Association of Paroxysmal Supraventricular Tachycardia with Ischemic Stroke: A National Case-Control Study

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Background and Purpose: Cardioembolic stroke accounts for approximately 15%-20% of all ischemic strokes. Atrial fibrillation constitutes one-half to two-thirds of all cardioembolic stroke events. The association of paroxysmal supraventricular tachycardia (PSVT) with ischemic stroke remains unclear. A national case–control study was conducted to identify the risk factors, including PSVT, for ischemic stroke in Taiwan. *Methods:* We designed a national case–control study comprising patients diagnosed with ischemic stroke (n = 5633) from 1997 to 2011; each patient from the case group was randomly matched with the control group (n = 30,895) in Taiwan. Data were retrospectively collected from Taiwan's National Health Insurance Research Database, which contains not only claims data on hospitalization, emergency room visits, and outpatient department visits, but also patient characteristics. *Results:* Logistic regression analysis was used to identify the risk factors for ischemic stroke. Independent risk factors for ischemic stroke included age (in 5-year intervals; odds ratio [OR], 1.76; 95% confidence interval [CI], 173–1.78), the male sex (versus the female sex; OR, 1.88; 95% CI, 1.74-2.01), chronic kidney disease (OR, 3.09; 95% CI, 2.67-3.57), PSVT (OR, 2.05; 95% CI, 1.30-3.19), and aspirin use (OR, .04; 95% CI, .03-0.05). *Conclusions:* Our study is the first in Taiwan to identify PSVT as a significant risk factor for ischemic stroke. New antithrombotic regimens, including aspirin, can be recommended for the primary prevention of stroke and for reducing the burden of stroke for patients with PSVT. **Key Words:** Paroxysmal supraventricular tachycardia—ischemic stroke—aspirin—Taiwan.

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Introduction

Stroke was the second leading cause of death and seventh leading cause of disability in the year 2000 worldwide,[1] and stroke prevalence increased from 16.4% in 1986 to 19.1% per 1000 persons in 2001 in Taiwan.[2] Approximately 11,736 persons died of stroke (mortality rate 50.1 per 100,000 persons), making stroke the third leading cause of death in 2014 in Taiwan.[3] Approximately 87% of patients experience ischemic strokes, and the most common causes are transient ischemic attack, thrombotic stroke, and embolic stroke.[4] Mortality was the lowest in lacunar stroke, intermediate in atherothrombotic stroke, and highest in cardioembolic stroke.[5] Furthermore, patients with cardioembolic stroke exhibited the worst prognosis, and more than half of them died within 1.5 years.[5] Cardioembolic stroke accounts for approximately 15%-20% of all ischemic strokes.[6] In addition, the common high-risk cardioembolic conditions include atrial fibrillation (Af), recent myocardial infarction (MI),

mechanical prosthetic valve, dilated myopathy, and mitral rheumatic stenosis.[7] One-third of ischemic stroke events remain cryptogenic[8]; however, paroxysmal supraventricular tachycardia (PSVT) is a novel risk factor for cryptogenic stroke.[9]

PSVT is a common arrhythmia, with an incidence of 35 per 100,000 patient-years and a prevalence of 2.25 per 1000 persons in the United States.[10] The mean age of patients with PSVT was 57 years, and the female sex and age >65 years were the significant risk factors.[10] The mechanism of PSVT varies with age. Atrioventricular nodal reentrant tachycardia (AVNRT) is the most common condition across all ages.[11] Younger patients often have AVNRT, reflecting the presence of a bypass tract. By contrast, older patients often experience focal atrial tachycardia, reflecting the possible age-related changes in the atrioventricular node; these patients also experience atrial myocardial and additional injury because of the acquired factors associated with cardiovascular diseases.[12] The most frequent symptoms of PSVT were palpitations (96%), dizziness (75%), and shortness of breath (47%).[13] The primary consequence of PSVT in most patients is the decline in the quality of life.[14] In rare cases, incessant PSVT can cause tachycardia-induced cardiomyopathy[15] and sudden death.[16] In the absence of Wolff–Parkinson–White syndrome, the risk of sudden death because of PSVT is extremely low. Furthermore, it remains unclear whether ischemic stroke is associated with PSVT. Most patients with PSVT can be temporally managed using physiological maneuvers, medications, and occasionally even electrical cardioversion. Catheter ablation is a permanent method for patients who either desire to undergo treatment or are unresponsive or intolerant to the aforementioned therapies.

