Using antidepressants and the risk of stroke recurrence: report from a national representative cohort study

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Abstract

Background: Evidence about the association between antidepressants and the risk of stroke recurrence was scanty. This study evaluated the risk of stroke recurrence according to using antidepressants in patients with stroke from a national representative cohort.

Methods: This cohort study followed 16770 patients aged ≥20 years who had an incident stroke from 2000 to 2009 from the National Health Insurance Research Database in Taiwan. Records of each antidepressant prescription were obtained during follow-up. The types of antidepressants were categorized by Anatomical Therapeutic Chemical classification system: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and other antidepressants. The main outcome was a recurrent stroke during the follow-up period. The time-dependent Cox proportional hazards model was used in the analyses.

Results: During 63715 person-years of follow-up, we documented 3769 events for stroke recurrence. Antidepressants use was associated with an increased risk of stroke recurrence (adjusted hazard ratio [HR], 1.42; 95 % confidence interval [C.I.], 1.24–1.62), especially for ischemic stroke (HR, 1.48; 95 % C.I., 1.28–1.70), but not for hemorrhagic stroke (HR, 1.22; 95 % C.I., 0.86–1.73). The increased risk of stroke recurrence was found for TCAs use only (HR, 1.41; 95 % C.I., 1.14–1.74), SSRIs use only (HR, 1.31; 95 % C.I.,1.00–1.73), use of other types of antidepressants only(HR, 1.46; 95 % C.I.,1.15–1.84), or use of multiple types of antidepressants (HR, 1.84; 95 % C.I.,1.04–3.25).

Conclusions: We demonstrated that use of antidepressants was associated with an increased risk of stroke recurrence, especially in ischemic stroke among Taiwanese. Further studies are warranted to confirm the possible underlying mechanisms of these findings.

Background

Stroke is one of the leading causes of adult disability and mortality worldwide, resulting in tremendous socio-economic burden [1, 2]. The recurrence rate of stroke re-admission within one year was 13 % in Taiwan [3]. Compared with incident stroke events, recurrent events were likely to have higher mortality rates, greater levels of disability, and increased costs [4].

Use of antidepressants had positive effect on the management of stroke patients due to the reduction in incidence rate of post-stroke depression [5] and improvement in functional recovery [6, 7], but use of antidepressants also increased side effects [8]. In the cochrane review, the authors concluded that SSRIs might improve recovery after stroke, and that there was heterogeneity between published trials and methodological limitations [9]. Recent epidemiological studies had shown antidepressants use was associated with an increased risk of developing stroke [10]; however, data on stroke recurrence were limited [11, 12]. Moreover, some studies have indicated depression was associated with a higher risk of stroke [13], including recurrent events [11]. The association of fatal stroke in patients with depression who receiving antidepressants was even stronger [14]. The role of depression in the association between antidepressants use and stroke recurrence remains unclear. We used the National Health Insurance Research Database in Taiwan to evaluate...
whether antidepressants use is associated with increased risk of stroke recurrence.

Methods

Data source and study subjects

This cohort study used the Longitudinal Health Insurance Database (LHID), a sub-dataset of National Health Insurance (NHI) Research Database containing healthcare claims between 1996 and 2010 for a cohort of one million people randomly sampled from beneficiaries of NHI. The NHI provides coverage to 99% or more of Taiwanese population. LHID consists of many data files, including inpatient records, ambulatory care records, contracted pharmacies records, and registries for beneficiaries and contracted medical facilities.

Included in this study were patients who had a first hospitalization with diagnosis of stroke during 2000 and 2009. The date of the first hospitalization for stroke was identified as the index date. Stroke was identified by principal diagnosis with ICD-9-CM code (International Classification of Diseases, 9th revision, Clinical Modification codes) 430 to 432 for hemorrhagic stroke and 433 to 437 for ischemic stroke. Those who had any diagnosis of stroke from 1996 to 1999 were excluded to reduce the possibility of including prevalent stroke cases. We further excluded patients who were aged <20 years (N = 91), who had inappropriate data with index date after the date of withdrawing from insurance (N = 293), and patients with recurrent stroke or died within 30 days after index date (N = 2232). Patients who had use of combinations of antidepressants and psycholeptics (amitriptyline-psycholeptics or melitracen-psycholeptics) (N = 1553) or too high dose (>3 DDDs, defined daily doses) (N = 69) during the follow-up period were also excluded. Therefore, the study included 16770 patients with stroke (Fig. 1). This study was approved by the institutional ethics review board at the National Taiwan University Hospital.

