Antidepressant Use and Risk of Recurrent Stroke:
A Population-Based Nested Case-Control Study

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ABSTRACT

Objective: Antidepressants may carry an increased risk for incident stroke, but there is little safety evidence regarding poststroke antidepressant use. This study aimed to examine whether antidepressants are associated with an increased risk of stroke recurrence.

Method: A population-based nested case-control study was conducted analyzing the Taiwan universal health care claims database from January 1, 2000, to December 31, 2008. We followed up 19,825 patients who survived a first admission for stroke at the age of ≥ 18 years, among which 3,536 hospitalized cases with stroke recurrence (*ICD-9-CM* codes 430.xx–437.xx) were identified and individually matched to 6,679 randomly-selected controls. Multivariate conditional logistic regression models were used to characterize the risk associated with antidepressant use.

Results: The study cohort had a mean age of 66 years and was followed up for a median of 2.9 person-years. Use of any tricyclic antidepressants (TCAs) was associated with a 1.41-fold (95% CI, 1.19–1.67) increased risk of stroke recurrence, whereas any use of selective serotonin reuptake inhibitors (SSRIs) or other antidepressants showed no association. Stopping TCAs for 1–30 days was associated with a 1.87-fold (95% CI, 1.22–2.86) increased risk of stroke recurrence, and the risk was attenuated for a longer discontinuation. The stroke risk associated with TCA use was not present in a dose-dependent or duration-dependent manner.

Conclusions: Use of TCAs, but not SSRIs or other antidepressants, was associated with an increased risk of stroke recurrence. The risk is particularly elevated with abrupt cessation of TCA therapy. Health care professionals should be vigilant to that risk during TCA therapy in poststroke patients.

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Recurrent stroke is the most severe cardiovascular consequence in patients suffering a first stroke,[1,2] with an incidence rate estimated at 12% in the first year and 30% over 5 years.[3] Stroke recurrence causes poorer prognosis, greater disability, and increased mortality.[2]

Depression is the most frequently occurring psychiatric condition, affecting approximately 30% of stroke patients.[4] Poststroke depression negatively affects improvements in physical and cognitive recovery as well as overall survival rates.[5,6] While antidepressant therapy in poststroke depression is recommended,[7] the guidelines are not specific as to which particular class of therapies should be prescribed, with side effect profiles being the main factor to consider.[8] To date, little is known about the safety of various classes of antidepressants in the poststroke population.

Emerging evidence has suggested that use of antidepressants is related to an increased risk of incident stroke, including selective serotonin reuptake inhibitors (SSRIs),[9–14] tricyclic antidepressants (TCAs),[9–13] and other antidepressants,[10,12–14] whereas other studies have reported neutral findings.[15–18] The internal validity of these studies are possibly threatened by small sample sizes,[11,15] lack of inpatient medication records,[14–16] and assessment of mixed classes of antidepressants[9,10,13,14,16–18] as well as inclusion of prevalent stroke events,[12] which leave open the possibility that stroke risk associated with antidepressant use may vary by therapeutic class.

The risk of incident stroke from antidepressant use was observed particularly in patients at high risk of stroke, such as elderly patients[11,14] and menopausal women.[9] Only 1 study[19] has examined the association of recurrent stroke with SSRI use in another high-risk population: patients experiencing their first stroke. However, this study[19] was limited by an inadequate examination of other types of antidepressants and misclassification of SSRI users and nonusers. Accordingly, whether use of antidepressants in different classes increases risk of recurrent stroke remains unclear.

We aimed to clarify the relationship between use of antidepressants of individual classes and risk of recurrent stroke by analyzing a nationwide health care claims database and to assess whether the association varies by discontinuation of antidepressant therapy, dose, or duration of antidepressant use.

METHOD

Data Source

We performed a nested case-control study from January 1, 2000, to December 31, 2008, using data retrieved from the Longitudinal Health Insurance Database (LHID), which contains comprehensive information on health care utilization of 1 million randomly selected National Health Insurance (NHI) beneficiaries.[20] Two sets of LHIDs were combined for the analysis. The NHI is a universal health insurance program in which 99% of 23 million Taiwanese inhabitants are covered. Beneficiaries identified from the LHID are reported to be representative of the entire Taiwanese population.[21] Detailed records of physician services, medical procedures/

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Clinical Points

- Use of tricyclic antidepressants (TCAs) is associated with an increased risk of stroke recurrence, particularly for abrupt cessation of TCAs. Use of selective serotonin reuptake inhibitors or other antidepressants seems to not carry the risk among stroke patients.
- The observed TCA-associated risk of recurrent stroke needs to be taken into account for choosing a poststroke antidepressant therapy.
- Clinicians should be aware of this potential recurrent stroke risk when prescribing TCAs or discontinuing TCAs in stroke patients.

diagnoses, and prescription drugs from outpatient, inpatient, or emergency care are available from the database.[20] The LHID is routinely used to study drug effectiveness[22] and safety,[23] including drug-related stroke adverse events.[24] The Institutional Review Board of Tri-Service General Hospital National Defense Medical Center (Taipei, Taiwan) approved this study (1-102-05-028).