PSVT is a novel risk factor for cryptogenic stroke[9]; however, its association with stroke has not been investigated in Taiwan. Therefore, this study explored the association between the clinically documented diagnosis of PSVT and subsequent stroke events in Taiwan.

Methods

Data Source

In this nationwide, population-based, case-control study, we analyzed data from the computerized National Health Insurance Research Database (NHIRD) of Taiwan. Taiwan's NHI program, established in 1995, is a single-payer health insurance system, which covers up to 99.9% of all residents in 2012; 97% of medical providers nationwide are affiliated to the program. In 2012, 502 hospitals and 20,935 clinics were present in Taiwan, and approximately 69 hospital beds and 20 physicians were available per 10,000 persons and physicians, respectively.[17] The NHIRD, a nationwide representative database containing all original claims data for 1 million NHI beneficiaries from 1996 to 2012, is a random, systemic sample of the 23.22 million NHI enrollees. We followed patients until December 2012 by using the 2000 Longitudinal Health Insurance Database (LHID2000). The patients were linked to the LHID2000 to obtain the medical claims data collected from 1997 to 2011. Furthermore, to verify the accuracy of the diagnosis, the Taiwan Bureau of NHI randomly interviews patients and reviews the charts of 1 per 100 ambulatory and 1 per 20 inpatient claims.[18]

Study Population and Identification

Patients

The patients in the LHID2000 registered with ischemic stroke from 1997 to 2011 were selected as the case group. Three patients from the control group were randomly matched with 1 patient from the case group. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used for defining ischemic stroke as 433.x1, 434.x1, or 436 for case group, and excluded stroke accompanying trauma (ICD-9-CM 800-804 or 850-854), subarachnoid hemorrhage (430), intracerebral hemorrhage (431), and rehabilitation (V57). Moreover, we excluded the known cardiovascular risk factors for ischemic stroke: Af and atrial flutter (ICD-9-CM 427.3, 427.31, and 427.32), acute MI (ICD-9-CM 410-414), peripheral arterial occlusive disease (ICD-9-CM 444.2 and 444.2x), and congestive heart failure (ICD-9-CM 428 and 428.x); chronic obstructive pulmonary disease (ICD-9-CM 490-492, 494, and 496) was also excluded.[10,19-21] Patients aged <20 years and those with PSVT receiving catheter ablation (ICD-9-CM 37.34) were excluded because catheter ablation for PSVT was typically considered a curative procedure.

Exposure Assessment

The claims data included medical records of the outpatient department, emergency department, and hospital discharge. The risk assessment included age, sex, hypertension, diabetes, hepatitis B virus (HBV), hepatitis C virus (HCV), chronic kidney disease (CKD), and aspirin use. Previous studies reported that hepatitis C virus infection is associated with the risk of stroke, and inflammation is a key mediator.[22,23] One study reported that HBV carriers tend to have relatively increased atherothrombotic risk due to platelet activation.[24] Taiwan is a hyperendemic area of liver diseases, with 15%-20% of the general population suffering from chronic HBV infection and 4.4% of the general population with chronic HCV infection.[25,26] So, the HBV and HCV infection were analyzed in this study. The definition of cases with PSVT (ICD-9-CM 427.0) in this study was that if they received ≥2 PSVT diagnoses. To increase the validity of the diagnosis of diabetes as well as hypertension, we included only patients with 3 events of the ICD-9-CM for the aforementioned diseases in their medical claims.

The study protocol was reviewed and approved by the Research Ethics Committee of the Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B10304018). The NHIRD only contained de-identified secondary data; therefore, the review board waived the requirement for informed consent.