Exposure to antidepressants and covariates

For each patient, the records (detail information of drug code by Bureau of National Health Insurance, total dosage and days of use for each prescription) of prescriptions of antidepressants were obtained during the follow-up. The types of antidepressants were categorized by Anatomical Therapeutic Chemical (ATC) classification system [15]: non-selective monoamine reuptake inhibitors (tricyclic antidepressants, TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and other antidepressants. The average dosage for the each prescription of antidepressants per day was calculated. We classified average dose by defined daily doses (DDDs) [15], as defined by the World Health Organization, into <0.5, 0.5–1, and > =1 DDDs.

Other covariates included sex, age, related-disease and prescriptions of other drugs within one year before the index date such as antipsychotics (ATC code: N05A), antithrombotic agents included anticoagulant (ATC code: B01A03) and antiplatelet (ATC code: B01AC06, B01AC04, B01AC05, B01AC23, B01AC07), anti-inflammatory (ATC code: M01A), antidepressants use before stroke (ATC code: N06A), depression (ICD-9-CM code: 296.2, 296.3, 300.4, 311), other mood disorders or (ICD-9-CM code: 296.0, 296.1, 296.4–296.9) anxiety (ICD-9-CM code: 300.0), atrial fibrillation (ICD-9-CM code: 427.3), coronary heart disease (ICD-9-CM code: 410–414), congestive heart failure (ICD-9-CM code: 428), chronic obstructive pulmonary disease (ICD-9-CM code: 490,491,492,493,494,495,496), cancer (ICD-9-CM code: 140–208), diabetes mellitus or medicine treatment (ICD-9-CM code: 250; ATC code: A10), hypertension or medicine treatment (ICD-9-CM code: 401–405; ATC code: C02, C03, C07, C08, C09), and hyperlipidemia or medicine treatment (ICD-9-CM code: 272; ATC code: C10). These variables were all possible confounders between antidepressants and stroke recurrence. The presence of depression during the follow-up was also obtained.

Main outcome

The main outcome was a re-hospitalization with hemorrhagic stroke or ischemic stroke during the follow-up period. The follow-up started from the index
date, which was between 2000 and 2009, and ended on the date of stroke recurrence, the date of withdrawing from insurance, or date of termination of this study, December 31, 2010; whichever came first.

Statistical analyses
Demographic and clinical characteristics between use of antidepressants group (at least one prescription of antidepressants during follow-up) and non-use were compared by the chi-square test. We also divided the type of antidepressants into TCAs, SSRIs, MAOIs, others, or multiple types, as well as dose groups into >0.5, 0.5–1, and > =1 DDDs to perform the descriptive analyses. Because of the time-varying nature of drug use, we defined the duration of antidepressants exposure as days of use for each prescription from database at ambulatory care, and contracted pharmacies, but not at inpatient records because data on days supplied for each prescription were not obtained. We classified the exposure status into "use" during the duration of antidepressants and "non-use" during the days of no prescriptions. We computed their incidence rate (per 1000 person-year) by dividing number of events of recurrent stroke with person-years of exposure to each antidepressant. We used the Simon and Makuchimethod [16] to graphically represent survival curves for time to use of antidepressants by Stata to compute ‘Kaplan-Meier’ estimates for time-dependent covariates [17].

We used univariable and multivariable models to estimate the hazard ratios (HR) and 95 % confidence interval (C.I.) by the Cox proportional hazards model with time-varying antidepressants use to assess the association between each antidepressants use category and recurrent stroke with “non-use” as the reference group and adjusted the models for demographic and clinical characteristics. Moreover, subgroup analyses were performed including antidepressants use before stroke or not (prevalent users, or new users), depression status (no-diagnosed depression, prevalent depression, or post-stroke depression with newly-diagnosed depression), other drugs use, and other disease. Finally, we performed two sensitivity analyses. First, the duration of antidepressants exposure was redefined by adding seven days to the end of days supply for each prescription in order to take into account for the potential carry over effect and gaps in therapies [10]. Second, we added the prescriptions of antidepressants in the inpatient settings. Because the inpatients claims do not contain information on the days supply for medications, we defined the duration of antidepressants exposure using the length of hospital stay. All analyses were carried out with SAS 9.2 and Stata 10. A two-sided p value < 0.05 was considered statistically significant.