Study Cohort

The study cohort comprised all patients who survived during a first hospitalization with any stroke diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 430.xx–437.xx)[25] at the age of ≥ 18 years between January 1, 2001, and December 31, 2007. First-stroke survivors were determined based on their status of having no inpatient mortality records and no disenrollment from the NHI within 7 days of being discharged,[26,27] a validated proxy indicator of in-hospital mortality in Taiwan.[27] The discharge date of the first hospitalization for stroke, defined as no previous stroke-related inpatient and outpatient visits, marked the cohort entry. Patients were excluded if they had less than 1 year of NHI enrollment, any diagnosis of brain tumor (*ICD-9-CM* codes 191.xx, 225.xx, 239.6x), or coagulopathy (*ICD-9-CM* codes 284.xx, 286.xx, 287.xx) including aplastic anemia, coagulation defects, and purpura in the year before cohort entry.

The study cohort was followed from cohort entry until subsequent hospitalization with a primary diagnosis of stroke, disenrollment from the NHI, or the end of the study period (December 31, 2008), whichever came first.

Case Identification and Control Selection

Cases were identified as those readmitted to hospital with a primary diagnosis of stroke (*ICD-9-CM* codes 430.xx–437.xx).[10] Only the first stroke-related hospital readmission was considered if several readmissions occurred. The date of the first hospital readmission for stroke was defined as the index date.

By using an incidence density sampling approach, each case was matched with up to 2 randomly selected controls by age (± 5 years), sex, cohort entry date (± 180 days), any diagnosis of hypertension, and atrial fibrillation in the year preceding cohort entry. Each control was assigned the same index date as the corresponding case.

We excluded cases and controls if they had any head trauma diagnosis and received ≥ 2 different classes of antidepressants in the 3 months and in the year preceding the index date, respectively. Cases without corresponding controls or controls without corresponding cases were also excluded.

Measurement of Antidepressant Use

Any use of antidepressants by classes in the year preceding the index date was assessed from all prescription drug records, including SSRIs, TCAs, and other antidepressants. According to the time gap from the end of the most recent prescription to the index date, antidepressant use was further categorized as current use (covered the index date), discontinued use for 1–30 days, and discontinued therapy for 31–365 days. We adopted the 1-day gap to distinguish the current users from discontinued users because adverse effects could occur within 1 to several days after cessation of antidepressant therapy.[28] Additionally, the mean daily dose of all antidepressants prescribed within the 90 days of the last prescription was calculated and categorized as low (≤ 0.5 defined daily dose [DDD]) and high (> 0.5 DDD) dose. Furthermore, continuous use of antidepressants, determined based on a ≤ 7-day gap between successive prescriptions most proximal to the index date, was categorized as short-term (≤ 30 days), medium-term (31–90 days), and long-term (> 90 days) use. All included individual antidepressants by each class consist of (1) SSRIs: citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline; (2) TCAs: amitriptyline, clomipramine, dothiepin, doxepin, imipramine, melitracen, and maprotiline; and (3) other antidepressants: bupropion, duloxetine, mirtazapine, milnacipran, moclobemide, trazodone, and venlafaxine. Nonusers were defined as those without any antidepressant prescription in the year preceding the index date.

Measurement of Covariates

We considered the following potential confounders: proxy measures of stroke severity during the first stroke-related hospitalization,[25] including stroke subtype, length of hospital stay (< 8, ≥ 8 days), and admission to an intensive care unit; proxy indicators of depression severity,[29] consisting of any inpatient/outpatient visit for depression or psychiatry; comorbid conditions; and comedications prescribed (listed in Table 1). We measured the proxies of depression severity/comorbidities and comedications in the year and 6 months prior to the index date, respectively. Confounders are detailed in Supplementary eTable 1 (available at PSYCHIATRIST.COM).

Statistical Analyses

The association of antidepressants with recurrent stroke expressed as an odds ratio (OR) with 95% CIs was quantified by using conditional logistic analysis. All covariates with statistical significance ($P < .05$) in a univariate analysis were

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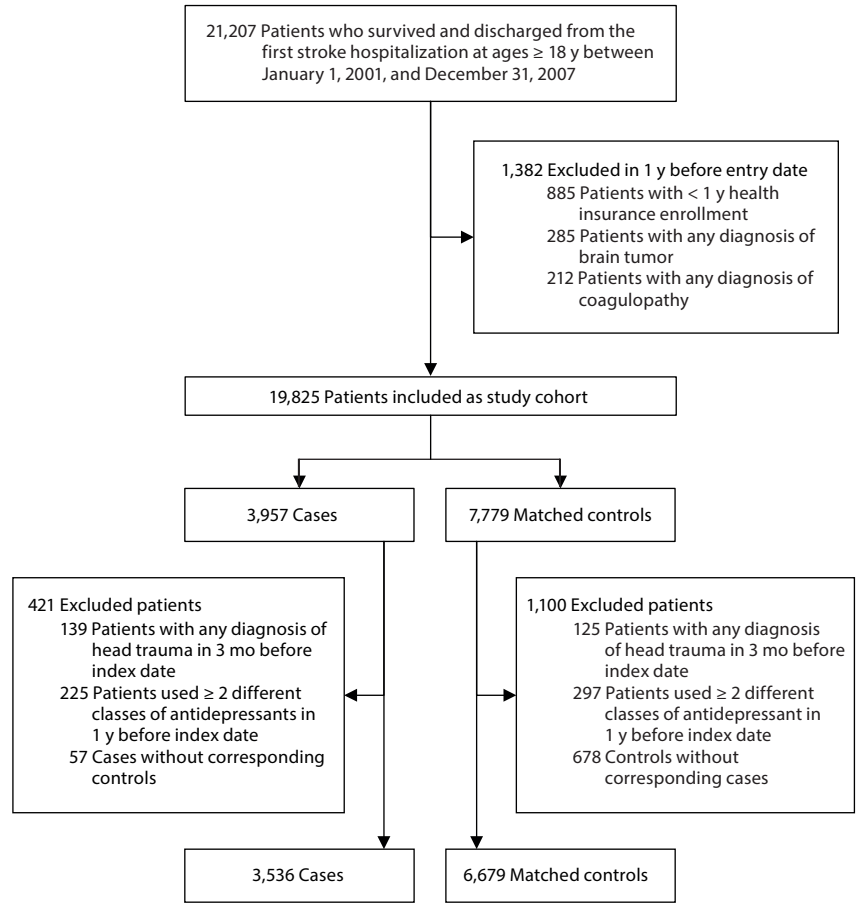
Figure 1. Flow Diagram Depicting Selection Process of Study Subjects



