



Evaluation of Stroke Risk Associated with the Use of Typical or Atypical Antipsychotics among Patients with Cardiovascular Diseases

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Background: Concerns regarding stroke safety associated with the use of atypical antipsychotics among dementia patients have been raised. Although observational studies have found conflicting associations of stroke risk with the use of typical or atypical antipsychotics among the elderly with or without dementia, patients with cardiovascular diseases (CVDs), a high-risk for the stroke population, have not been examined. Little evidence has been provided regarding comparison of the stroke risk between the two antipsychotic classes. This study aimed to evaluate the comparative stroke risk with atypical versus typical antipsychotic use among CVD patients. **Materials and Methods:** We conducted a population-based nested case-control study analyzing the Taiwan National Health Insurance Research Database from January 1, 1996 to December 31, 2007. A total of 7,460 CVD patients was followed-up, among which 580 hospitalized cases with stroke were identified and matched to 5,398 randomly selected controls. Conditional logistic regressions were employed to quantify the difference in stroke risk associated with atypical versus typical antipsychotics. **Results:** Any use and current use of atypical antipsychotics were associated with a 1.67-fold (95% confidence interval [CI], 1.21-2.30) and a 2.30-fold (95% CI, 1.56-3.40) increased risk of stroke relative to any typical antipsychotic use, respectively. The stroke risk associated with current use of atypical antipsychotics persisted even compared with current use of typical antipsychotics (adjusted odds ratio, 1.53; 95% CI, 1.02-2.33). **Conclusions:** Use of atypical antipsychotics is associated with an increased risk of stroke requiring hospitalization compared to typical antipsychotic use among CVD patients. Healthcare professionals should take this risk into account when choosing between typical and atypical antipsychotic treatments among CVD patients.

Key words: Stroke, antipsychotics, drug safety, nested case-control, pharmacoepidemiology

INTRODUCTION

Stroke imposes a significant burden on mortality and morbidity, presently accounting for the top three leading causes of deaths and disability-adjusted life years globally.^{1,2} Drug-induced stroke adverse events are, accordingly, of great public concern, including a potential cerebrovascular risk from antipsychotic use.³

From 2002, multiple regulatory agencies across different countries have issued warnings that atypical antipsychotics (second generation) might be associated with an increased risk of stroke or mortality.⁴⁻⁷ This initiated numerous observational studies evaluating more severe stroke,^{8,9} enrolling patients

with more diverse diseases,^{10,11} and following-up patients for a longer period;¹² however, the findings were inconsistent.^{8,11,13-15} These studies were primarily limited by the differences in the unmeasured and measured characteristics between antipsychotic users and nonusers.

Due to a substantial increasing trend of atypical antipsychotic use in recent years,¹⁶ several studies have begun to assess the comparative stroke risk of atypical versus typical antipsychotics, but the results were also conflicting.^{9,12,17-20} The discrepant findings among these studies^{9,12,17-20} might result from inadequate sample sizes due to few antipsychotic users or uncommon stroke events,^{12,18,20} inclusion of patients with a history of stroke,^{9,20} and examination of different populations.^{17,18} Failure to take the time-dependent stroke risk from antipsychotics into account could also contribute to the discrepant findings because the evidence suggests that the highest risk of stroke develops during the 1-week of antipsychotic use.^{21,22}

There exist several lines of evidence indicating that antipsychotics may be associated with an increased risk of

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stroke among high-risk patients. A higher stroke risk upon receipt of antipsychotics has been observed in a substantial proportion of patients with vascular dementia,^{21,22} a type of dementia primarily attributable to small vessel infarcts. Accordingly, vascular risk factors potentially play an important role in antipsychotic-related stroke events.²³ Additionally, Gill *et al.* observed an elevated risk of stroke among dementia patients at high-risk of stroke, such as those with atrial fibrillation, as compared to a general dementia population.¹² Cardiovascular disease (CVD) has been reported to be a major independent risk factor for stroke;²⁴ however, this high-risk for the stroke population has not been examined with regards to the link between stroke risk and antipsychotic use.