Results
Of the 16770 stroke patients with mean age of 67.3 years, 4695 (28 %) were taking any antidepressant during follow-up (median, 3.04 years; interquartile range, 1.31–5.64). Table 1 showed the baseline characteristics of subjects with use of antidepressants compared with those with non-use of antidepressants. Stroke patients with use of antidepressants were more female and ischemic stroke, as well as had a higher prevalence of diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, cancer, depression, anti-inflammatory, anti-thrombotic agents, antipsychotics, and antidepressants use before stroke. Among4695stroke patients with antidepressants use, the most commonly type of antidepressants was TCAs use only (n = 1814 [38 %]) and SSRIs use only (n =661 [14 %]), and MAOIs use only (n = 95 [2 %]) were less common. In dose groups, the group of <0.5 DDDS (50 %) was common, and the proportion of the group of 0.5–1 DDDs and >1 DDDs were 21 % and 28 % respectively.

Figure 2 depicted increased risk of recurrent stroke with antidepressants use. In Cox proportional hazards model with time-varying antidepressants use for the univariate analyses, use of antidepressants was found to have a higher risk of stroke recurrence (HR,1.49;95 % confidence interval [C.I.],1.30–1.70) (Table 2). After controlling for potential confounding variables, use of antidepressants also had a significantly increased risk of stroke recurrence (HR, 1.42; 95 % C.I.,1.24–1.62). A significantly increased risk of stroke recurrence was found with TCAs use only (HR, 1.41; 95 % C.I.,1.14–1.74), SSRIs use only (HR, 1.31; 95 % C.I.,1.00–1.73), other antidepressants use only (HR, 1.46; 95 % C.I.,1.15–1.84), and multiple types use (HR, 1.84; 95 % C.I.,1.04–3.25). We had similar results for the increased risk of recurrent stroke with antidepressants use in different dose groups of <0.5 DDDS (HR, 1.40; 95 % C.I.,1.17–1.67), 0.5–1 DDDs (HR, 1.46; 95 % C.I.,1.10–1.94), and 1 DDDs (HR, 1.43; 95 % C.I.,1.11–1.84). Table 3 summarizes the association between subtype of stroke and antidepressants use category. We found a similar pattern in ischemic stroke recurrence and a non-significantly increased risk of hemorrhagic stroke recurrence.

In subgroup analysis (Table 4), recurrent stroke risk estimates were similar among different depression statuses. The increased risk of recurrent stroke with antidepressants use in prevalent users (HR, 1.23; 95 % C.I.,0.99–1.53) was lower than in new users (HR, 1.57; 95 % C.I.,1.32–1.86). The data provided significant differences (p for interaction = 0.01) in risk between diabetes users (HR, 1.70; 95 % C.I.,1.41–2.05) and non-diabetes users (HR, 1.20; 95 % C.I.,0.99–1.45). The data did not show significant evidence of differences in risk related to other drugs use and other disease. In sensitivity analyses, we
found that the stroke risk was slightly lower but still significant with antidepressants use in duration plus 7 days (HR, 1.33; 95% C.I., 1.17–1.52) and adding inpatient records (HR, 1.19; 95% C.I., 1.05–1.36).

Discussion
This study showed that stroke patients prescribed for antidepressants had 40% greater risk of stroke recurrence. The association was stronger for ischemic stroke than for hemorrhagic stroke. The increased risk was observed in association with prescriptions for antidepressants subclass of TCAs, SSRIs, the group of others, and multiple types. In addition, a higher risk of stroke recurrence with antidepressants among diabetic patients was found.