included in a multivariate conditional logistic regression. Nonuse was treated as the reference group across all analyses. Data cleaning and statistical analyses were performed using SAS version 9.2 (SAS Institute; Cary, North Carolina) and STATA version 10.1 (STATACorp; College Station, Texas), respectively.

The number needed to harm (NNTH) for each of the significant findings was estimated using the following formula[30]: NNTH = 1/[(OR – 1) UER], where OR and UER represent our estimated odds ratio and unexposed event rate, respectively. We calculated UER among patients with a first-ever stroke but not on any antidepressant.

Several sensitivity analyses were conducted to assess the robustness of our main findings: (1) excluding patients with antidepressant use at baseline and those with concomitant antipsychotic use; (2) restricting recurrent stroke events to those examined by computed tomography (CT) or magnetic resonance imaging (MRI) within 14 days before or after the stroke diagnosis; (3) performing stratified analyses by subtypes of recurrent stroke and by concomitant use of antiplatelets; (4) employing different model selection approaches in multivariate analyses, which adjusted for all variables in Table 1 (model 1) as well as controlled for a disease risk score[31] of stroke recurrence estimated using a multiple logistic regression and classified into deciles (model 2); and (5) using a 3-day and 7-day gap to redefine discontinuation of antidepressant use.

RESULTS

A total of 19,825 patients aged ≥ 18 years and who experienced a first stroke were identified from January 1, 2001, to December 31, 2007 (Figure 1), with a median follow-up of 2.9 person-years (interquartile range, 1.3–4.7). The mean age of the study cohort was 66 years, and 56% were male. Among the study cohort, 3,957 patients were identified as eligible cases and matched to 7,779 randomly selected controls. After executing the exclusion criteria, we analyzed 3,536 cases and 6,679 controls.

Table 1 indicates that cases and controls were comparable in most of the examined characteristics. Compared with antidepressant nonuse, neither use of any SSRIs (adjusted OR = 1.10; 95% CI, 0.84–1.45) nor use of other antidepressants (adjusted OR = 1.04; 95% CI, 0.84–1.29) was associated with an increased risk of recurrent stroke after adjustment for the confounders (Table 2). Conversely, treatment with any TCA was related to a 1.41-fold increased risk (95% CI, 1.19–1.67).

The insignificant risks of stroke recurrence by SSRIs and other antidepressants remained, regardless of recency, dose,

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Table 1. Demographic and Clinical Characteristics of Patients With Recurrent Stroke and Matched Controls

Characteristic	Cases (n = 3,536)	Controls (n = 6,679)	OR (95% CI)	*P* Value[a]
Age, mean ± SD, y[b]	67.58 ± 12.14	67.50 ± 11.86	1.03 (1.01–1.04)	.005
Male sex, n (%)[b]	2,099 (59.4)	3,974 (59.5)	NA	
Stroke severity, n (%)				
Stroke subtype				
Hemorrhagic	570 (16.1)	1,152 (17.3)	Reference	
Ischemic	2,421 (68.5)	4,520 (67.7)	1.08 (0.97–1.22)	.17
Other	545 (15.4)	1,007 (15.1)	1.11 (0.96–1.29)	.17
Length of hospital stay, d[c]				
< 8	1,548 (43.8)	3,126 (46.8)	Reference	
≥ 8	1,988 (56.2)	3,553 (53.2)	1.13 (1.04–1.22)	.005
ICU admission	706 (20.0)	1,389 (20.8)	0.94 (0.85–1.05)	.28
Depression severity, n (%)				
Outpatient visit with depression	110 (3.1)	211 (3.2)	0.99 (0.78–1.26)	.95
Inpatient stay with depression	13 (0.4)	21 (0.3)	1.24 (0.62–2.47)	.55
Psychotherapy visit	40 (1.1)	94 (1.4)	0.83 (0.57–1.21)	.34
Comorbidities, n (%)				
Ischemic heart disease	819 (23.2)	1,584 (23.7)	0.97 (0.88–1.07)	.54
Myocardial infarction	39 (1.1)	70 (1.1)	1.03 (0.70–1.54)	.87
Peripheral vascular disease	193 (5.5)	321 (4.8)	1.15 (0.96–1.39)	.13
Heart failure	704 (19.9)	1,238 (18.5)	1.10 (0.98–1.22)	.10
Atrial fibrillation	261 (7.4)	389 (5.8)	1.51 (1.20–1.89)	< .001
Diabetes mellitus	1,328 (37.6)	2,112 (31.6)	1.32 (1.21–1.44)	< .001
Hypertension	2,644 (74.8)	4,926 (73.8)	1.08 (0.97–1.21)	.16
COPD	514 (14.5)	1,006 (15.1)	0.97 (0.86–1.09)	.56
Migraine	38 (1.1)	92 (1.4)	0.76 (0.52–1.11)	.16
Chronic liver disease	220 (6.2)	480 (7.2)	0.85 (0.72–1.01)	.06
Renal failure	238 (6.7)	414 (6.2)	1.10 (0.94–1.30)	.24
Comedications, n (%)				
Thiazide diuretics	769 (21.8)	1,418 (21.2)	1.04 (0.94–1.15)	.50
Nonthiazide diuretics	769 (21.8)	1,318 (19.7)	1.14 (1.03–1.26)	.01
Cardioselective β-blockers	513 (14.5)	1,085 (16.2)	0.88 (0.78–0.98)	.03
Non–cardioselective β-blockers	666 (18.8)	1,106 (16.6)	1.16 (1.04–1.29)	.006
CCBs	1,772 (50.1)	3,449 (51.6)	0.94 (0.86–1.02)	.13
ACEIs	1,189 (33.6)	2,090 (31.3)	1.10 (1.01–1.21)	.03
ARBs	778 (22.0)	1,614 (24.2)	0.89 (0.80–0.98)	.02
Statins	470 (13.3)	964 (14.4)	0.91 (0.81–1.03)	.13
Nonstatin antilipemic	148 (4.2)	284 (4.3)	1.00 (0.81–1.23)	.99
Antiplatelets[d]	1,905 (53.9)	3,365 (50.4)	1.16 (1.06–1.26)	.001
Anticoagulants	268 (7.6)	444 (6.7)	1.14 (0.96–1.35)	.12
Antipsychotics	316 (8.9)	482 (7.2)	1.27 (1.10–1.48)	.001
COX-2 selective NSAIDs	209 (5.9)	394 (5.9)	1.00 (0.84–1.20)	.96
Nonselective NSAIDs[d]	1,633 (46.2)	3,272 (49.0)	0.89 (0.82–0.97)	.006
HRT	41 (1.2)	101 (1.5)	0.74 (0.51–1.08)	.12
Prevalent use of antidepressants, n (%)	546 (15.4)	954 (14.3)	1.10 (0.98–1.24)	.10

