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Impact of Diabetes on Stroke Risk and Outcomes

Two Nationwide Retrospective Cohort Studies

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Abstract: Several limitations existed in previous studies which suggested that diabetic patients have increased risk of stroke. We conducted this study to better understand the stroke risk and poststroke outcomes in patients with diabetes.

From the claims data of Taiwan's National Health Insurance, we identified 24,027 adults with new-diagnosed diabetes and 96,108 adults without diabetes between 2000 and 2003 in a retrospective cohort study. Stroke events (included hemorrhage, ischemia, and other type of stroke) during the follow-up period of 2000 to 2008 were ascertained and adjusted risk of stroke associated with diabetes was calculated. A nested cohort study of 221,254 hospitalized stroke patients (included hemorrhage, ischemia, and other type of stroke) between 2000 and 2009 was conducted. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for adverse events after stroke hospitalization in patients with and without diabetes.

The incidences of stroke in cohorts with and without diabetes were 10.1 and 4.5 per 1000 person-years, respectively. During the follow-up period, diabetic patients had an increased risk of stroke (adjusted hazard ratio: 1.75; 95% CI: 1.64–1.86) than those without diabetes. Associations between diabetes and stroke risk were significant in both sexes and all age groups. Previous diabetes was associated with poststroke mortality (OR: 1.33; 95% CI: 1.19–1.49), pneumonia (OR: 1.30; 95% CI: 1.20–1.42), and urinary tract infection (OR: 1.66; 95% CI: 1.55–1.77). The impact of diabetes on adverse events after stroke was investigated particularly in those with diabetes-related complications.

Diabetes was associated with stroke risk, and diabetic patients had more adverse events and subsequent mortality after stroke.

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Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, OR = odds ratio.

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INTRODUCTION

As the global prevalence of diabetes is predicted to reach 4.4% in all age groups by 2030, diabetes is clearly a pandemic chronic disease causing widespread disability and death worldwide.[1] Costs associated with diabetes in the United States were estimated to reach as high as $245 billion in 2012.[2] Although the epidemiology, pathogenesis, prevention, and treatment of diabetes have been well established over the past 2 centuries,[3] complications after diabetes require further study.

Stroke is one of the major causes of disability and mortality worldwide.[4,5] Although global mortality from stroke fell in the past 2 decades (1990–2010), an increased incidence of stroke in low-income and middle-income countries was investigated.[5] An international multicentre study identified stroke risk factors including cardiac disease, hypertension, diabetes, smoking, alcohol intake, unhealthy diet, abdominal obesity, lack of exercise, psychosocial stress and depression, and said these factors could explain 90% of stroke risk.[4]

A systematic review with meta-analysis and several previous epidemiological reports suggested that patients with diabetes had increased risk of stroke.[6–18] The impact of diabetes on outcomes after stroke was also investigated.[19–28] However, these previous studies may have bias because they were limited by several factors, including case-control study design,[9] reporting only a single type of stroke,[7,8,10,12,15,19,21,22,24,25,27,28] a small sample of diabetic patients,[8,11,12,24,26,27] a focus on a specific population,[9,14,17,23,25] not distinguishing separate subtypes of diabetes,[7–13,15–28] inadequate adjustment for potential confounders,[8,12,13,15,16,18,26,28] and lack of appropriate comparison groups.[11,13]

We used Taiwan's National Health Insurance reimbursement claims to investigate the incidence and risk of stroke after adjustment for potential confounding factors for adults with diabetes in a nationwide retrospective cohort study. More importantly, we conducted a nested cohort study to investigate the impact of diabetes on poststroke outcomes.

PARTICIPANTS AND METHODS

Data Collection

This study's data came from medical claims in the National Health Insurance Research Database established by the National Health Research Institutes in Taiwan. Taiwan implemented a universal-care National Health Insurance system (included inpatient and hospitalization medial cares) in March 1995 that covers >99% of the country's 23 million residents. The available information used in this study including diagnoses for admission and discharge, treatments, medications, characteristics of medical institutions where care was accessed, medical expenditures, and all the services physicians provided. For the purpose of data management, research, and administration, Taiwan's National Health Research Institutes released a random-selected database consisting 1 million medical beneficiaries (including all age groups) that represents ~4.3% of Taiwan's insurance enrollees.[29–31] In addition, the All Stroke Database used in this study was also extracted from Taiwan National Health Insurance Research Database obtained between 1996 and 2010.