This study aimed to evaluate the comparative stroke risk in CVD patients receiving atypical versus typical antipsychotics by analyzing the Taiwan nationwide health care claims database, and to evaluate whether the stroke risk associated with atypical antipsychotics varies depending on how recently the treatment was initiated in comparison with typical antipsychotics.

MATERIALS AND METHODS

Data source

A nested case-control study was performed with analysis of data retrieved from the Psychiatric Inpatient Medical Claim (PIMC) database, a subset of the National Health Insurance Research Database (NHIRD) between January 1, 1996 and December 31, 2007. Figure 1 displays the detailed timeline for conducting this study. The NHIRD contains all claims data for reimbursements from the Taiwan National Health Insurance (NHI), which is a universal health insurance covering 99%

of 23 million Taiwan inhabitants.^{25,26} The claims data are routinely managed and constructed to build the NHIRD by the National Health Research Institutes (NHRI). Specifically, the PIMC contains all the detailed medical and pharmacy claims of outpatient, inpatient, and emergency care of all patients hospitalized for psychiatric diseases within a specified time frame.²⁶ Diagnoses of diseases in the database were made based on the International Classification of Disease, 9th Revision, Clinical Modification code (ICD-9 code) and another disease coding system, the A-code. The latter diagnosis coding was constructed on the basis of abridged ICD-9 codes and employed in the diagnosis of medical outpatients until December 31, 1999. The database is routinely used to study drug utilization, drug effectiveness and drug safety.²⁷⁻²⁹ Access to and analysis of the PIMC was approved by the NHRI. The Institutional Review Board of Tri-Service General Hospital National Defense Medical Center approved this study.

Identification of the study cohort

Patients with CVDs in which a typical or atypical antipsychotic monotherapy was initiated between January 1, 1998 and December 31, 2006 were identified as the eligible study cohort. The initial use of antipsychotics was defined as no previous prescription records of antipsychotics in the previous year. The presence of CVDs was determined based on the diagnosis codes from inpatient/outpatient care, including acute myocardial infarction (ICD-9 code: 410 or A-code: A270), other ischemic heart disease (ICD-9 code: 411-414 or A-code: A279), arrhythmia (ICD-9 code: 427; A-code: A281), atherosclerosis (ICD-9 code: 440 or A-code: A300), and arterial embolism (ICD-9 code: 444 or A-code: A 301). The date of the first antipsychotic

