Comparison of the Effects of Serotonin-Norepinephrine Reuptake Inhibitors Versus Selective Serotonin Reuptake Inhibitors on Cerebrovascular Events

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ABSTRACT

Background: Use of selective serotonin reuptake inhibitors (SSRIs) has been associated with an increased risk of intracranial hemorrhage. However, little is known about cerebrovascular risk in users of serotonin-norepinephrine reuptake inhibitors (SNRIs). Our aim was to determine the differential risk of cerebrovascular events between SSRIs and SNRIs.

Method: A nationwide population-based cohort study was conducted in adult patients who started taking SSRIs or SNRIs during the time period 2005 through 2009. The outcome of interest was defined by the first hospitalization diagnosis for ischemic stroke (*ICD-9-CM* codes 433, 434, 436) or intracranial hemorrhage (*ICD-9-CM* codes 430, 431, 432). We used a Cox regression model with time-varying medication use and adjusted for stroke risk factors to estimate the hazard ratios (HRs) of ischemic stroke and intracranial hemorrhage associated with SNRI use, using SSRI use as a reference.

Results: Among 582,650 SSRI and 76,920 SNRI initiators with an average follow-up period of 3.2 years, there was a nonsignificantly increased trend toward intracranial hemorrhage (adjusted HR = 1.24 [95% CI, 0.97–1.58]) in SNRI users compared to SSRI users. The risk of ischemic stroke was comparable between the 2 treatment groups (adjusted HR = 1.01 [0.90–1.12]). Similar results were obtained in sensitivity analyses, considering a dose-response relation, allowance of a 7-day grace period between study drug discontinuation and outcome occurrence, and restriction to exclusive users, who remained on the initial treatment. In the subgroup analysis, there was an increased incidence of intracranial hemorrhages in SNRI users compared to SSRI users in patients without prior depression (adjusted HR = 1.63 [1.14–2.32]).

Conclusions: Use of SNRIs is not associated with an increased risk of either ischemic stroke or intracranial hemorrhage as compared to use of SSRIs in adult patients with depression or anxiety. However, SNRIs should be used cautiously in patients without depression.

J Clin Psychiatry 2016;77(1):e1–e7
dx.doi.org/10.4088/JCP.14m09394

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Depression is a highly prevalent neuropsychiatric disorder with a lifetime prevalence of more than 16% in the general population.[1] Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the most frequently prescribed medications for treatment of depression and general anxiety disorder.[2,3] Depression per se is associated with an increased risk of stroke,[4] one of the leading causes of death and permanent disability in the world, which results in significant economic burden on society.[5] Recently, the use of antidepressants, especially serotonergic drugs, has garnered attention due to their potential impacts on the risks of both ischemic stroke and intracranial hemorrhages.[6,7]

A recent study showed that the use of SSRIs may increase the incidence of intracranial hemorrhage.[8] SNRIs, a relatively new class of antidepressants, are increasingly used to treat depression and anxiety disorders[3]; however, little is known about the risk of stroke. Mechanistically, both SSRIs and SNRIs block serotonin transporter, reduce the intracellular concentration of serotonin in platelets, inhibit platelet aggregation, and thus increase the risk of intracerebral hemorrhage.[9] Given that SNRIs increase norepinephrine levels in neuronal synapses, resulting in elevated norepinephrine concentrations compared to SSRIs,[10] it was hypothesized that these unique pharmacodynamic characteristics of SNRIs might have an impact on the sympathetic cardiovascular system and affect the cerebrovascular risk. Given that both depression and anxiety are known risk factors for stroke,[4,11] comparing SNRI users with nonusers is subject to confounding by indication. Thus, we conducted a population-based cohort study to investigate the differential risks of SNRIs and SSRIs for ischemic stroke and intracranial hemorrhages in new users of these 2 medications, using SSRI users as the reference group.

METHOD

Data Source

A single-payer and compulsory national health insurance program was implemented in Taiwan in 1995, and there was 99% enrollment by 2010. The Taiwan National Health Insurance (NHI) database includes complete outpatient visits, hospital admissions, prescriptions, as well as the disease and vital statuses for 99% of the country's population (approximately 23 million). The current analyses linked

Clinical Points

- Recent studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) may increase the incidence of intracranial hemorrhage. However, little is known about the risk of stroke for users of serotonin-norepinephrine reuptake inhibitors (SNRIs), an increasingly prescribed new class of antidepressant.
- With regard to the risk of ischemic stroke or intracranial hemorrhage, SNRIs were comparable with SSRIs in adult patients with either depression or anxiety.

several large computerized claim datasets with the National Death Registry through the use of birth dates and the civil identification number unique to each beneficiary. Written consent from study subjects was not obtained because the NHI dataset consists of deidentified secondary data for research purposes, and the Institutional Review Board of National Taiwan University Hospital issued a formal written waiver for the need for consent.