Ethics Approval

To protect personal privacy, patient's identifications from National Health Insurance Research Database were decoded and scrambled for any potential research access. This study was approved both by the Taiwan's National Health Research Institutes (NHIRD-103-121) and Taipei Medical University's Institutional Review Board (TMU-JIRB 201505055; TMU-JIRB 201404070) and was exempted from the patient informed consent, which was not required because patients' identifications have been decoded and scrambled.[29-31]

Study Design

Excluding people with previous medical records of stroke and/or diabetes within 1996 to 1999 in the insurance data of the 1,000,000 persons, the incident diabetic cohort included 24,027 adults aged ≥20 years was identified in 2000 to 2003 under the definition of >3 visits of ambulatory care or hospitalization for diabetes was required. With the frequency-matching procedure by the age and the gender at the same study time interval, 96,108 adults were selected as nondiabetic cohort who had no medical records of diabetes previously. At the beginning of follow-up, diabetic and nondiabetic cohorts had no history of stroke. We started the follow-up from the beginning of 2000 and lasted until the end of 2008. Incident cases of stroke (included hemorrhage, ischemia, and other type of stroke) were identified during the follow-up period. The purpose of this retrospective cohort study is to report the risk of stroke in patients with diabetes.

Among 221,254 new-onset stroke patients (included hemorrhage, ischemia, and other type of stroke) who were admitted for inpatient care in 2000 to 2009, we identified 9998 stroke patients had history of diabetes. Using this All Stroke Database of Taiwan's National Health Insurance Research Database, complications, consumption of medical resources, and the case fatality within 30 days after stroke were analyzed for diabetic patients and nondiabetic people.

Definitions and Measurements

The low level of income was defined according to the standards income registered in database of Taiwan's Ministry of Health and Welfare. The urbanized definition and category of residential area were based on our previous investigations.[30,31] In this study, we considered the use of cardiovascular medications, such as aspirin, anticoagulant, statins, and antihypertension drugs.

Diagnostic codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) were used to define diseases and morbidities in this study, such as diabetes mellitus (250), cerebrovascular diseases (430–438), hypertensive diseases (401–405), mental diseases (290–319), ischemic heart disease (410–414), chronic obstructive pulmonary disease (490–496), hyperlipidemia (272.0, 272.1, and 272.2), liver cirrhosis (571), heart failure (428), atrial fibrillation (427.3), epilepsy (345), head injury (800–804, 850–854), pneumonia (480–486), and urinary tract infection (599.0). Hemodialysis and/or peritoneal dialysis were also recorded by the administrative code. Medications, such as recombinant tissue plasminogen activator, aspirin, anticoagulant, statin, and antihypertension drug, were considered in this study.

Statistical Analysis

We used chi-square tests to examine the distributions of categorical data included age, sex, low income, urbanization, history of diseases, and medications between diabetic and nondiabetic cohorts. Using the multiple Cox proportional hazards models, the hazard ratios (HRs) with 95% confidence intervals (CIs) for stroke risk in diabetic cohort were calculated with the adjustment of all covariates. The subgroup analysis was also performed for the association between diabetes and stroke risk.

In the All Stroke Database, the balances of age, sex, low income, urbanization, history of diseases, and medications between diabetic stroke patients and nondiabetic stroke patients were examined in the chi-square tests. We performed multiple logistic regressions to estimate odds ratios (ORs) and 95% CIs of complications and mortality after stroke in diabetic patients by adjusting sociodemographic factors, history of diseases, and medications. All significance tests were 2-sided using $P < 0.05$ as the level of significance. All data analyses were performed by the SAS, version 9.1 (SAS Institute Inc., Cary, NC) statistical software.

RESULTS

The distributions of age and sex were balanced between diabetic and nondiabetic cohorts because frequency matching was used in this study (Table 1). The prevalence of low urbanization, low-income, hypertension, mental disorders, ischemic heart disease, chronic obstructive pulmonary disease, hyperlipidemia, liver cirrhosis, congestive heart failure, atrial fibrillation, epilepsy, and renal dialysis were higher in diabetic cohort than in nondiabetic cohort, as well as the use of aspirin, anticoagulants, statins, and antihypertension drugs (all $P < 0.0001$).