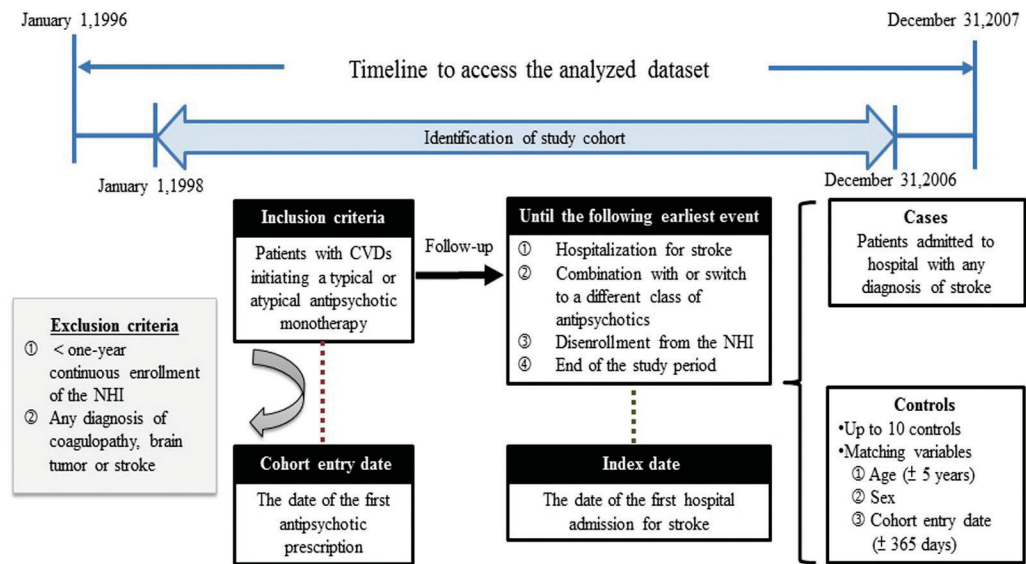


Figure 1. Overview of the adopted nested case-control study design. CVD refers to cardiovascular disease; NHI represents to National Health Insurance

prescription was marked as the cohort entry date. The eligible study patients were excluded if they had <1-year of continuous enrollment in the NHI preceding cohort entry in order to allow a sufficient time window in which to measure the baseline clinical characteristics; had any diagnosis of coagulopathy or brain tumor to enhance the causality that the observed stroke risk was attributable to antipsychotic use; and had any diagnosis of stroke from emergency, outpatient and inpatient care in the year before cohort entry to ensure that the outcome event was incident and occurred after antipsychotic use. The study cohort was followed from the cohort entry date until the following earliest event: Hospitalization for stroke, combination with or switching to a different class of antipsychotics, disenrollment from the NHI, or the end of the study period (December 31, 2007).

Case identification and control selection

Cases were identified as those admitted to hospital with any diagnosis of stroke (ICD-9 codes 430.xx-438.xx; A-code A29). The date of the first hospital admission for stroke was defined as the index date. Up to 10 controls were randomly selected per case, matched for age (± 5 years), sex, and cohort entry date (± 365 days) using the incidence density sampling approach.³⁰ Control patients were assigned the same index date as their corresponding cases.

Measurement of antipsychotic use

All prescription records from the cohort entry date to the index date were examined to determine whether or not cases and controls were exposed to any use of typical or atypical antipsychotics. Based on the time gap from the last prescription date to the index date, use of atypical antipsychotics was further defined as current use (< 30 days), recent use (31-180 days), and past use (> 180 days). The same time frame was adopted to define current users of typical antipsychotics for a further comparison of the difference in the risk of stroke between current users of atypical antipsychotics and of typical antipsychotics. Prescribed typical antipsychotics within the study period included chlorpromazine, clopenthixol, clothiapine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, methotrimeprazine, perphenazine, pipotiazine, sulpiride, thioridazine, thiothixene, and trifluoperazine. The individual medications of atypical antipsychotics comprised amisulpride, clozapine, olanzapine, quetiapine, risperidone, and zotepine.

Assessment of confounders

In addition to the CVDs measured at baseline, the following comorbid conditions were assessed in the 6 months before the index date: Bipolar disorder, dementia, depression, diabetes mellitus, hyperlipidemia, hypertension, Parkinson disease and schizophrenia. The medications potentially used for treatment for the baseline CVDs were measured in the 6 months preceding

the cohort entry, including anti-arrhythmic agents, anti-coagulants, anti-platelets, hypoglycemic agents, lipid-lowering agents, and nonsteroidal anti-inflammatory medications. Psychotropic medications consisted of anti-convulsants, anti-depressants, benzodiazepines, and lithium, which were also measured in the 6 months prior to the index date.

Statistical analyses

Conditional logistic analyses were performed to estimate the odds ratios (ORs) for the association between the risks of stroke associated with atypical versus typical antipsychotics. Covariates with a statistical significance in univariate analyses were adjusted for during multivariate conditional logistic regressions. Patients with any use of typical antipsychotics were included as the reference group across all analyses except for the comparison of stroke risk between current use of atypical antipsychotics and of typical antipsychotics. SAS version 9.2 (SAS Institute, Cary, NC, USA) and STATA version 10.1 (STATA, College, Station, TX, USA) were employed to perform data cleaning and statistical analyses, respectively.