[a]*P* was obtained by conditional logistic regression.
[b]Matching variables.
[c]The cutoff point was based on the median length of hospital stay.
[d]Low dose (≤ 325 mg/d) and high dose (> 325 mg/d) of aspirin (acetylsalicylic acid) use was categorized as use of antiplatelets and nonselective NSAIDs, respectively.
Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blockers, CCB = calcium channel blockers, COPD = chronic obstructive pulmonary disease, COX-2 = cyclooxygenase 2, HRT = hormone replacement therapy, ICU = intensive care unit, NA = not applicable, NSAID = nonsteroidal anti-inflammatory drugs.

or duration of therapy (Table 3). Nevertheless, cessation of TCAs for 1 to 30 days was associated with an 87% increased risk of recurrent stroke (adjusted OR = 1.87; 95% CI, 1.22–2.86), and the risk was attenuated with a longer period of TCA discontinuation. The risk was also present for TCAs prescribed at a low mean daily dose (adjusted OR = 1.47; 95% CI, 1.23–1.75) or continuously used for ≤ 30 days (adjusted OR = 1.59; 95% CI, 1.28–1.99).

The estimation of NNTH for TCA use pointed out that 39 (95% CI, 24–83), 18 (95% CI, 9–88), 39 (95% CI, 13–529), 34 (95% CI, 21–69), and 27 (95% CI, 16–57) patients needed to be exposed to any use of TCAs, discontinued TCA use for 1–30 days, discontinued TCA therapy for 31–365 days, low-dose TCAs, and short-term use of TCAs, respectively, to cause 1 additional recurrent stroke. These figures were estimated based on the calculated UER as 6.3 per 100 person-years.

Discontinued TCA therapy was consistently observed to increase the risk of recurrent stroke, irrespective of whether different gaps were employed to define discontinued therapy (3-day gap: adjusted OR = 1.67; 95% CI, 1.05–2.65; 7-day gap: adjusted OR = 1.89; 95% CI, 1.08–3.30). The main findings were also robust to the majority of other sensitivity analyses (Figure 2).

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Table 2. Odds Ratios for Stroke Recurrence by Antidepressant Class, Unadjusted and Adjusted for Confounders

	n (%)		OR (95% CI)	
Antidepressant use	Cases (n = 3,536)	Controls (n = 6,679)	Unadjusted	Adjusted[a]
Nonuse of antidepressants	3,027 (85.6)	5,907 (88.4)	1.00 (reference)	1.00 (reference)
SSRIs	89 (2.5)	150 (2.3)	1.17 (0.89–1.53)	1.10 (0.84–1.45)
TCAs	276 (7.8)	367 (5.5)	1.47 (1.25–1.74)	1.41 (1.19–1.67)
Other antidepressants	144 (4.1)	255 (3.8)	1.11 (0.90–1.37)	1.04 (0.84–1.29)

[a]Adjusted for age, length of hospital stay, atrial fibrillation, diabetes mellitus, nonthiazide diuretics, cardioselective β-blockers, noncardioselective β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antiplatelets, antipsychotics, nonselective nonsteroidal anti-inflammatory drugs.
Abbreviations: SSRI = selective serotonin receptor inhibitor, TCA = tricyclic antidepressant.