Statistical Analysis

The distributional properties of continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as the frequency and percentage. Normality was examined using the Shapiro–Wilk test. The two-sample *t*, Wilcoxon rank sum, chi-squared, and Fisher exact tests were used for examining the differences in the distributions of continuous and categorical variables between the 2 groups.

Univariate logistic regressions were performed. A multivariable analysis was conducted by fitting a multiple logistic regression model with the stepwise variable selection procedure for determining the vital predictors of ischemic stroke. Furthermore, generalized additive models were fitted to detect the potential nonlinear effects of continuous covariates and determine the appropriate cutoff points for discretizing the covariates if necessary during stepwise variable selection.

We assessed the goodness of fit of the final logistic regression model according to the estimated area under the receiver operating characteristic (ROC) curve (AUC; also known as the *c* statistic). Statistical tools of regression diagnostics, including residual analysis, detection of influential cases, and assessment of multicollinearity, were applied to discover any problems associated with the regression model or data. All statistical operations were performed using R 3.0.2 software (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P \leq .05$ was considered statistically significant.

Results

The case group comprised 22,713 patients diagnosed with stroke from 1997 to 2011, and each patient was randomized with 3 patients from the control group (n = 68,139). We excluded patients aged <20 years at death (n = 5318); those with no insurance claims in their last year of life (n = 12,955); those with inaccurate data or missing data (n = 16,932); those who experienced stroke with accompanying trauma, subarachnoid hemorrhage, intracerebral hemorrhage, or rehabilitation (n = 3118); those diagnosed with Af, acute MI, peripheral arterial occlusive disease, congestive heart failure, and chronic obstructive pulmonary disease (n = 15,977); and those receiving catheter ablation for PSVT (n = 24). Finally, the study enrolled 5633 and 30,895 patients in the case and control groups, respectively. The study flow chart was presented in Figure 1.

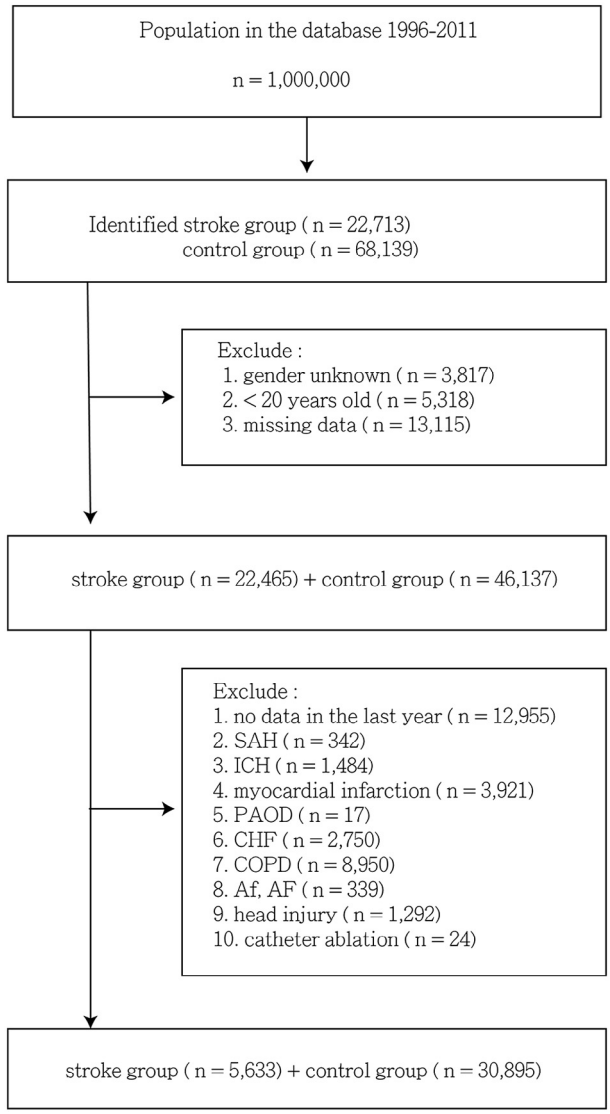

Figure 1. *Study flow chart. Abbreviations: Af, atrial fibrillation; AF, atrial flutter; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ICH, intracerebral hemorrhage; PAOD, peripheral arterial occlusive disease; SAH, subarachnoid hemorrhage.*