Study Population

From the source population, we identified adult patients aged over 20 years who initiated treatment with an SNRI or SSRI between January 1, 2005, and December 31, 2009. *Initiation* was defined as not receiving treatment with any studied medication for 12 months prior to the first prescription (index date). Subjects were excluded if they (1) were without continuous insurance coverage for 12 months before the index date, (2) received both an SNRI and an SSRI on the index date, (3) had a prior history of head injury, or (4) had been diagnosed with ischemic stroke or intracranial hemorrhage before the index date.

Use of Study Drugs

The exposure drugs of interest in this study included SSRIs (paroxetine, sertraline, fluoxetine, citalopram, escitalopram, fluvoxamine) and SNRIs (venlafaxine, duloxetine, milnacipran) (the Anatomical Therapeutic Chemical [ATC] codes are provided in Supplementary eTable 1). The outpatient pharmacy prescription database was used to obtain prescribed drug types, dosages, dates of prescriptions, supply days, and total numbers of pills dispensed. We defined *discontinuation of therapy* if no medication refill was available. Due to possible drug switching during the follow-up period, exposure to study medications was treated as a time-varying factor in the analysis. For each patient, the mean daily dose was estimated by multiplying the cumulative number of pills dispensed by the dose prescribed, divided by the follow-up duration. Data were presented as the number of defined

Table 1. Baseline Characteristics Among Initiators of SSRIs and SNRIs

	SSRIs (n = 582,650)	SNRIs (n = 76,920)
Patient characteristics		
Age at initiation, mean ± SD, y	48.59 (17.75)	47.60 (16.80)
Male, n (%)	215,544 (36.99)	28,694 (37.30)
Initiation year, n (%)		
2005	124,813 (21.42)	14,565 (18.94)
2006	118,303 (20.30)	15,012 (19.52)
2007	116,641 (20.02)	16,118 (20.95)
2008	111,946 (19.21)	15,719 (20.44)
2009	110,944 (19.04)	15,506 (20.16)
Comorbidities, n (%)		
Diabetes mellitus	67,953 (11.66)	8,901 (11.57)
Hypertension	139,013 (23.86)	16,783 (21.82)
Cardiovascular disease	61,393 (10.54)	7,012 (9.12)
Ischemic heart disease	51,604 (8.86)	6,149 (7.99)
Myocardial infarction	3,816 (0.65)	426 (0.55)
Angina	27,639 (4.74)	3,390 (4.41)
Arrhythmia	40,403 (6.93)	4,829 (6.28)
Atrial fibrillation	7,010 (1.20)	790 (1.03)
Heart failure	16,352 (2.81)	1,812 (2.36)
Transient cerebral ischemia	11,643 (2.00)	1,401 (1.82)
Migraine	16,705 (2.87)	2,812 (3.66)
Peripheral arterial occlusion disease	8,048 (1.38)	1,069 (1.39)
Chronic liver disease	46,368 (7.96)	6,473 (8.42)
Chronic lung disease	68,846 (11.82)	9,030 (11.74)
Chronic kidney disease	25,457 (4.37)	3,131 (4.07)
Rheumatoid arthritis	18,789 (3.22)	2,972 (3.86)
Osteoarthritis	83,234 (14.29)	11,048 (14.36)
Osteoporosis	23,010 (3.95)	2,966 (3.86)
Gastritis or peptic ulcer disease	196,673 (33.75)	26,234 (34.11)
Cancer	23,157 (3.97)	3,775 (4.91)
Gout	29,177 (5.01)	3,781 (4.92)
Thyroid disease	14,397 (2.47)	2,043 (2.66)
Seizure	8,214 (1.41)	1,233 (1.60)
Dementia	16,868 (2.90)	1,902 (2.47)
Depressive disorder	380,368 (65.28)	55,957 (72.75)
Anxiety disorder	260,760 (44.75)	35,828 (46.58)
Psychotic disorder	29,236 (5.02)	3,617 (4.70)
Bipolar disorder	21,163 (3.63)	3,002 (3.90)
Medication use, n (%)		
Nonselective NSAIDs	447,397 (76.79)	59,624 (77.51)
COX-2 selective NSAIDs	29,625 (5.08)	4,684 (6.09)
ACE inhibitors	50,964 (8.75)	5,762 (7.49)
Angiotensin receptor blockers	47,914 (8.22)	6,226 (8.09)
β-blockers	171,022 (29.35)	22,062 (28.68)
Calcium channel blockers	125,516 (21.54)	15,061 (19.58)
Diuretics	77,623 (13.32)	9,282 (12.07)
Other antihypertensive agents	33,019 (5.67)	3,825 (4.97)
Insulin	7,713 (1.32)	1,145 (1.49)
Sulfonylurea	41,568 (7.13)	5,328 (6.93)
Metformin	40,992 (7.04)	5,337 (6.94)
Thiazolidinediones	8,954 (1.54)	1,298 (1.69)
Glinides	6,691 (1.15)	901 (1.17)
α-Glucosidase inhibitor	9,781 (1.68)	1,289 (1.68)
Anticoagulants	4,242 (0.73)	553 (0.72)
Nonaspirin antiplatelet agents	110,102 (18.90)	13,477 (17.52)
Aspirin	103,222 (17.72)	12,853 (16.71)
Histamine-2 receptor antagonists	168,026 (28.84)	21,212 (27.58)
Proton pump inhibitors	49,055 (8.42)	7,443 (9.68)
Nitrates	42,185 (7.24)	5,025 (6.53)
Statins	47,496 (8.15)	6,328 (8.23)
Fibrates	18,504 (3.18)	2,367 (3.08)
Antiarrhythmic agents	11,347 (1.95)	1,366 (1.78)
Digoxin	8,588 (1.47)	918 (1.19)
Estrogen	38,947 (6.68)	5,594 (7.27)
First-generation antipsychotics	75,577 (12.97)	10,551 (13.72)
Second-generation antipsychotics	24,404 (4.19)	3,460 (4.50)
Tricyclic antidepressants	50,647 (8.69)	8,432 (10.96)
Anxiolytics	349,546 (59.99)	47,640 (61.93)
Dopaminergic agents	20,553 (3.53)	2,748 (3.57)
Antiepileptics	77,128 (13.24)	13,406 (17.43)
Thyroid therapy	11,393 (1.96)	1,554 (2.02)
Antigout preparations	34,371 (5.90)	4,368 (5.68)