Table 3. Risk of Stroke Recurrence Associated With Any Use of Different Classes of Antidepressants, Stratified by Recency, Dose, and Duration of Use

	n (%)		OR (95% CI)	
Antidepressant use	Cases (n = 3,536)	Controls (n = 6,679)	Unadjusted	Adjusted[a]
Nonuse of antidepressants	3,027 (85.6)	5,907 (88.4)	1.00 (reference)	1.00 (reference)
SSRIs				
By recency[b]				
Current use	35 (1.0)	68 (1.0)	1.03 (0.68–1.55)	0.96 (0.63–1.46)
Discontinuation 1–30 d	14 (0.4)	22 (0.3)	1.27 (0.64–2.52)	1.15 (0.57–2.29)
Discontinuation 31–365 d	40 (1.1)	60 (0.9)	1.31 (0.87–1.98)	1.26 (0.83–1.91)
By dose				
≤ 0.5 DDD	20 (0.6)	30 (0.5)	1.39 (0.78–2.46)	1.40 (0.79–2.49)
> 0.5 DDD	69 (2.0)	120 (1.8)	1.12 (0.83–1.52)	1.04 (0.76–1.41)
By duration				
≤ 30 d	44 (1.2)	70 (1.1)	1.23 (0.84–1.80)	1.17 (0.79–1.72)
31–90 d	19 (0.5)	38 (0.6)	1.01 (0.58–1.76)	0.96 (0.55–1.68)
≥ 91 d	26 (0.7)	42 (0.6)	1.21 (0.74–1.98)	1.12 (0.68–1.85)
TCAs				
By recency[b]				
Current use	90 (2.6)	133 (2.0)	1.33 (1.01–1.75)	1.26 (0.94–1.65)
Discontinuation 1–30 d	44 (1.2)	44 (0.7)	1.91 (1.26–2.91)	1.87 (1.22–2.86)
Discontinuation 31–365 d	142 (4.0)	190 (2.8)	1.47 (1.17–1.85)	1.41 (1.12–1.78)
By dose				
≤ 0.5 DDD	262 (7.4)	336 (5.0)	1.53 (1.29–1.81)	1.47 (1.23–1.75)
> 0.5 DDD	14 (0.4)	31 (0.5)	0.87 (0.46–1.65)	0.82 (0.43–1.57)
By duration				
≤ 30 d	162 (4.6)	190 (2.8)	1.65 (1.33–2.04)	1.59 (1.28–1.99)
31–90 d	60 (1.7)	95 (1.4)	1.25 (0.90–1.74)	1.17 (0.84–1.64)
≥ 91 d	54 (1.5)	82 (1.2)	1.30 (0.92–1.84)	1.25 (0.88–1.78)
Other antidepressants				
By recency[b]				
Current use	63 (1.8)	115 (1.7)	1.08 (0.79–1.48)	1.02 (0.74–1.40)
Discontinuation 1–30 d	23 (0.5)	31 (0.5)	1.54 (0.89–2.64)	1.43 (0.83–2.47)
Discontinuation 31–365 d	58 (1.6)	109 (1.6)	1.03 (0.74–1.42)	0.96 (0.69–1.33)
By dose				
≤ 0.5 DDD	118 (3.3)	203 (3.0)	1.15 (0.91–1.45)	1.08 (0.85–1.37)
> 0.5 DDD	26 (0.7)	52 (0.8)	0.97 (0.60–1.56)	0.89 (0.55–1.44)
By duration				
≤ 30 d	81 (2.3)	122 (1.8)	1.28 (0.96–1.70)	1.20 (0.90–1.60)
31–90 d	30 (0.9)	61 (0.9)	0.98 (0.63–1.53)	0.93 (0.60–1.46)
≥ 91 d	33 (0.9)	72 (1.1)	0.92 (0.61–1.40)	0.86 (0.56–1.31)

[a]Adjusted for age, length of hospital stay, atrial fibrillation, diabetes mellitus, nonthiazide diuretics, cardioselective β-blockers, noncardioselective β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers; antiplatelets, antipsychotics, nonselective nonsteroidal anti-inflammatory drugs.
[b]Current use was defined as the supplied days of an antidepressant prescription covering the index date.
Abbreviations: DDD = defined daily dose, SSRI = selective serotonin receptor inhibitor, TCA = tricyclic antidepressant.