Diabetic cohort had higher incidence of stroke than nondiabetic cohort (10.1 vs 4.5 per 1000 person-years, $P < 0.0001$) and the corresponding HR of stroke associated with diabetes was 1.75 (95% CI: 1.64–1.86) during the follow-up period (Table 2). Type 2 diabetes (HR: 1.76; 95% CI: 1.65–1.87) was more likely to be associated with stroke risk than type 1 diabetes (HR: 1.50; 95% CI: 1.23–1.83). Diabetes was more associated with stroke risk in women (HR: 1.93; 95% CI: 1.76–2.12) than in men (HR: 1.60; 95% CI: 1.47–1.75). In every age group, diabetes was associated with stroke risk. The adjusted HRs for stroke associated with diabetes in people with 0, 1, 2, and ≥3 medical conditions were 1.56 (95% CI: 1.33–1.84), 1.86 (95% CI: 1.65–2.09), 1.71 (95% CI: 1.51–1.94), and 1.44 (95% CI: 1.28–1.62), respectively.

Diabetes-related indicators, such as peripheral circulatory disorder (HR: 1.88; 95% CI: 1.60–2.21), coma (HR: 1.89; 95% CI: 1.43–2.50), and insulin injections (HR: 1.93; 95% CI: 1.75–2.13) were more significant associated with risk of stroke. HRs of hemorrhagic stroke, ischemic stroke, and other stroke for

TABLE 1. Sociodemographic Factors, Coexisting Medical Conditions, and Medication in People With and Without Diabetes

	No Diabetes (N = 96,108)		Diabetes (N = 24,027)		*P* Value
Age, years					1.0000
20–29	4884	(5.1)	1221	(5.1)	
30–39	11,240	(11.7)	2810	(11.7)	
40–49	23,264	(24.2)	5816	(24.2)	
50–59	24,712	(25.7)	6178	(25.7)	
60–69	19,888	(20.7)	4972	(20.7)	
≥70	12,120	(12.6)	3030	(12.6)	
Sex					1.0000
Female	49,364	(51.4)	12,341	(51.4)	
Male	46,744	(48.6)	11,686	(48.6)	
Low income	1996	(2.1)	728	(3.0)	<0.0001
Urbanization					<0.0001
Low	24,752	(25.8)	6494	(27.0)	
Moderate	22,979	(23.9)	5715	(23.8)	
High	22,164	(23.1)	5590	(23.3)	
Very high	26,213	(27.3)	6228	(25.9)	
Coexisting medical conditions					
Hypertension	25,520	(26.6)	10,545	(43.9)	<0.0001
Mental disorders	23,458	(24.4)	8030	(33.4)	<0.0001
Ischemic heart disease	12,642	(13.2)	5660	(23.6)	<0.0001
COPD	16,653	(17.3)	5452	(22.7)	<0.0001
Hyperlipidemia	6665	(6.9)	4250	(17.7)	<0.0001
Liver cirrhosis	2772	(2.9)	2081	(8.7)	<0.0001
Congestive heart failure	1928	(2.0)	941	(3.9)	<0.0001
Atrial fibrillation	1246	(1.3)	459	(1.9)	<0.0001
Renal dialysis	416	(0.4)	326	(1.4)	<0.0001
Epilepsy	530	(0.6)	191	(0.8)	<0.0001
Traumatic brain injury	8	(0.01)	3	(0.01)	0.5465
Medications					
Aspirin	22,163	(23.1)	10,678	(44.4)	<0.0001
Statin	9014	(9.4)	8617	(35.9)	<0.0001
Antihypertension drug	18,383	(19.1)	8064	(33.6)	<0.0001
Anticoagulant	3662	(3.8)	1805	(7.5)	<0.0001

COPD = chronic obstructive pulmonary disease.

diabetic patients were 1.31 (95% CI 1.11–1.54), 2.00 (95% CI 1.83–2.19), and 2.03 (95% CI 1.82–2.25), respectively.