Table 1 Characteristics of Study Subjects

|                      | Use of Antidepressants (N = 4695, 28%) | Non-use of Antidepressants (N = 12075, 72%) | p-value |
|----------------------|---------------------------------------|---------------------------------------------|---------|
| Sex (Female)         | n=2046 (43.6)                         | n=4806 (39.8)                               | <.001   |
| Age (years)          |                                       |                                             |         |
| 18–44                | 240 (5.11)                            | 797 (6.60)                                  | <.001   |
| 45–54                | 593 (12.6)                            | 1580 (13.1)                                 | <.001   |
| 55–64                | 957 (20.4)                            | 2321 (19.2)                                 | <.001   |
| 64–74                | 1536 (32.7)                           | 3399 (28.1)                                 | <.001   |
| > = 75               | 1369 (29.2)                           | 3978 (32.9)                                 | <.001   |
| Stroke type          |                                       |                                             |         |
| Hemorrhagic stroke   | 761 (16.2)                            | 2493 (20.6)                                 | <.001   |
| Ischemic stroke      | 3934 (83.8)                           | 9582 (79.4)                                 | <.001   |
| Antipsychotics       | 1515 (32.3)                           | 3338 (27.6)                                 | <.001   |
| Antithrombotic agents|                                       |                                             |         |
| anticoagulant        | 133 (2.83)                            | 395 (3.27)                                  | 0.14    |
| antiplatelet         | 3130 (66.7)                           | 7240 (60.0)                                 | <.001   |
| Anti-inflammatory     | 3970 (84.6)                           | 9354 (77.5)                                 | <.001   |
| Antidepressants use before index date | 1617 (34.4) | 964 (7.98) | <.001 |
| Depression           | 397 (8.46)                            | 176 (1.46)                                  | <.001   |
| Anxiety or other mood disorders* | 354 (7.54) | 449 (3.72) | <.001 |
| Atrial fibrillation  | 302 (6.43)                            | 935 (7.74)                                  | 0.004   |
| Coronary heart disease | 1065 (22.7) | 2534 (21.0) | 0.016 |
| Congestive heart failure | 317 (6.75) | 959 (7.94) | 0.009 |
| Chronic obstructive pulmonary disease | 804 (17.1) | 1912 (15.8) | 0.042 |
| Cancer               | 59 (1.26)                             | 88 (0.73)                                   | <.001   |
| Diabetes mellitus†   | 1775 (37.8)                           | 4120 (34.1)                                 | <.001   |
| Hypertension†        | 4210 (89.7)                           | 10724 (88.8)                                | 0.11    |
| Hyperlipidemia†      | 1673 (35.6)                           | 3765 (31.2)                                 | <.001   |

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*Other mood disorders included manic disorder, bipolar disorder or anxiety  
†A patient was identified as having these comorbidities if he or she had a ICD-9-CM diagnosis code of that comorbidity on outpatient or inpatient claims, or a prescription for its medications, i.e., antidiabetic medications for diabetes, antihypertensives for hypertension, and antihyperlipidemic agents for hyperlipidemia.
Few epidemiological studies have reported the association between antidepressants use and risk of stroke recurrence. A study in China found an elevated risk of recurrent stroke after 1-year follow-up in antidepressants users, but the association was statistically non-significant, partly because of small sample size (RR, 1.96; 95% CI, 0.95–4.04) [11]. Another study in Denmark using propensity score–matching analysis focused on SSRI use [12]. SSRI exposure was associated with statistically non-significant lower risk of recurrence of ischemic stroke (RR, 0.67; 95% CI, 0.44–1.02), and non-significantly higher risk of intracranial bleedings (RR, 1.14; 95% CI, 0.62–2.12) [12]. The discrepancy in findings among these studies and ours may reflect different methodology among studies, including differences in patient populations, reported type of stroke, and methods of data analysis. We used Cox models with antidepressant exposure as time-dependent covariates to take into account for switch between classes of antidepressants and use to non-use. The actual number of days prescribed was the days of exposure in our analysis. However, all drugs in the Denmark study were included as time-dependent variables with an assumed average prescription length of 90 days. The extent of drug exposure in their study might be different from that in ours. A cochrane review [9] has concluded that SSRIs might improve recovery after stroke. However, different from our study, the outcomes assessed in the review were neurological impairment or depression after stroke, but not stroke recurrence. Furthermore, the authors of the review found high heterogeneity between trials and methodology limitations in these trials. Well-designed trials are needed before a firm conclusion can be made.

The biological mechanisms have been proposed for the association between antidepressants and stroke. Antidepressant drugs inhibit the re-uptake receptors or the activity of metabolic enzymes, thereby increasing the concentration of serotonin, which induces local vasoconstriction and increases risk of ischemic stroke [18, 19]. In contrast, evidence also revealed that antidepressants may inhibit platelet activity and aggregation, thereby preventing ischemic events [20–22]. This mechanism also could explain the underlying association between antidepressants and the increased risk of bleeding. However, epidemiological studies showed inconclusive results in the association between antidepressants and risk of hemorrhagic stroke [23–26]. A study of meta-analysis reported increased risk of brain hemorrhage associated with SSRIs [23], whereas other studies, in line with our analysis, suggested no increased risk [24–26]. Of note, different from previous studies, our analysis focused on risk of recurrent stroke. More investigations with stroke recurrence as the primary end point are required to confirm our findings.