Sensitivity analyses

The robustness of the main findings was examined by performing several sensitivity analyses. First, we restricted the analyzed cases and controls to those identified before April 2003. The observed antipsychotic prescribing might have been affected by the early safety warnings regarding atypical antipsychotic-associated cerebrovascular adverse effects, such as a potentially increased stroke risk with the use of risperidone in dementia patients, which was issued by the US Food and Drug Administration (FDA) in April 2003.⁵ Accordingly, physicians could prescribe typical antipsychotics rather than atypical antipsychotics to patients at risk of stroke after the US FDA's warning, potentially biasing our results.¹³ Second, in order to increase the validity of the employed coding to identify patients with stroke, the stroke events were restricted to those examined by magnetic resonance imaging (MRI) or computed tomography (CT) within 14 days before or after the observed stroke events. Third, as the employment of the A-code system could not precisely identify several comorbid conditions, we repeated the analyses limited to the time period spanning from January 1, 2001 to December 31, 2007, during which disease diagnoses were solely made on the basis of ICD-9 codes. Fourth, a 3-year period was employed prior to the cohort entry to exclude patients with any history of stroke events at baseline.

RESULTS

Figure 2 displays the selection process of the study cohort over an 8-year study period. A total of 10,387 eligible patients

Risk of stroke associated with antipsychotics

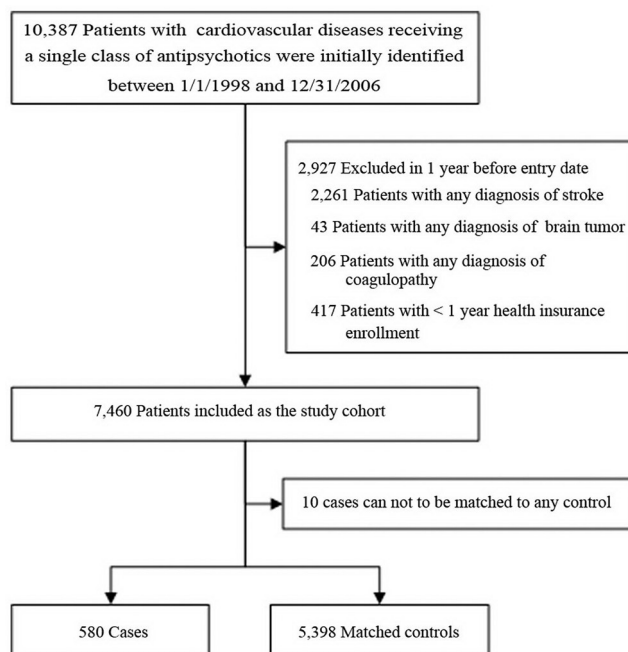


Figure 2. Study flow diagram displaying the selection process of cases and controls

with CVDs receiving a single class of antipsychotics was initially identified. After excluding patients with any history of stroke ($n = 2,261$), a brain tumor diagnosis ($n = 43$), a coagulopathy diagnosis ($n = 206$), and those without continuous enrollment in the NHI within the year prior to cohort entry ($n = 417$), we identified 7,460 CVD patients with a median follow-up time of 2.6 person-years (interquartile range 1.0-5.4). After the further exclusion of 10 cases that were unable to be matched with any controls, 580 cases and 5,398 corresponding randomly selected matched controls were analyzed.

The cases and controls were comparable in terms of the majority of the demographic and clinical characteristics [Table 1]. However, the cases were statistically more likely than the controls to have any diagnosis of dementia, diabetes mellitus, hyperlipidemia, and hypertension, and to have received any prescription of anticonvulsants, antiplatelets, benzodiazepines and hypoglycemic agents. The imbalances in the characteristics between the cases and controls justified the employment of multivariate analyses to adjust for these covariates.