Among 221,254 patients with stroke (Table 3), diabetic patients had higher proportions of women ($P < 0.0001$), older people ($P < 0.0001$), low income ($P < 0.0001$), hypertension ($P < 0.0001$), ischemic heart disease ($P < 0.0001$), mental disorders ($P < 0.0001$), chronic obstructive pulmonary disease ($P < 0.0001$), atherosclerosis ($P < 0.0001$), renal dialysis ($P < 0.0001$), hyperlipidemia ($P < 0.0001$), congestive heart failure ($P < 0.0001$), liver cirrhosis ($P < 0.0001$), epilepsy ($P < 0.0001$), and use of cardiovascular medication (anticoagulants, antiplatelet agents, or lipid-lowering agents) compared with nondiabetic patients.

In Table 4, diabetic patients had higher risk of mortality (OR: 1.33; 95% CI: 1.19–1.49), pneumonia (OR: 1.30; 95% CI: 1.20–1.42), and urinary tract infection (OR: 1.66; 95% CI: 1.55–1.77) after stroke compared with those without diabetes in the nested stroke cohort study. Previous diabetes was also associated with poststroke prolonged length of stay (OR: 1.52; 95% CI: 1.44–1.60). The mean of length of stay for stroke patients with and without diabetes were 9.59 ± 7.10 days and 8.61 ± 7.04 days, respectively ($P < 0.0001$). Poststroke pneumonia, urinary tract infection, adverse events, prolonged length of hospital stay, and mortality were associated with type 1 and type 2 diabetes.

In Table 5, diabetes-related clinical characteristics were associated with poststroke adverse events, such as ketoacidosis (OR: 2.14; 95% CI: 1.77–2.58), peripheral circulatory disorder (OR: 1.76; 95% CI: 1.57–1.98), inadequate control of diabetes (OR: 1.63; 95% CI: 1.50–1.78), coma (OR: 1.64; 95% CI: 1.44–1.86), type 1 diabetes (OR: 1.65; 95% CI: 1.40–1.94), insulin injections (OR: 1.59; 95% CI: 1.48–1.71), renal manifestations (OR: 1.58; 95% CI: 1.45–1.73), and eye involvement (OR: 1.49; 95% CI: 1.29–1.72).

DISCUSSION

Using the claims data of Taiwan's National Health Insurance, we validated the long-term increased risk for all types of stroke in type 1 or type 2 diabetes adult patients in this nationwide retrospective cohort study. Another nested cohort study showed that patients with diabetes had increased rates of pneumonia, urinary tract infection, and mortality during stroke hospitalization. The impact of diabetes on adverse events after

TABLE 2. Incidence and Risk of Stroke for Cohorts With and Without Diabetes[||]

		n	PY	Stroke	Incidence*	HR (95% CI)†
No diabetes		96,108	655,178	2945	4.50	1.00 (reference)
All diabetes		24,027	166,385	1684	10.1	1.75 (1.64–1.86)
Type 1 diabetes		1486	10,560	104	9.85	1.50 (1.23–1.83)
Type 2 diabetes		22,541	155,825	1580	10.1	1.76 (1.65–1.87)
Diabetes with						
Ketoacidosis		596	4232	47	11.1	1.70 (1.27–2.27)
Peripheral circulatory disorder		1620	11,567	159	13.7	1.88 (1.60–2.21)
Inadequate control of diabetes		2888	20,347	253	12.4	1.62 (1.42–1.85)
Coma		349	2403	51	21.2	1.89 (1.43–2.50)
Insulin injections		4063	27,932	496	17.8	1.93 (1.75–2.13)
Renal manifestations		3290	23,629	303	12.8	1.77 (1.56–2.00)
Eye involvement		3949	28,504	297	10.4	1.58 (1.39–1.79)
Sex‡						
Female	No diabetes	49,364	337,192	1265	3.75	1.00 (reference)
	Diabetes	12,341	86,249	812	9.41	1.93 (1.76–2.12)
Male	No diabetes	46,744	317,986	1680	5.28	1.00 (reference)
	Diabetes	11,686	80,136	872	10.9	1.60 (1.47–1.75)
Age§						
20–39 years	No diabetes	16,124	112,218	65	0.58	1.00 (reference)
	Diabetes	4031	28,651	45	1.57	1.49 (0.95–2.34)
40–49 years	No diabetes	23,264	160,793	254	1.58	1.00 (reference)
	Diabetes	5816	41,072	217	5.28	2.07 (1.69–2.54)
50–59 years	No diabetes	24,712	168,176	506	3.01	1.00 (reference)
	Diabetes	6178	42,812	392	9.16	2.00 (1.73–2.31)
60–69 years	No diabetes	19,888	135,033	956	7.08	1.00 (reference)
	Diabetes	4972	33,982	541	15.9	1.79 (1.60–2.01)
≥70 years	No diabetes	12,120	78,958	1164	14.7	1.00 (reference)
	Diabetes	3030	19,867	489	24.6	1.46 (1.31–1.63)
Medical conditions						
0 condition	No diabetes	40,270	275,282	664	2.41	1.00 (reference)
	Diabetes	5236	36,133	255	7.06	1.56 (1.33–1.84)
1 condition	No diabetes	28,749	195,588	925	4.73	1.00 (reference)
	Diabetes	7033	48,463	486	10.0	1.86 (1.65–2.09)
2 conditions	No diabetes	15,828	107,649	672	6.24	1.00 (reference)
	Diabetes	5709	39,615	440	11.1	1.71 (1.51–1.94)
≥3 conditions	No diabetes	11,261	76,307	673	8.82	1.00 (reference)
	Diabetes	6049	42,174	503	11.9	1.44 (1.28–1.62)