Our study showed that the greater risk of stroke recurrence with antidepressants in patients with diabetes. Diabetes patients with antidepressants had poor adherence with medication [27], which was associated with adverse outcomes such as higher glycosylated hemoglobin, systolic and diastolic blood pressure, and low-density lipoprotein cholesterol levels [28]. The risk of stroke recurrence associated with antidepressants use did not change materially in the analysis stratified by depression statuses. The indication for antidepressants was not only for the treatment of mood disorders but also for patients with various anxiety disorders and off-label

### Table 2 The Risk of Stroke Recurrence in association with Antidepressants

| Dose Group* | N for Stroke Recurrence/Person-years | Rate per 1000 Person-Years | Crude HR (95 % CI) Adjusted HR* (95 % CI) |
|-------------|-------------------------------------|---------------------------|------------------------------------------|
| Non-use of Antidepressants | 3532/59400 | 69.5 | 1 | 1 |
| Use of Antidepressants | 237/2440 | 97.1 | 1.49 (1.30, 1.70) | 1.42 (1.24, 1.62) |
| Type of Antidepressants | | | |
| TCAs only | 88/910 | 96.8 | 1.48 (1.20, 1.83) | 1.41 (1.14, 1.74) |
| SSRIs only | 53/617 | 86.0 | 1.38 (1.05, 1.81) | 1.31 (1.00, 1.73) |
| MAOIs only | 10/91 | 110.4 | 1.45 (0.78, 2.70) | 1.41 (0.76, 2.63) |
| Others only | 74/732 | 101.1 | 1.53 (1.22, 1.93) | 1.46 (1.15, 1.84) |
| Multiple types | 12/91 | 132.4 | 1.93 (1.09, 3.40) | 1.84 (1.04, 3.25) |
| Dose Group* | | | |
| <0.5 DDDs | 126/1294 | 97.4 | 1.47 (1.23, 1.75) | 1.40 (1.17, 1.67) |
| 0.5–1 DDDs | 48/492 | 97.6 | 1.54 (1.16, 2.05) | 1.46 (1.10, 1.94) |
| > = 1 DDDs | 63/654 | 96.4 | 1.50 (1.17, 1.92) | 1.43 (1.11, 1.84) |

*HR indicates hazard ratio; 95% CI: 95% confidence interval  
*Dose Group = The Average Dose of the Prescriptions for Antidepressants per day/Defined Daily Dose; unit: DDDs  
*Adjusted for sex, age group, stroke type of the first hospitalization, antipsychotics, antithrombotic agents, anticoagulant, antiplatelet, antidepressant drugs use before stroke, depression, anxiety or other mood disorders, atrial fibrillation, coronary heart disease, congestive heart failure, COPD, cancer, diabetes mellitus or medicine treatment, hypertension or medicine treatment, hyperlipidemia or medicine treatment
|                  | Ischemic Stroke |                  |                  |                  | Hemorrhagic Stroke |                  |                  |                  |
|-----------------|----------------|-----------------|-----------------|-----------------|-------------------|-----------------|-----------------|-----------------|
|                  | Number of Recurrent Stroke/Person-years | Rate per 1000 Person-Years | Crude HR | (95 % CI) | Adjusted HR \(^a\) | (95 % CI) | Number of Recurrent Stroke/Person-years | Rate per 1000 Person-Years | Crude HR | (95 % CI) | Adjusted HR \(^a\) | (95 % CI) |
| Non-use of Antidepressants | 3012/61194 | 49.2 | 1 | 1 | 681/68749 | 9.9 | 1 | 1 |
| Use of Antidepressants | 217/2521 | 86.1 | 1.58 | (1.38, 1.82) | 1.48 | (1.28, 1.70) | 35/3098 | 11.3 | 1.10 | (0.78, 1.54) | 1.22 | (0.86, 1.73) |