Table 2 indicates that any use of atypical antipsychotics was associated with a 67% increase in the risk of stroke as compared with any use of typical antipsychotics after adjustment for the potential confounders (adjusted OR, 1.67; 95% confidence interval [CI], 1.21-2.30). The most profound increased risk of stroke was associated with current use of atypical antipsychotics in comparison with any use of typical antipsychotics (adjusted OR, 2.30; 95% CI, 1.56-3.40), whereas the risk was absent for

Table 1. Baseline characteristics between cases and controls

Characteristic	Cases ($n = 580$)	Controls ($n = 5398$)
Age, median (IQR)	70.65 (59.4-76.9)	70.0 (58.1-75.8)
Male, number (%)	378 (65.2)	3527 (65.3)
Cardiovascular diseases, number (%)		
Acute myocardial infarction	19 (3.3)	163 (3.0)
Arrhythmia	179 (30.9)	1851 (34.3)
Arterial embolization	4 (0.7)	60 (1.1)
Atherosclerosis	46 (7.9)	388 (7.2)
Other ischemic heart disease	369 (63.6)	3202 (59.3)
Comorbidities, number (%)		
Bipolar disorder	58 (10.0)	496 (9.2)
Dementia	135 (23.3)	779 (14.4)***
Depression	173 (29.8)	1732 (32.1)
Diabetes mellitus	152 (26.2)	917 (17.0)***
Hyperlipidemia	68 (11.7)	510 (9.5)*
Hypertension	299 (51.6)	2111 (39.1)***
Parkinson disease	46 (7.9)	321 (6.0)
Schizophrenia	50 (8.6)	578 (10.7)
Comedications, number (%)		2996 (59.24)
Antiarrhythmic agents	221 (38.1)	2240 (41.5)
Anticoagulants	161 (27.8)	1624 (30.1)
Anticonvulsants	131 (22.6)	997 (18.5)**
Antidepressants	263 (45.3)	2286 (42.4)
Antiplatelets	14 (2.4)	49 (0.9)**
Benzodiazepines	427 (73.6)	3619 (67.0)***
Hypoglycemic agents	102 (17.6)	653 (12.1)***
Lipid-lowering agents	30 (5.2)	276 (5.1)
Lithium	15 (2.6)	189 (3.5)
NSAIDs	390 (67.2)	3362 (67.2)

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. IQR = interquartile range; NSAIDs = nonsteroidal anti-inflammatory drugs

recent use (adjusted OR, 0.97; 95% CI, 0.59-2.49) or past use of atypical antipsychotics (adjusted OR, 1.03; 95% CI, 0.56-1.94). Additionally, even compared with current use of typical antipsychotics, an elevated risk of stroke associated with current use of atypical antipsychotics remained [data not shown in Table 2, adjusted OR, 1.53; 95% CI, 1.02-2.33].

Our main findings were robust during the majority of the sensitivity analyses [Figure 3]. Specifically, after repeating the analyses prior to the US FDA's warning of the increased stroke risk from risperidone use, issued in April 2003, the increased stroke risk associated with any use (adjusted OR, 1.91; 95% CI, 1.30-2.81) or current use of atypical antipsychotics (adjusted OR, 2.50; 95% CI, 1.58-3.94)