CI = confidence interval, HR = hazard ratio, PY = person-years.
* Per 1000 person-years.
† Adjusted for age, sex, urbanization, low income, coexisting medical conditions, and types of medication.
‡ Adjusted for all variables except sex.
§ Adjusted for all variables except age. Adjusted for all variables except medical conditions.
|| HRs of hemorrhagic stroke, ischemic stroke, and other stroke for diabetic patients were 1.31 (95% CI 1.11–1.54), 2.00 (95% CI 1.83–2.19), and 2.03 (95% CI 1.82–2.25), respectively.

stroke was investigated particularly in those with diabetes-related complications.

Although the association between diabetes and risk of stroke is not a novel finding, previous studies had many limitations that may lead to bias.[7–28] Large sample size (reduced selection bias), cohort study design (more evidence in causal inference), multivariate adjustment (reduced confounding bias), including all types of stroke and diabetes (providing more comprehensive information), and not being restricted by specific populations (reduced selection bias) are the strengths of this investigation.

Sex, age, low income, and urbanization were associated with stroke as well as with diabetes.[3,6,29–31] Therefore, these sociodemographics should be considered as potential confounding factors when investigating the association between diabetes and stroke. To investigate risk and outcomes of stroke in diabetic patients in this study, we adjusted these sociodemographic characteristics in the multivariate Cox proportional hazard regression models and logistic regression models.

Patients with diabetes mellitus were more likely to have stroke compared with those without diabetes.[6–18] Hypertension, mental disorders, ischemic heart disease, chronic obstructive pulmonary disease, hyperlipidemia, liver cirrhosis, congestive heart failure, atrial fibrillation, epilepsy, traumatic brain injury, and renal dialysis have been shown to be independently associated with higher risk of stroke.[4,29–31] These medical conditions

TABLE 3. Sociodemographic Factors, Coexisting Medical Conditions, and Medication in Hospitalized Stroke Patients With and Without Diabetes