Type of Antidepressants

| Type of Antidepressants | | | | | | | | |
|-------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| TCAs only | 83/930 | 945.2 | 1.64 | (1.32, 2.04) | 1.53 | (1.23, 1.90) | 12/1113 | 10.8 | 1.03 | (0.58, 1.83) | 1.08 | (0.61, 1.91) |
| SSRIs only | 49/653 | 649.7 | 1.46 | (1.10, 1.93) | 1.34 | (1.01, 1.79) | 8/794 | 10.1 | 1.03 | (0.51, 2.06) | 1.23 | (0.61, 2.48) |
| MAOIs only | 8/93 | 92.6 | 1.36 | (0.68, 2.72) | 1.24 | (0.62, 2.49) | 2/111 | 18.0 | 1.53 | (0.38, 6.11) | 2.15 | (0.54, 8.68) |
| Others only | 11/92 | 761.1 | 1.59 | (1.24, 2.03) | 1.50 | (1.17, 1.92) | 10/963 | 10.4 | 1.01 | (0.54, 1.88) | 1.12 | (0.60, 2.10) |
| Multiple types | 66/756 | 922.2 | 2.06 | (1.14, 3.73) | 1.95 | (1.08, 3.54) | 3/117 | 25.7 | 2.51 | (0.81, 7.80) | 2.78 | (0.39, 8.68) |

Dose Group\(^*\)

| Dose Group | | | | | | | | |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <0.5 DDDs | 116/1322 | 87.7 | 1.58 | (1.31, 1.90) | 1.49 | (1.23, 1.79) | 16/1638 | 9.8 | 0.93 | (0.57, 1.53) | 1.00 | (0.61, 1.64) |
| 0.5–1 DDDs | 46/502 | 91.7 | 1.73 | (1.29, 2.31) | 1.59 | (1.19, 2.13) | 6/617 | 9.7 | 0.97 | (0.44, 2.18) | 1.11 | (0.50, 2.49) |
| > = 1 DDDs | 55/697 | 78.9 | 1.48 | (1.13, 1.93) | 1.37 | (1.05, 1.80) | 13/844 | 15.4 | 1.53 | (0.89, 2.66) | 1.81 | (1.04, 3.16) |

HR indicates hazard ratio; 95 % CI: 95 % confidence interval

\(^a\) Adjusted for sex, age group, stroke type of the first hospitalization, antipsychotics, antithrombotic agents, anticoagulant, antiplatelet, antidepressant drugs use before stroke, depression, anxiety or other mood disorders, atrial fibrillation, coronary heart disease, congestive heart failure, COPD, cancer, diabetes mellitus or medicine treatment, hypertension or medicine treatment, hyperlipidemia or medicine treatment.
use such as sleep disorder, chronic pain [29]. Although
the increased risk of recurrent stroke with antidepressants
use in prevalent users was lower but non-significant than in new users, the reduction in the risk
with long-term drug users might happened [30] with
the attrition for susceptible people [31]. We did not ob-
serve dose–response relationship between antidepressants
use and stroke recurrence.

The strengths of our study included a large population-
based follow-up study and the integrated details of pre-
scription records such as the drug used, dosages, days of
supply dispensed from database. However, our study had
several potential limitations. First, the history of stroke
prior to 1996 was unknown, but patients with any record
of stroke before 1999 were excluded to reducing misclassi-
ﬁed as an incident case. Second, the validity of diagnosis
of stroke and the recording of prescription in database
may influence our results, even the accuracy of recording
stroke diagnoses and prescriptions in NHIRD was high
[32]. Third, the data of antidepressants use in admission
were excluded due to no information of the duration of
use for each prescription from inpatient records. We used
the length of stay for each admission as an estimate for
duration of antidepressants exposure, and we found the
association weakened but remained statistically signiﬁcant.
Fourth, we not only lacked for lifestyle information such
as weight, drinking, or smoking status, but also for any
data on stroke location or severity. Fifth, we were unable
to assess the adherence of the antidepressants be-
cause the information is not available in the claims
database. Poor adherence to antidepressant treatment
may lead to misclassiﬁcation of exposures resulting in
under-estimation of the drug effect. Sixth, misclassiﬁca-
tion of depression might occur if a patient did not seek
medical care for his or her depressive disorders or if
diagnostic codes were accurate. In our analysis, depression
was treated as a confounder in multivariable analysis.
Misclassiﬁcation of depression may result in residual
confounding. Finally, we cannot draw conclusions on
causal association from our analysis, as this is an obser-
vational study. This study was national representative
and population-based. The results can be generalizable
to populations in Chinese ethnicity.

