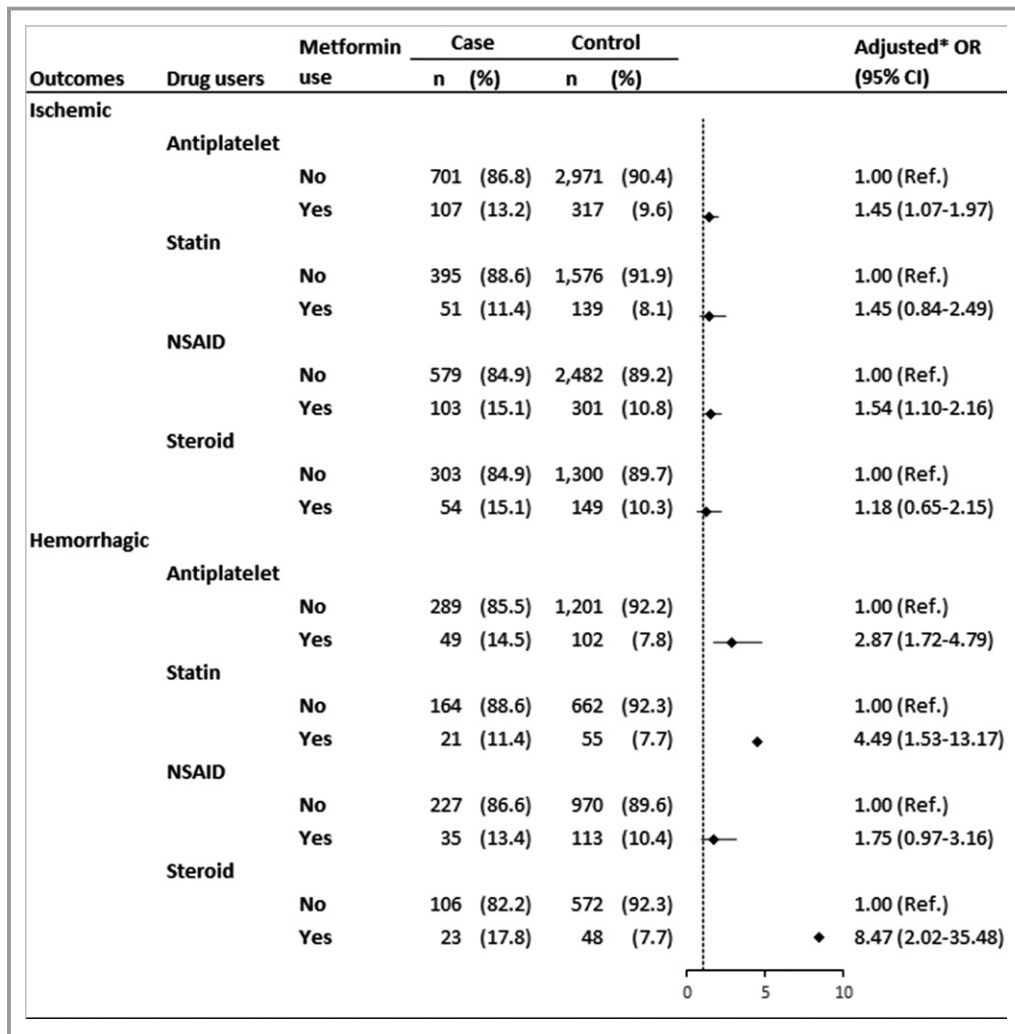| Outcomes	Drug users	Metformin use	Case n	(%)	Control n	(%)		Adjusted* OR (95% CI)
Ischemic								
	Antiplatelet							
		No	701	(86.8)	2,971	(90.4)		1.00 (Ref.)
		Yes	107	(13.2)	317	(9.6)		1.45 (1.07–1.97)
	Statin							
		No	395	(88.6)	1,576	(91.9)		1.00 (Ref.)
		Yes	51	(11.4)	139	(8.1)		1.45 (0.84–2.49)
	NSAID							
		No	579	(84.9)	2,482	(89.2)		1.00 (Ref.)
		Yes	103	(15.1)	301	(10.8)		1.54 (1.10–2.16)
	Steroid							
		No	303	(84.9)	1,300	(89.7)		1.00 (Ref.)
		Yes	54	(15.1)	149	(10.3)		1.18 (0.65–2.15)
Hemorrhagic								
	Antiplatelet							
		No	289	(85.5)	1,201	(92.2)		1.00 (Ref.)
		Yes	49	(14.5)	102	(7.8)		2.87 (1.72–4.79)
	Statin							
		No	164	(88.6)	662	(92.3)		1.00 (Ref.)
		Yes	21	(11.4)	55	(7.7)		4.49 (1.53–13.17)
	NSAID							
		No	227	(86.6)	970	(89.6)		1.00 (Ref.)
		Yes	35	(13.4)	113	(10.4)		1.75 (0.97–3.16)
	Steroid							
		No	106	(82.2)	572	(92.3)		1.00 (Ref.)
		Yes	23	(17.8)	48	(7.7)		8.47 (2.02–35.48)