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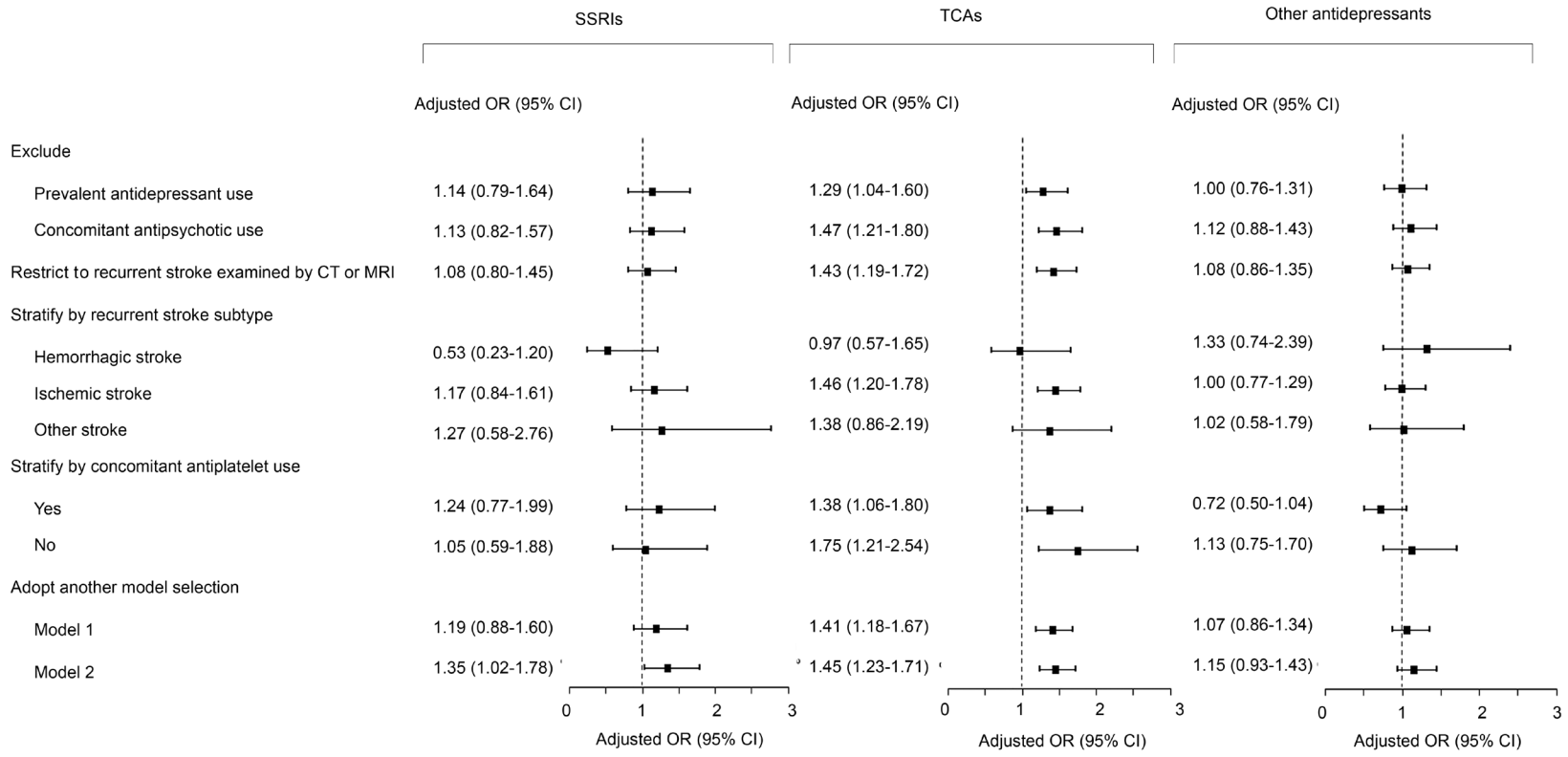
Figure 2. Sensitivity Analyses for the Recurrent Stroke Risk Related to Any Use of Antidepressant Therapy in Different Classes



Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

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Examination of the individual antidepressants revealed that neither all examined individual SSRIs (except paroxetine) nor those in the group of other antidepressants were associated with an increased risk of stroke recurrence (Supplementary eTable 2). Melitracen was associated with the highest risk among TCAs, followed by imipramine.

DISCUSSION

In this large observational nested case-control study of patients surviving a first hospitalization for stroke, we observed a significant 41% increase in recurrent stroke for patients with any use of TCAs ($P < .001$). This risk was particularly increased as TCAs were abruptly discontinued, with an approximate doubling of the risk. Conversely, use of SSRIs or other antidepressants was not found to carry the risk.

Our findings on SSRIs are in line with another study[19] investigating risk of recurrent stroke associated with antidepressants confined to SSRIs. Mortensen et al[19] reported that SSRI use versus nonuse was not related to an increased risk of recurrent stroke in a Danish nationwide cohort study of ischemic stroke patients. However, the reference group, SSRI nonusers, could include TCA users or patients receiving SSRIs in inpatient settings because neither TCA use was measured nor inpatient prescription records were included in the analyzed database. After addressing these limitations and considering different treatment regimens, we consistently observed a null association between SSRIs and stroke recurrence. Despite the reported increased risk of incident stroke related to SSRIs from a meta-analysis[32] of 13 observational studies, SSRI therapy in the subacute phase of poststroke has been found to enhance motor recovery.[33,34] Our nonsignificant findings might be attributable to the balanced adverse and beneficial effects from SSRIs in stroke survivors.

Recently, another Taiwanese study by Lee and colleagues[35] reported that SSRI use was associated with a 33% reduction in the risk of hospitalization for stroke as compared to TCA use among patients with depression or anxiety in a 9-year cohort study. There exist several different attributes in study designs, patients included in the study, and outcomes of interest between Lee and colleagues' study[35] and ours. Despite these inconsistencies, our study provides new types of information that are not available from the previous study.[35] We studied the outcome of stroke recurrence as opposed to examination of incident stroke in the previous study.[35] In addition, the findings of Lee et al[35] on a reduced stroke risk of SSRIs over TCAs could not be interpreted as evidence that SSRI use is devoid of stroke risk, in contrast to the interpretation of our SSRI findings. Furthermore, evidence as to whether the risk of stroke recurrence varied by dose, duration, and discontinuation of antidepressant therapy was additionally provided in our study.

To our knowledge, the current study provides novel evidence suggesting patients exposed to TCAs are at an increased risk of recurrent stroke. Overall, 18 to 39 stroke patients needed to be treated with TCAs to cause an additional stroke recurrence, indicating a high absolute risk of treatment.