Conclusions

We found that use of antidepressants was associated
with an increased risk of stroke recurrence, especially
for ischemic stroke. TCAs, SSRIs, the group of others,
or multiple types users had increased risk of stroke recur-
rence. In addition, a higher risk associated with antidepressants
was observed in patients with diabetes. Although those patients had low dosage of antidepressants, the
closely monitoring the side effects was necessary, particularly for diabetes patients.

Table 4 The Risk of Stroke Recurrence in association with Antidepressants in Subgroup of Other Drugs Use and Comorbidities

| Variable                                      | Adjusted HR* | (95% CI)   |
|-----------------------------------------------|--------------|------------|
| Without antipsychotics                        | 1.40         | (1.18, 1.66) |
| With antipsychotics                           | 1.45         | (1.16, 1.82) |
| Without anticoagulant                         | 1.44         | (1.25, 1.65) |
| With anticoagulant                            | 1.24         | (0.76, 2.00) |
| Without antiplatelet                          | 1.41         | (1.23, 1.62) |
| With antiplatelet                             | 1.52         | (0.72, 3.22) |
| Without anti-inflammatory                     | 1.29         | (0.90, 1.85) |
| With anti-inflammatory                        | 1.44         | (1.24, 1.67) |
| Without anxiety or other mood disorders       | 1.40         | (1.07, 1.82) |
| With anxiety or other mood disorders          | 1.42         | (1.21, 1.66) |
| Without atrial fibrillation                   | 1.40         | (1.22, 1.62) |
| With atrial fibrillation                      | 1.57         | (0.98, 2.50) |
| Without coronary heart disease                | 1.36         | (1.16, 1.60) |
| With coronary heart disease                   | 1.59         | (1.24, 2.05) |
| Without congestive heart failure              | 1.44         | (1.25, 1.65) |
| With congestive heart failure                 | 1.15         | (0.68, 1.97) |
| Without chronic obstructive pulmonary disease | 1.49         | (1.29, 1.73) |
| With chronic obstructive pulmonary disease    | 1.09         | (0.77, 1.54) |
| Without cancer                                | 1.42         | (1.24, 1.63) |
| With cancer                                   | 1.04         | (0.26, 3.32) |
| Without diabetes mellitus                     | 1.20         | (0.99, 1.45) |
| With diabetes mellitus*                       | 1.70         | (1.41, 2.05) |
| Without hypertension                          | 1.25         | (0.69, 2.27) |
| With hypertension                             | 1.42         | (1.24, 1.64) |
| Without hyperlipidemia                        | 1.41         | (1.18, 1.68) |
| With hyperlipidemia                           | 1.42         | (1.15, 1.76) |

Antidepressants use before index date

| Type                  | HR  | (95% CI)   |
|-----------------------|-----|------------|
| No–New Users          | 1.57| (1.32, 1.86) |
| Yes–Prevalent Users   | 1.23| (0.99, 1.53) |

Depression at Baseline (index date) or Post-stroke

| Type                  | HR  | (95% CI)   |
|-----------------------|-----|------------|
| No Depression         | 1.55| (1.32, 1.82) |
| Depression at Baseline| 1.49| (0.99, 2.26) |
| Post-stroke Depression| 1.44| (1.01, 2.07) |

HR indicates hazard ratio; 95% confidence interval
*p-value for the interaction term of diabetes was 0.01, and that of other
variables were all >0.05

*Adjusted for sex, age group, stroke type of the ﬁrst hospitalization,
antipsychotics, antithrombotic agents, anticoagulant, antiplatelet,
antidepressant drugs use before stroke, depression, anxiety or other mood
disorders, atrial fibrillation, coronary heart disease, congestive heart failure,
COPD, cancer, diabetes mellitus or medicine treatment, hypertension or
medicine treatment, hyperlipidemia or medicine treatment

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Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
HT1 conceptualized the study, conducted the data analysis, interpreted the data, and drafted and revised the manuscript. PCC participated in conception and design, contributed to acquisition of the data, supervised the data analysis, and critically revised the manuscript. KLC participated in conception and design, supervised data analysis, interpreted the data, and contributed to drafting and revising the manuscript. All authors read and approved the final manuscript.

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