Table 1 summarized the demographic characteristics of the cohort stratified by the diagnosis of ischemic stroke in this study. Compared to the control group, the stroke group was older ($P < .001$); with more male sex ($P < .001$); and with higher proportions of hypertension ($P < .001$), diabetes ($P < .001$), CKD ($P < .001$), HCV infection ($P < .001$), and PSVT ($P = .001$), but fewer proportions of HBV infection ($P < .001$) and aspirin administration ($P < .001$).

In univariate analyses, we found that age (in 5-year intervals, odds ratio [OR]: 1.70, 95% confidence interval [CI]: 1.68-1.73, $P < .001$), male sex (versus female; OR: 1.54, 95% CI: 1.46-1.63, $P < .001$), hypertension (OR: 21.48, 95% CI: 19.90-23.22, $P < .001$), diabetes (OR: 7.58, 95% CI: 7.11-8.09, $P < .001$), hepatitis C (OR: 1.77, 95% CI: 1.52-2.07, $P < .001$), and PSVT (OR: 2.00, 95% CI: 1.38-2.85, $P < .001$) were the significant risk factors for ischemic stroke. However, patients who took aspirin before ischemic stroke

Table 1. *Demographic characteristics of the cohort stratified by the diagnosis of ischemic stroke*

Characteristics	Total (n = 36528)	Control group (n = 30895, 84.6%)	Stroke group (n = 5633, 15.4%)	*P* value
Age	52.07 ± 14.6	49.0 ± 12.8	68.9 ± 11.9	<.001
Gender				<.001
Female	18,563 (50.8%)	16,213 (52.5%)	2350 (41.7%)	
Male	17,965 (49.2%)	14,682 (47.5%)	3283 (58.3%)	
Vascular risks				
Hypertension	10,974 (30.0%)	6220 (20.1%)	4755 (84.4%)	<.001
Diabetes	5503 (15.1%)	2982 (9.7%)	2521 (44.8%)	<.001
CKD	1340 (3.7%)	674 (2.2%)	666 (11.8%)	<.001
HBV infection	2785 (7.6%)	2457 (8.0%)	328 (5.8%)	<.001
HCV infection	886 (2.4%)	672 (2.2%)	214 (3.8%)	<.001
PSVT	150 (.4%)	110 (.4%)	40 (.7%)	.001
Aspirin	3615 (9.9%)	3542 (11.5%)	73 (1.3%)	<.001

Abbreviations: CKD, chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; PSVT: paroxysmal supraventricular tachycardia.

Table 2. *Univariate logistic analyses of the potential risk factors for ischemic stroke among Taiwanese adults from 1997 to 2011*

	OR	95% CI	*P* value
Age (per 5 years)	1.70	1.68-1.73	<.001
Gender, male versus female	1.54	1.46-1.63	<.001
Hypertension	21.48	19.90-23.22	<.001
Diabetes	7.58	7.11-8.09	<.001
HBV infection	.72	.63-.80	<.001
HCV infection	1.77	1.52-2.07	<.001
PSVT	2.00	1.38-2.85	<.001
Aspirin	.10	.08-.13	<.001

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; PSVT: paroxysmal supraventricular tachycardia.

Table 3. *Multiple logistic analyses of risk factors for ischemic stroke among Taiwanese adults from 1997 to 2011*

	OR	95% CI	*P* value
Age (per 5 years)	1.76	1.73-1.78	<.001
Male versus female	1.88	1.74-2.01	<.001
CKD	3.09	2.67-3.57	<.001
PSVT	2.05	1.30-3.19	.002
Aspirin	.04	.03-0.05	<.001

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; OR, odds ratio; PSVT: paroxysmal supraventricular tachycardia.