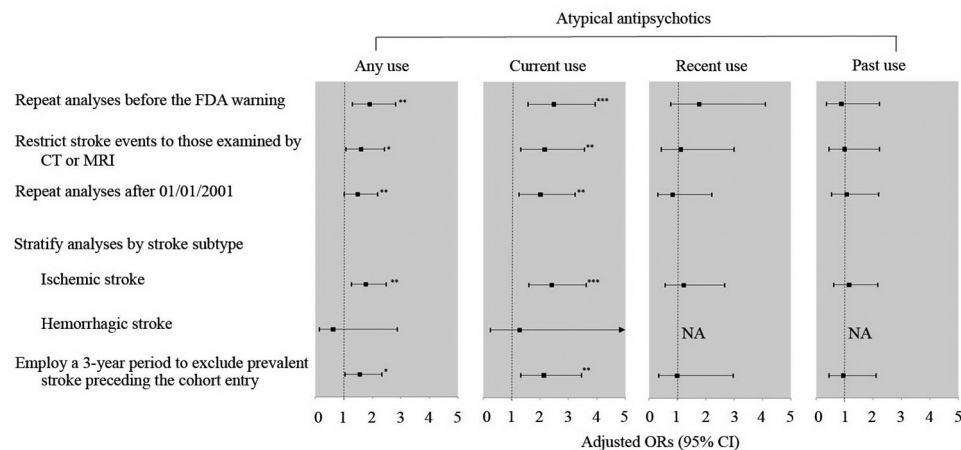


Figure 3. Sensitivity analyses for stroke risk associated with the use of atypical versus typical antipsychotics. FDA indicates Food and Drug Administration; CT, computed tomography; MRI, magnetic resonance imaging; NA, not available; OR, odds ratio. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 2. Risk of stroke associated with the use of atypical versus typical antipsychotics by how recent atypical antipsychotics were initiated

Antipsychotic use	Cases (<i>n</i> = 580)	Controls (<i>n</i> = 5398)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)
Any use of typical antipsychotics [‡]	518 (89.3)	5036 (93.3)	1.00 (reference)	1.00 (reference)
Any use of atypical antipsychotics [‡]	62 (10.7)	362 (6.7)	1.82 (1.34-2.48)**	1.67 (1.21-2.30)*
Current use (≤30 days)	41 (7.1)	162 (3.0)	2.74 (1.89-3.97)**	2.30 (1.56-3.40)**
Recent use (31–180 days)	8 (1.4)	64 (1.2)	1.29 (0.64-2.74)	0.97 (0.59-2.49)
Past use (>180 days)	13 (2.2)	136 (2.5)	0.97 (0.53-1.77)	1.03 (0.56-1.94)

* $P < 0.01$; ** $P < 0.001$. [†]Adjusted for history of dementia, diabetes mellitus, hypertension, hyperlipidemia, anticonvulsants, antiplatelet drugs, benzodiazepines and hypoglycemic agents; [‡]Measured from cohort entry date to the index date. OR = odds ratio; CI = confidence interval

persisted relative to any use of typical antipsychotics. Compared to use of typical antipsychotics, use of atypical antipsychotics was consistently associated with an increased risk of stroke when stroke events were restricted to those examined by CT or MRI or when the database after January 1, 2001 were analyzed in order to limit disease diagnoses to those made in the absence of A-codes.

DISCUSSION

The results of this large population-based nested case-control study revealed that any use of atypical versus typical antipsychotics was associated with a nearly 70% increased risk of stroke among patients with CVDs. The most profound increased stroke risk associated with atypical antipsychotic use was present during the first 30-day of treatment, exceeding a doubling of the risk. These findings were robust during the majority of the sensitivity analyses. To the best of our knowledge, this is the first population-based observational study directly evaluating the comparative stroke risk associated with the use of atypical versus typical antipsychotics among CVD patients.

There exist several attributes supporting our findings. The results of our study were in accordance with those of previous studies^{9,17} directly comparing the stroke risk between users of typical and of atypical antipsychotics. An Italian cohort study of the elderly observed that atypical antipsychotic use is associated with a 1.42-fold (95% CI, 1.12-1.93) increased risk of stroke in comparison with the use of typical antipsychotics.¹¹ By analyzing the Taiwan claims database from January 1, 1997 to December 31, 2007, Wu *et al.*¹⁷ conducted a case-crossover study of 14,582 patients with an incident stroke, and reported a 91% increased risk of stroke related to atypical versus typical antipsychotic use (adjusted OR, 1.91; 95% CI, 1.67-2.18). Additionally, the highest stroke risk in our study was observed to be concentrated in the 1-month of atypical antipsychotic treatment, which corroborates the previous results of a time-varying risk of stroke associated with antipsychotics.^{21,22}