Figure 4. Subgroup analysis of the risk of metformin use and stroke among hemodialysis patients with type 2 DM who received antiplatelet drugs, statins, NSAIDs, and steroids. *Adjustment for covariates including hemodialysis frequency, previous and existing medical conditions (including hypertension, dyslipidemia, heart failure, COPD, pneumonia, asthma, chronic liver diseases, osteoarthritis, and rheumatism), and prescribed medications before hemodialysis (including metformin, thiazolidinediones, sulfonylureas, α-glucosidase inhibitors, insulin, DPP4 [dipeptidyl peptidase 4], angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, beta blockers, diuretics, calcium channel blockers, antiplatelet drugs, statins, NSAIDs, and steroids). CI indicates confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; Ref., reference group.

hemodialysis patients with DM who received sulfonylureas but not insulin.

In this study, we discussed the association between metformin use and the risk of stroke in hemodialysis patients. The type of stroke was broadly classified into ischemic and hemorrhagic. Cerebral infraction can be cardiogenic or noncardiogenic, and noncardiogenic can be further categorized into atherosclerotic, lacuna, or unknown. The risk factors for those stroke types are different and might have affected the results of this study. Unfortunately, the data we used were unable to investigate the risk factors for different stroke subtypes. Further study is encouraged to clarify the association.

The strengths of our study include the large sample size, the use of a national database, the consideration of time-dependent drug use, and the execution of subgroup analyses. Moreover, this population-based observational study included adjustments for all potential risk factors. The major limitation of this study was a retrospective claim-based study design in which the data on the relevant events for each individual were collected from existing records; therefore, the potential bias could have affected the results of the study. First, the data on drug exposure were based on prescription records, which might not reflect actual drug use. Second, the NHIRD lacks information on patients' risk behavior and clinical

characteristics, which might affect the findings. Third, although this population-based observational study included adjustments for all potential risk factors, unmeasured factors might have biased our observations; therefore, the results should be interpreted cautiously. Finally, this study included a cohort of Taiwanese patients; therefore, our results might not be applicable to other populations.

In conclusion, this study is the first to examine the outcome of metformin use and stroke events in hemodialysis patients with DM. It revealed that of hemodialysis patients with DM, metformin users had a significantly higher risk of stroke (ischemic and hemorrhagic) than did nonusers. Our findings support the clinical recommendations that metformin should not be prescribed to hemodialysis patients with type 2 DM.

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Disclosures

None.

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Supplemental Material

Table S1. The Rate of Metformin Users of Patients with Ischemic or Hemorrhagic Stroke

Year of stroke diagnosis	Metformin users (%)	
	Ischemic	hemorrhagic
2001	43.2%	38.5%
2002	22.1%	25.7%
2003	15.6%	16.4%
2004	15.2%	18.0%
2005	15.6%	13.1%
2006	9.0%	8.7%
2007	9.6%	7.3%
2008	8.3%	4.6%
2009	4.4%	7.4%
2010	4.0%	4.9%
2011	3.3%	0.5%
2012	3.1%	1.9%
2013	1.4%	6.0%