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 10.44/1000 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.

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. Costs associated with diabetes in the United States were estimated to reach as high as $245 billion in 2012. Although the epidemiology, pathogenesis, prevention, and treatment of diabetes have been well established over the past 2 centuries, complications after diabetes require further study.

Stroke is one of the major causes of disability and mortality worldwide. 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. 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.

A systematic review with meta-analysis and several previous epidemiological reports suggested that patients with diabetes had increased risk of stroke. The impact of diabetes on outcomes after stroke was also investigated. However, these previous studies may have bias because they were limited by several factors, including case-control study design, reporting only a single type of stroke, and lack of appropriate comparison groups.

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 medical 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 (NIHRD-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 scrambled29,31

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 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
The risk of stroke among diabetic patients was assessed through various analyses. Table 1 shows the sociodemographic factors, coexisting medical conditions, and medication in people with and without diabetes. The table indicates that diabetic patients were more likely to be older, female, have low income, hypertension, ischemic heart disease, COPD, hyperlipidemia, liver cirrhosis, congestive heart failure, atrial fibrillation, renal dialysis, epilepsy, aspirin use, statin use, antihypertension drug use, and anticoagulant use compared to nondiabetic patients.

Disproportionate risks were also observed for specific complications after stroke, as detailed in Table 2. Diabetic patients had higher risks of mortality (OR: 1.33; 95% CI: 1.19–1.49), pneumonia (OR: 2.00; 95% CI: 1.83–2.19), urinary tract infection (OR: 1.66; 95% CI: 1.55–1.77), and prolonged hospital stay (OR: 1.52; 95% CI: 1.44–1.60) compared to nondiabetic patients.

The DISCUSSION section emphasizes the importance of diabetes in increasing the risk of adverse events and mortality after stroke. The findings highlight the need for targeted interventions to mitigate these risks, particularly among diabetic patients. The implications of these findings extend to public health strategies aimed at reducing the burden of diabetes and stroke.
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 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) |
| 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.

jj 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.
also commonly coexist with diabetes. However, previous studies were limited by inadequate control of coexisting medical conditions when investigating the association between diabetes and stroke. 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. Previous studies also demonstrated diabetic patients’ increased risk of infectious diseases after stroke. 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.
### TABLE 4. Risks of Adverse Outcomes in Hospitalized Stroke Patients With and Without Previous Diabetes

| Post-Stroke Outcomes | No Diabetes (N = 211,256) | Diabetes (N = 9998) | Type 1 Diabetes (N = 921) | Type 2 Diabetes (N = 9996) |
|----------------------|-----------------------------|---------------------|---------------------------|-----------------------------|
|                      | Events (%)                  | OR (95% CI)         | Events (%)                | OR (95% CI)                |
| Mortality            | 8075 (3.8)                  | 1.33 (1.19–1.49)    | 47 (5.1)                  | 1.63 (1.19–2.24)           |
| Pneumonia            | 13462 (6.4)                 | 1.30 (1.20–1.42)    | 68 (7.4)                  | 1.48 (1.15–1.90)           |
| Urinary tract infection | 18155 (8.6)                | 1.66 (1.55–1.77)    | 114 (12.4)                | 1.63 (1.33–2.00)           |
| Any adverse events   | 35019 (16.6)                | 1.52 (1.44–1.60)    | 204 (22.2)                | 1.57 (1.34–1.85)           |
| Admission to ICU     | 56992 (27.0)                | 1.05 (0.99–1.12)    | 204 (22.2)                | 1.16 (0.96–1.39)           |
| LOS, days            | 8.61 ± 7.04                 | 9.59 ± 7.10         | 9.52 ± 6.84               | 9.59 ± 7.11                |

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 | n       | Events | Incidence (%) | Risk of Outcome |
|----------------------------|---------|--------|---------------|-----------------|
| 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. 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. However, this point needs future 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. 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 post-stroke adverse outcomes for this patient population.

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