There might exist several plausible mechanisms or pathological pathways potentially underling our findings. Antipsychotic medications with a high binding affinity of α_2 -adrenergic receptors or of M_1 muscarinic receptors have been linked to an increased risk of stroke.¹⁷ However, there is no substantial difference in the binding affinity of the latter receptor

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between the two types of antipsychotics.¹⁷ Antagonism of α_2 -adrenergic receptors can lead to tachycardia and hypotension³¹ as well as to a significant decrease in cerebral blood flow,³² which can subsequently cause the occurrence of stroke, especially ischemic stroke. Accordingly, our findings of an elevated overall stroke or of an increased ischemic stroke risk associated with atypical over typical antipsychotics could be explained in part by a higher affinity to α_2 -adrenergic receptors of the majority of the atypical antipsychotics as compared with typical antipsychotics.¹⁷ Facilitation of thrombosis could be an alternative pathological pathway.²¹ An increased risk of venous thromboembolism from atypical antipsychotics as compared with typical antipsychotics has been reported in the literature.^{33,34} The thrombi, which is thus expected to occur more frequently from atypical than typical antipsychotics, could potentially dislodge into the arterial circulation and cause ischemic stroke. This also supports our findings of a nonsignificantly increased hemorrhagic stroke risk but an elevated risk of ischemic stroke from the use of atypical versus typical antipsychotics.

On the other hand, the findings of the current study were dissimilar to those of several studies^{12,18-20} directly evaluating the difference in stroke risk between the two classes of antipsychotics. Gill *et al.*¹² reported a nonstatistical difference in stroke risk between patients receiving atypical and typical antipsychotics. A retrospective cohort study of Canadian patients over the age of 65 years suggested that the use of olanzapine or risperidone was not statistically associated with an increased risk of stroke as compared to typical antipsychotic use.¹⁸ Wang *et al.*²⁰ performed another cohort study of the elderly aged ≥ 65 years, and observed a 9% increased stroke risk from use of typical antipsychotics within 120 days of the initial of treatment as compared with atypical antipsychotic use (adjusted hazard ratio, 1.09; 95% CI, 1.02-1.16). A nested case-control study of dementia patients aged ≥ 65 years, with analysis of the UK General Practice Research Database between 1995 and 2007, found a significantly higher risk of stroke with the use of typical antipsychotics relative to the atypical antipsychotic use (OR, 1.83; 95% CI 1.57-2.14).²¹ Despite indirect comparison between the two classes of antipsychotics in schizophrenic patients from 2001 to 2009, Hsieh *et al.*¹¹ analyzed the Taiwan Longitudinal Health Insurance Database and reported a significantly increased stroke risk with the use of typical (adjusted OR, 2.75; 95% CI, 1.34-5.64) rather than the use of atypical antipsychotics (adjusted OR, 0.46; 95% CI, 0.11-1.88) as compared with nonuse.

These above-mentioned studies,^{11,12,18-20} however, had several limitations. First, inadequate sample sizes resulting from few subjects being exposed to antipsychotics or limited subjects with stroke events,^{11,12,18,20} substantially impeded the ability to detect a meaningful risk estimate. Second, confounding by prior stroke events could not be ruled out,^{12,18,20} potentially

jeopardizing the causality between antipsychotic use and stroke risk. Third, because a potential stroke risk from use of atypical antipsychotics has been reported by several regulatory authorities worldwide since 2002, patients at high-risk of stroke could have been prescribed typical rather than atypical antipsychotics, which were included in studies conducted across or after the dates of the issued warnings.^{11,19,20} This affected prescribing pattern could cause an observed elevated stroke risk of typical antipsychotics as compared with atypical antipsychotics. Fourth, not all individual atypical antipsychotics were examined, with only two individual atypical antipsychotics being examined in the studies of Herrmann *et al.*¹⁸ Last, the use of antipsychotics was examined only in a short period of time or merely based on the first prescription,²⁰ which might cause misclassification of antipsychotic use. Collectively, these aforementioned limitations and different populations being examined might have contributed to the discrepancies among the findings of the previous studies and our study.