Of greater concern is that discontinuation of TCA therapy is associated with an approximately 2-fold increased risk of stroke recurrence. Previous literature[11,14] has highlighted that the most profound risk of first-ever stroke from the examined antidepressant therapy is due to stopping TCA therapy, but in these studies, TCA users who were admitted to hospital for stroke-related events could be identified as discontinued TCA users because inpatient medication records were unavailable. This issue was addressed in our study. There are, however, several alternative explanations for our findings on discontinued TCAs. Patients could have stopped taking TCAs for experiencing atrial fibrillation, a major contributor to stroke,[36] and subsequently suffered a recurrent stroke. Nevertheless, our findings with discontinued TCAs are similar after excluding patients with atrial fibrillation (adjusted OR = 1.79; 95% CI, 1.15–2.81). Alternatively, our findings on discontinued TCA use could be attributed to depression relapse. However, that is unlikely to be the case because all classes of antidepressants exhibit a similar effect on a reduced risk of depressive relapse.[37]

The plausible mechanism underpinning an increased risk of stroke recurrence from discontinued TCA use is unclear. Abrupt cessation of TCAs had previously been reported to cause rebound hypertension and cardiac arrhythmia,[38] which are thought to be mediated through cholinergic overdrive accompanied by secondary adrenergic rebound.[39] It is unclear whether such a mechanism underlies the increased risk of stroke recurrence from TCA discontinuation, which warrants further research.

Continuous use of TCAs for ≤ 1 month but not for longer periods was observed to increase the risk of stroke recurrence in this study, probably reflecting depletion of patients susceptible to stroke recurrence. Similarly, several prior studies have acknowledged the highest risk of incident stroke was observed in patients obtaining 1 to 2 antidepressant prescriptions[13] or in those receiving the shortest duration of antidepressant therapy.[11,14] Patients who were susceptible to stroke recurrence could encounter the stroke events soon after receiving poststroke TCA therapy, which left patients who remained on the therapy and could tolerate the stroke risk.

Our data also indicated that the risk of stroke recurrence associated with TCAs was not present in a dose-dependent manner. Tricyclic antidepressants are generally initiated at a low dose and gradually titrated up to the lowest effective dose because of a greater side-effect burden in high doses and toxicity in overdose.[40–42] This prescribing behavior limited our ability to examine the effect of high-dose TCAs on stroke recurrence. Additionally, the observed increased risk was confined to low-dose TCAs, probably because stroke patients receiving the initial low-dose TCA therapy may have stopped therapy due to a stroke-recurrence event, which left those who tolerated the risk and received higher doses in the maintenance therapy. To examine the suspected

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effect modification, we conducted further stratified analyses by discontinuation and dose of TCA therapy and found that the increased risk by low-dose TCAs existed among only the discontinued TCA users, but not in the current users (current TCA use: adjusted OR = 1.29 [95% CI, 0.97–1.73]; discontinued TCA use for 1–30 days: adjusted OR = 2.24 [95% CI, 1.44–3.50]).

The analysis of the individual antidepressants revealed a class effect of antidepressants on stroke recurrence. Notably, unlike other SSRIs, paroxetine was observed to increase the risk of recurrent stroke in our study. Paroxetine has the highest receptor affinity for both serotonin and norepinephrine transporters among SSRIs,[13,43] which probably can not only increase hemorrhagic stroke risk through depleting platelet serotonin levels but also enhance risk of ischemic stroke by vasoconstricting large cerebral arteries. However, given a wide range of the 95% CI of the OR and the lower 95% CI bound close to 1, our finding on paroxetine might be caused by the small sample size. The findings on the individual antidepressants should be confirmed in a large study.

Collectively, our findings support the use of SSRIs in the treatment of poststroke depression, which is of great clinical importance, especially in the countries where SSRIs are the dominant prescribing antidepressants,[44,45] such as the United States.[44] Selective serotonin reuptake inhibitors are the currently preferred poststroke depression therapy over TCAs because of their safety profile as opposed to the cardiovascular concerns for TCA use.[8] The findings also suggest that health care professionals be aware of a potential risk of recurrent stroke when prescribing TCAs and avoid abrupt cessation of TCA therapy in poststroke patients. More attention needs to be paid especially in the countries where use of TCAs is prevalent,[14,46] such as the United Kingdom.[14] Medical professionals also need to educate stroke patients about complying with TCA therapy and to gradually taper down doses of TCAs if discontinued TCA therapy is required.

Several strengths in this study merit emphasis. First, selection bias was minimized by employing a nested case-control design, supported by the balanced stroke severity indicators between cases and controls. Second, we assessed antidepressant use from comprehensive prescription drug claims, minimizing recall bias and immeasurable time bias. Third, a large nationwide representative population of stroke survivors was resembled, which enhanced the external validity of the main findings. Fourth, our findings were robust based on the results of sensitivity analyses.

Several limitations of this study should be discussed. First, despite the adjustment for proxies of depression severity, confounding by depression cannot be ruled out. However, if this confounder really plays a role, an increased recurrent stroke risk by each class of antidepressants should have been observed. Second, accuracy of the used *ICD-9* codes for the stroke identification was not fully elucidated. Although the coding for ischemic stroke has been validated in Taiwan,[47] the coding of hemorrhagic stroke is uncertain. Nevertheless, 91% of our analyzed hemorrhagic stroke cases had received CT or MRI within 14 days before or after diagnosis. Third, patients with antidepressant prescription records may not actually take the medications, potentially causing an underestimated risk for TCAs. Fourth, some important confounders, such as blood pressure profile, were not available from the LHID. Fifth, this analysis was performed in a Taiwanese stroke population, which may limit the generalizability of our reported results. However, the absence of dramatic differences in the characteristics between our study cohort and stroke patients identified from other countries,[19,48,49] the comprehensive measurement of antidepressants from both outpatient and inpatient visits, and the validated coding for identification of ischemic stroke events might make our results generalizable to other ethnic groups. Sixth, despite controversial literature data,[9,10,13,16] SSRI use is reported to cause bleeding events, including hemorrhagic stroke.[9,13] We did not find an increased risk of hemorrhagic stroke from SSRIs in the sensitivity analysis, which could be attributed to limited hemorrhagic stroke events.