(OR: .10, 95% CI: .08-.13, $P < .001$) and those with hepatitis B (OR: .72, 95% CI: .63-.80, $P < .001$) were the negative risk factors for ischemic stroke (Table 2).

In multiple logistic regression, age (in 5-year intervals, OR: 1.76, 95% CI: 1.73-1.78, $P < .001$), male sex (versus female, OR: 1.88, 95% CI: 1.74-2.01, $P < .001$), CKD (OR: 3.09, 95% CI: 2.67-3.57, $P < .001$), and PSVT (OR: 2.05, 95% CI: 1.30-3.19, $P = .002$) were the significant risk factors for ischemic stroke. However, patients taking aspirin before stroke (OR: .04, 95% CI: .03-.05, $P < .001$) exhibited decreased risk of ischemic stroke (Table 3). The Nagelkerke R^2 of this model was .447, and the estimated AUC was .892 (95% CI: .888-.896; Fig 2).

Discussion

Our study is the first to determine that PSVT is a novel risk factor for ischemic stroke in Taiwan. We also found that age, male sex, and CKD were risk factors for ischemic stroke; however, patients receiving aspirin had a decreased risk of ischemic stroke.

PSVT has been recognized as an independent risk factor for ischemic stroke,[9,27] and our findings were similar to this observation. Af is a strong risk factor for stroke, independently increasing the risk by approximately 5-fold across all age groups.[19,28] Excessive supraventricular ectopic activity in apparently healthy participants is associated with the development of Af and stroke.[29] However, these studies were conducted in European countries and in the United States, and our study is the first in Taiwan. It is considered that the prevalence of risk factors for stroke globally has increased more than the improvements in stroke prevention. Therefore, stroke rates were possibly high from 1990 to 2000.[30] The strategies of treatment for patients with PSVT depend on their different situations. When the hemodynamic status of patient was stable, nonmedicine treatments included Valsalva maneuver, carotid massage, and even splashing ice water on the face were considered. Before carotid massage, it is better to examine the bruits. However, medicines including intravenous adenosine, diltiazem, or verapamil were applied in clinical practices. When the hemodynamic status of patient was unstable, cardioversion was the first choice

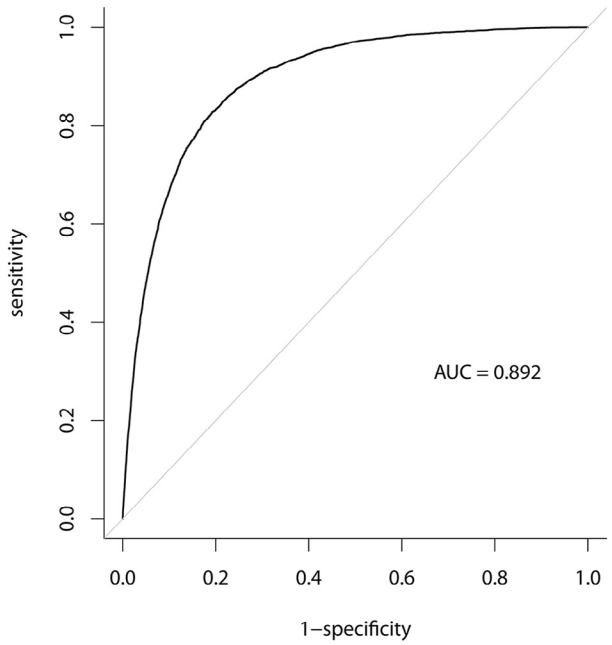

Figure 2. *Area under the receiver operating characteristic curve (AUC) was .892 for predicting ischemic stroke in our study.*

of treatment. For those patients with symptomatic and recurrent PSVT, catheter ablations or long-term medications were suggested.[31] To prevent ischemic stroke in PSVT, patients with PSVT should be advised to undergo catheter ablation,[32] or primary prevention with anticoagulants should be initiated immediately unless patients have contraindications, such as falls, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding.