	No Diabetes (N = 211,256)		Diabetes (N = 9998)		
	n	(%)	n	(%)	*P* Value
Gender					<0.0001
Female	82,448	(39.0)	5040	(50.4)	
Male	128,808	(61.0)	4958	(49.6)	
Age, years					<0.0001
20–34	5087	(2.4)	45	(0.5)	
35–44	14,162	(6.7)	244	(2.4)	
45–54	33,859	(16.0)	1178	(11.8)	
55–64	39,326	(18.6)	2249	(22.5)	
65–74	52,651	(24.9)	3321	(33.2)	
≥75	66,171	(31.3)	2961	(29.6)	
Low income	10,145	(4.8)	710	(7.1)	<0.0001
Type of stroke					<0.0001
Hemorrhagic	51,187	(24.2)	1238	(12.4)	
Ischemic	121,176	(57.4)	6761	(67.6)	
Others	38,893	(18.4)	1999	(20.0)	
Medical conditions					
Hypertension	95,662	(45.3)	5250	(52.5)	<0.0001
Ischemic heart disease	25,169	(11.9)	2359	(23.6)	<0.0001
Mental disorder	33,270	(15.8)	2295	(23.0)	<0.0001
COPD	33,639	(15.9)	1996	(20.0)	<0.0001
Renal dialysis	2114	(1.0)	1050	(10.5)	<0.0001
Traumatic brain injury	12,150	(5.8)	975	(9.8)	<0.0001
Hyperlipidemia	10,521	(5.0)	928	(9.3)	<0.0001
Congestive heart failure	6643	(3.1)	886	(8.9)	<0.0001
Liver cirrhosis	2279	(1.1)	251	(2.5)	<0.0001
Atrial fibrillation	3595	(1.7)	164	(1.6)	0.6425
Epilepsy	2958	(1.4)	278	(2.8)	<0.0001
Use of rt-PA	726	(0.3)	11	(0.1)	<0.0001
Medications					
Aspirin	68,876	(32.6)	6355	(63.6)	<0.0001
Anticoagulant	5043	(2.4)	417	(4.2)	<0.0001
Statin	14,478	(7.0)	3733	(37.4)	<0.0001
Antihypertension drug	41,268	(19.5)	3828	(38.3)	<0.0001

COPD = chronic obstructive pulmonary disease, rt-PA = recombinant tissue plasminogen activator.

also commonly coexist with diabetes.[3,6–18,19–28] However, previous studies were limited by inadequate control of coexisting medical conditions when investigating the association between diabetes and stroke.[8,12,13,15,16,18,26,28] To avoid the confounding bias from these coexisting medical conditions, the present study used a multivariate regression model to adjust for these medical confounders.

The burden of infections among people with diabetes remains an important issue.[32] Previous studies also demonstrated diabetic patients' increased risk of infectious diseases after stroke.[26] Therefore, it is not surprising that we found diabetic patients had higher risks of pneumonia and urinary tract infections after suffering from stroke compared with controls in this study. These infections were also contributors for the poststroke mortality in diabetic patients.

Type 1 diabetes, inadequate control of glucose, ketoacidosis, coma, renal manifestations, eye involvement, and peripheral circulatory disorder were considered as severity-related indicators for diabetic patients.[3,19] Our nested cohort study shows these severity-related diabetes indicators caused significant poststroke mortality. This original finding provides useful information for clinical scenarios and was not reported previously.[19–28]

To clarify associations between diabetes and stroke risk, some possible reasons may be stated. First, damaged vascular function in diabetic patients (such as pulse wave velocity, plaque, and carotid intima-media thickness) causes atherosclerosis, a significant predictor for stroke.[33,34] A second possible explanation is diabetic patients' hypoglycemic coma (due to inadequate control for glucose), obesity, cataract, glaucoma, retinopathy, osteoporosis, cognitive dysfunction, and mental illness that were also found as risk factors for fracture and traumatic brain injury.[35] Strong evidence also suggests that patients with hip fracture or traumatic brain injury were more likely to have stroke.[31] Third, less physical activity, unhealthy lifestyle factors such as smoking and drinking alcohol to excess were also contributors for developing stroke in patients with diabetes.[36,37] Fourth, people with diabetes may have poor knowledge, attitudes, and practices regarding disease prevention,[38] which were considered factors associated with the

TABLE 4. Risks of Adverse Outcomes in Hospitalized Stroke Patients With and Without Previous Diabetes