CONCLUSIONS

Stroke patients appear to be at an increased risk of recurrent stroke when receiving TCAs but not SSRIs or other antidepressants. The highest risk occurs after abrupt cessation of TCA therapy. Health care professionals should be vigilant about risk of recurrent stroke when prescribing TCAs or discontinuing TCA therapy in stroke patients.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), doxepin (Silenor and others), duloxetine (Cymbalta and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), milnacipran (Savella), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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Author contributions: Dr Wang and Mr Chu conceived and designed the study; Dr Wang and Mr Chu drafted the manuscript; and Mr Chu and Dr Yeh performed the statistical analyses. Drs Wang and Yeh acquired the database; Drs Wang and Chang obtained the funding; Drs Chang, Yeh, and Malone made critical revisions of the manuscript; Dr Liou interpreted the data and provided the administrative support; and Dr Wang supervised the study.

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Supplementary material: See accompanying pages.

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Supplementary Material

Article Title: Antidepressant Use and Risk of Recurrent Stroke: A Population-Based Nested Case-Control Study

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List of Supplementary Material for the article

1. eTable 1 Diagnosis Codes and NIH Procedure Codes Used to Define the Potential Confounders
2. eTable 2 Association Between Any Use of Antidepressants and Risk of Recurrent Stroke

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Supplementary eTable 1. Diagnosis Codes and NIH Procedure Codes Used to Define the Potential Confounders

Comorbidities	**ICD-9-CM codes**
Ischemic heart disease	411-414
Myocardial infarction	410
Peripheral vascular disease	440-448
Heart failure	428
Atrial fibrillation	427.3
Diabetes mellitus	250
Hypertension	401-405
COPD	491, 492, 496
Migraine	346
Chronic liver disease	571
Renal failure	584-588
Depression	296.2, 296.3, 300.4
Stroke subtype	
Hemorrhagic stroke	430-432
Ischemic stroke	433-435
Other stroke	436, 437
Medical procedures	**NIH Procedure codes**
Admission to an ICU	03010E, 03011F, 03012G, 03013H
Psychotherapy	45010A, 45010C, 45011B, 45012C, 45013A, 45013C, 45014B, 45015C, 45016A, 45016C, 45017B, 45018C, 45019A, 45019C, 45020B, 45021C, 45087C, 45094C, E3025C, E3026C

Abbreviations: COPD = Chronic obstructive pulmonary disease; ICU = intensive care unit; NHI = National Health Insurance.

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Supplementary eTable 2. Association between Any Use of Antidepressants[a] and Risk of Recurrent Stroke

	No. (%)		Odds Ratio (95% Confidence Interval)	
Antidepressant use	**Cases (n=3,536)**	**Controls (n=6,679)**	**Unadjusted**	**Adjusted[b]**
Nonuse of antidepressants	3,027 (85.6)	5,907 (88.4)	1.00 [Reference]	1.00 [Reference]
SSRIs	89 (2.5)	150 (2.3)	1.17 (0.89-1.53)	1.10 (0.84-1.45)
Fluoxetine	26 (0.7)	47 (0.7)	1.09 (0.67-1.78)	1.03 (0.63-1.69)
Sertraline	21 (0.6)	47 (0.7)	0.87 (0.51-1.46)	0.79 (0.46-1.34)
Paroxetine	14 (0.4)	13 (0.2)	2.35 (1.06-5.19)	2.31 (1.04-5.13)
Citalopram	13 (0.4)	17 (0.3)	1.59 (0.76-3.34)	1.50 (0.71-3.19)
TCAs	276 (7.8)	367 (5.5)	1.47 (1.25-1.74)	1.41 (1.19-1.67)
Imipramine	155 (4.4)	209 (3.1)	1.46 (1.18-1.81)	1.41 (1.13-1.76)
Melitracen	61 (1.7)	70 (1.1)	1.73 (1.22-2.45)	1.54 (1.06-2.24)
Amitriptyline	21 (0.6)	42 (0.6)	0.97 (0.57-1.64)	1.00 (0.59-1.71)
Doxepin	16 (0.5)	18 (0.3)	1.71 (0.87-3.36)	1.68 (0.85-3.32)
Other antidepressants	144 (4.1)	255 (3.8)	1.11 (0.90-1.37)	1.04 (0.84-1.29)
Trazodone	106 (3.0)	175 (2.6)	1.20 (0.94-1.54)	1.13 (0.88-1.45)
Moclobemide	19 (0.5)	30 (0.5)	1.20 (0.67-2.15)	1.18 (0.65-2.12)
Venlafaxine	10 (0.3)	19 (0.3)	1.03 (0.48-2.22)	0.93 (0.43-2.02)

[a]Neither all individual antidepressants within each antidepressant class nor combinations of individual antidepressants were evaluated due to the small sample sizes.

[b]Adjusted for age, length of hospital stay, atrial fibrillation, diabetes mellitus, non-thiazide diuretics, cardioselective β-blockers, non-cardioselective β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers; antiplatelets, antipsychotics, non-selective NSAIDs.

Abbreviation: SSRIs = selective serotonin receptor inhibitors; TCAs = tricyclic antidepressants.

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