Aspirin, the most widely studied antiplatelet drug, is one of the broadly used drugs for stroke prevention.[33] Studies have reported that aspirin reduced noncardioembolic stroke or transient ischemic attack, but did not prevent more severe strokes classified as cardioembolism.[34] Aspirin resulted in a 23% risk reduction for recurrent nonfatal stroke compared with placebo,[35] and the Antithrombotic Trialists reported that aspirin reduces the odds of the composite outcome of stroke, MI, or vascular death in secondary prevention by approximately 23%.[36] However, no evidence is present on the balance between risks and benefits of aspirin in primary prevention among low-risk patients. Ischemic stroke decreased by 33% after administering aspirin to patients with end-stage renal disease undergoing dialysis.[37] In this study, we observed that patients with aspirin administration could have a lesser risk of ischemic stroke by 96%; thus, aspirin was possibly associated with the primary prevention of ischemic stroke. A previous study reported that the benefits of aspirin in decreasing the risk of cardiovascular events and the relatively rare occurrence of major bleeding complications should not be underestimated.[38] The aspirin cardiovascular/gastrointestinal risk calculator can be found on the website http://www.asariskcalculator.com. This calculator might guide clinicians in choosing appropriate aspirin therapy and maximize the benefits of aspirin.[39]

Age and sex have been identified as significant risk factors for stroke. Previous studies have reported that the rate of stroke more than doubled for patients at 10-year intervals after the age of 55 years.[40] In this study, we observed that the rate of ischemic stroke increased by 76% at 5-year intervals. In brief, the risk of stroke increased by more than 3 times for patients at 10-year intervals (OR for age: for 10 years, $1.76 \times 1.76 = 3.10$). There were many significant factors in the Framingham study, such as low birthweight, family history of stroke, smoking, obesity, dyslipidemia, asymptomatic carotid stenosis, sickle cell disease, and physical inactivity.[41] However, these factors are not available in our administrative database. These factors might be associated with age, and might be the confounding factors in this study. It was one of the limitations for this study. Studies have reported that males experience more ischemic stroke events,[42-44] and stroke incidence rates are 1.25 times higher in men.[45] In this study, the risk of ischemic stroke risk was 1.88 times higher in men.

We found that patients with HCV infection were associated with increased risk of ischemic stroke in the univariate logistic analyses, and patients with HBV infection were associated with decreased risk of ischemic stroke. Similar results were also reported in previous studies.[22,46] Yet both did not show statistically significant effects on the occurrence of stroke in the multivariate logistic regression model. These associations need further exploration.

One-third of ischemic stroke events are attributable to the effects of diabetes alone or in combination with hypertension.[47] Hypertension and diabetes were significant risk factors for ischemic stroke in our univariate analyses but not in multivariate analyses, possibly because CKD or aspirin use remained a significantly positive or negative risk factor for stroke. CKD is a risk factor for stroke[48] and might also be a marker for other causes of cardiovascular diseases, thus reflecting residual confounding from these risk factors.[49]

Limitations

This study has the following limitations. First, there could have been a bias in this case-control study from claims data. For reducing the bias, we verified the diagnosis of diabetes, hypertension, and other comorbidities, whereas patients had ≥3 diagnoses of the ICD-9-CM for the aforementioned diseases in their medical claims. Furthermore, to verify the accuracy of the diagnosis, the Taiwan Bureau of NHI randomly interviewed patients and reviewed the charts of 1 per 100 ambulatory and 1 per 20 inpatient claims.[18] Second, we did not include PSVT etiologies, such as AVNRT, atrioventricular-reciprocating

tachycardia, hyperthyroidism, previous MI, mitral valve prolapse, rheumatic heart disease, pericarditis, pneumonia, chronic lung disease, current alcohol intoxication, and digoxin intoxication.[50,51] Moreover, we excluded patients with PSVT receiving catheter ablation to avoid the treatment effect of PSVT on ischemic stroke.

Conclusion

PSVT was a significant risk factor for ischemic stroke in Taiwan. A novel antithrombotic regimen, including aspirin, can be suggested for the primary prevention of stroke, thus reducing the substantial burden of stroke on public health.

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