Several alternatives accounting for our main findings could exist. Previous studies found that patients exposed to antipsychotics could carry the highest risk of stroke in the 1-week of treatment,^{21,22} which leaves open the possibility that there is a temporal relationship between risk of stroke and use of typical antipsychotics. Therefore, our findings might be because the majority of the patients in the reference group had not been recently treated with typical antipsychotics. However, we consistently observed an increased stroke risk associated with current use of atypical antipsychotics even compared with the current use of typical antipsychotics. In addition, Liperoti *et al.*⁸ indicated that a history of stroke events and use of atypical antipsychotics were observed to exert a synergistic effect on the subsequent stroke risk. This raises the concern that our observed increased antipsychotic-related stroke risk could be attributable to a prior history of stroke. Nevertheless, the patients included in the current study comprised CVD patients without prior stroke events.

Our findings deserve clinical attention regarding the observed association between stroke risk and use of atypical over typical antipsychotics. The US FDA's warning raises the concern of a stroke risk associated with the use of atypical antipsychotics in dementia patients.^{5,7} The data obtained in this study pinpoint another population, patients with CVDs, in whom a potentially elevated risk of stroke needs to be addressed with the use of atypical versus typical antipsychotics. When initiating atypical antipsychotic treatment or switching the prescription of typical to atypical antipsychotics among patients with CVDs, healthcare professionals should be cautious regarding the potential stroke risk, and monitor any preclinical symptoms of stroke. The observed increase in the stroke risk associated with the use of atypical over typical antipsychotics suggests

consideration of this stroke risk when weighing the benefits and risks of antipsychotic use in CVD patients.

Several strengths of this study merit emphasis. First, confounding by mental illness bias was minimized due to comparison of stroke risks between new users of typical and atypical antipsychotics. Second, the observed association between antipsychotics and stroke was strengthened due to the exclusion of a prior history of stroke events at baseline. Third, we potentially minimized the selection bias with the adoption of a nested case-control design, because the cases and matched controls were selected from the same study cohort. This was supported by the balanced CVDs between the two groups. Fourth, all prescription records from emergency care, inpatient and outpatient care, were assessed to determine antipsychotic use, which minimized and potentially avoided immeasurable time bias and recall bias. Fifth, the performed sensitivity analyses revealed the robustness of our main findings. Last, this was the first study to evaluate the comparative stroke risk of atypical versus typical antipsychotics in patients with CVDs.

There are, however, several limitations that needed to be considered when interpreting the results of the current study. Although the employed ICD-9 coding for identification of ischemic stroke has been validated,³⁵ the accuracy of the diagnosis coding used for measurement of hemorrhagic stroke is uncertain. Nevertheless, our observed main findings remained consistent when restricting the stroke events to those examined by MRI or CT within 14 days before or after the stroke diagnosis. This supports the validity of the employed ICD-9 codes for identification of stroke events. Additionally, use of antipsychotics was measured on the basis of prescription records; consequently, it is uncertain as to whether patients really took the medications. However, nonadherence to antipsychotics is believed to be nondifferential between cases and controls, potentially causing the estimated comparative stroke risk toward the null value. The increased stroke risk with the use of atypical versus typical antipsychotics was accordingly expected to be higher than our estimated data. Furthermore, several important confounders such as alcohol consumption and smoking were not available in the analyzed database, and our results might be limited by the immeasurable confounders. Moreover, the effects of individual atypical and typical antipsychotics on the comparative risk of stroke were unable to be assessed due to the limited sample sizes. Future studies investigating the comparative stroke safety of individual antipsychotics in patients with CVDs are warranted.

SUMMARY

Use of atypical antipsychotics is associated with an increased risk of hospitalization for stroke as compared with

typical antipsychotic use among CVD patients. The highest risk occurs within the 1-month of treatment with atypical antipsychotics. Healthcare professionals need to consider this risk when choosing between typical and atypical antipsychotic treatment in CVD patients.

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