	No Diabetes (N = 211,256)		Diabetes (N = 9998)				Type 1 Diabetes (N = 921)				Type 2 Diabetes (N = 9996)			
Post-Stroke Outcomes	**Events**	**(%)**	**Events**	**(%)**	**OR**	**(95% CI)***	**Events**	**(%)**	**OR**	**(95% CI)***	**Events**	**(%)**	**OR**	**(95% CI)***
Mortality	8075	(3.8)	419	(4.2)	1.33	(1.19–1.49)	47	(5.1)	1.63	(1.19–2.24)	419	(4.2)	1.33	(1.19–1.49)
Pneumonia	13462	(6.4)	723	(7.2)	1.30	(1.20–1.42)	68	(7.4)	1.48	(1.15–1.90)	723	(7.2)	1.31	(1.20–1.42)
Urinary tract infection	18155	(8.6)	1349	(13.5)	1.66	(1.55–1.77)	114	(12.4)	1.63	(1.33–2.00)	1349	(13.5)	1.66	(1.55–1.77)
Any adverse events	35019	(16.6)	2216	(22.2)	1.56	(1.47–1.64)	204	(22.2)	1.65	(1.40–1.94)	2216	(22.2)	1.56	(1.48–1.64)
Prolonged LOS	40642	(19.2)	2323	(23.2)	1.52	(1.44–1.60)	212	(23.0)	1.57	(1.34–1.85)	2323	(23.2)	1.52	(1.44–1.60)
Admission to ICU	56992	(27.0)	2100	(21.0)	1.05	(0.99–1.12)	204	(22.2)	1.16	(0.96–1.39)	2100	(21.0)	1.05	(0.99–1.12)
LOS, days	8.61 ± 7.04	9.59 ± 7.10	$P<0.0001$	9.52 ± 6.84	$P<0.0001$	9.59 ± 7.11	$P<0.0001$							

CI = confidence interval; ICU = intensive care unit; LOS = length of hospital stay; OR = odds ratio.

TABLE 5. Risks of In-hospital Complications and Mortality During Stroke Admission for Patients With Diabetes

	Adverse Event After Stroke*			Risk of Outcome
	n	**Events**	**Incidence (%)**	**OR (95% CI)†**
No diabetes	211,256	35,019	16.6	1.00 (Reference)
Diabetic patients with				
Ketoacidosis	615	161	26.2	2.14 (1.77–2.58)
Peripheral circulatory disorder	1719	411	23.9	1.76 (1.57–1.98)
Inadequate control of diabetes	3445	780	22.6	1.63 (1.50–1.78)
Coma	1390	348	25.0	1.64 (1.44–1.86)
Type 1 diabetes	921	204	22.2	1.65 (1.40–1.94)
Insulin injections	5219	1168	22.4	1.59 (1.48–1.71)
Renal manifestations	3400	754	22.2	1.58 (1.45–1.73)
Eye involvement	1336	248	18.6	1.49 (1.29–1.72)

CI = confidence interval; OR = odds ratio.
* Any adverse event includes pneumonia, urinary tract infection, and mortality.
† Adjusted for sex, age, low income, type of stroke, hypertension, ischemic heart disease, mental disorder, chronic obstructive pulmonary disease, renal dialysis, traumatic brain injury, hyperlipidemia, congestive heart failure, liver cirrhosis, atrial fibrillation, epilepsy, recombinant tissue plasminogen activator, anticoagulant, aspirin, statin, and antihypertension drugs.

development of stroke. In addition, diabetes was associated with increased levels of inflammation-sensitive plasma proteins identified as a contributor to risk of stroke and cardiovascular diseases.[39] Finally, we considered the side effect of medication in patients with type 2 diabetes also has partial contribution for risk of stroke, because a previous study suggested that thiazolidinedione treatment increased progression of subclinical atherosclerosis in patients with type 2 diabetes.[40] However, this point needs future further human or animal trials to provide biochemical mechanisms.

Readers should be cautioned against overinterpretation of our findings because of study limitations. First, there was no information on detailed sociodemographic factors, lifestyle, clinical risk scores of stroke, and the results of blood or urine tests in the National Health Insurance Research Database. Second, the histories of diseases for study subjects were identified by people who visited medical care services. We admitted that the misclassification may exist in this study because patients had impaired fasting glycemia or diabetes without symptoms might not visit medical care services. Therefore, the underestimated risk of stroke in diabetic cohort is possible. Third, the validation of codes of diseases may be one of limitations for this study even though many studies based on National Health Insurance were accepted by important journals.[29–31] Finally, the confounding effects remains a possible limitation of this study although several potential confounding factors were controlled by multiple regression models.

In conclusion, these 2 nationwide cohort studies showed the impact of diabetes on risk of stroke and poststroke adverse events such as pneumonia, urinary tract infection, and mortality. Poorly controlled diabetes and diabetes-related complications contributed to mortality after stroke. This analysis provides comprehensive assessment of stroke risk and poststroke outcomes in patients with diabetes. Further studies are needed to develop specific strategies to decrease stroke risks and poststroke adverse outcomes for this patient population.

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