(continued)

Table 1 (continued). Baseline Characteristics Among Initiators of SSRIs and SNRIs

	SSRIs (n = 582,650)	SNRIs (n = 76,920)
Resource utilization, mean ± SD		
Total no. of outpatient visits	22.63 (20.97)	23.00 (21.22)
Total no. of outpatient visits due to cardiovascular-related disease	3.29 (6.48)	3.01 (6.28)
Total no. of outpatient visits due to depression-related disease	0.63 (2.50)	0.88 (2.95)
Total no. of hospitalizations	0.38 (1.02)	0.43 (1.12)
Total no. of hospitalizations due to cardiovascular-related disease	0.14 (0.59)	0.14 (0.58)
Total no. of hospitalizations due to depression-related disease	0.02 (0.19)	0.04 (0.24)

Abbreviations: NSAID = nonsteroidal anti-inflammatory drug, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

daily doses (DDD), which was established by an expert panel as the typical maintenance dose required when the drug is used for its main indication in an adult. The DDD values for individual drugs of SSRIs and SNRIs are 10 mg for escitalopram; 20 mg for paroxetine, fluoxetine, and citalopram; 50 mg for sertraline; 60 mg for duloxetine; and 100 mg for fluvoxamine, venlafaxine, and milnacipran.

Outcome Ascertainment and Follow-Up

The outcome of interest was defined by the first hospitalization diagnosis for ischemic stroke (*ICD-9-CM* code 433, 434, 436) or intracranial hemorrhage (*ICD-9-CM* code 430, 431, 432). Validation studies in Taiwan have shown that the *ICD-9* diagnosis codes used to identify patients with ischemic strokes had a positive predictive value as high as 98%.[12,13] Also, a systematic review of published reports suggested that algorithms to evaluate the presence of ischemic stroke and intracranial hemorrhage had high positive predictive values (80% or greater).[14] In addition to *ICD-9-CM* codes, we also used the following criteria to increase outcome accuracy: (1) a record of computed tomography or magnetic resonance imaging of the brain during hospitalization and (2) a certificate for stroke. The Bureau of Taiwan NHI issues certificates to patients who suffer from major illnesses/injuries, including acute ischemic stroke and intracranial hemorrhage. This criterion was required in our study to increase the accuracy of the outcome definition.

Furthermore, we conducted a validation study by randomly sampling records of 226 hospitalized patients at 1 medical center with the above mentioned criteria. Their medical records were then reviewed by a physician (Y.-C.L.). The positive predictive value was 93.8% using these criteria, confirming the diagnostic accuracy of our algorithm.

Patients were followed from the index date to the earliest of the following: outcome occurrence, death, disenrollment from the NHI, or December 31, 2010.

Covariate Ascertainment and Propensity Score Adjustment

Inpatient and outpatient diagnosis files and prescription files during the 12-month period before the index date were used to ascertain patients' demographic data (including age, sex, and resource utilization [eg, number of outpatient visits and number of hospitalizations] 12 months prior to the index date), medical history (*ICD-9-CM* codes provided in Supplementary eTable 1), and medications (ATC codes provided in Supplementary eTable 1). All variables including demographic data, medical and psychiatric comorbidities, medications, and medical resource utilization (Table 1) were incorporated into a nonparsimonious logistic regression model. The probability of being treated with SNRIs, that is, the propensity score, was estimated and used to adjust for baseline differences between the 2 treatment groups in the subsequent analyses.

Statistical Analysis

The descriptive data of the baseline characteristics among initiators of SNRIs and SSRIs were summarized. Person-days of follow-up were computed for all patients in the cohort for each drug use category. The crude incidence rates for ischemic stroke and intracranial hemorrhage were calculated and their 95% confidence intervals (CIs) were estimated based on a Poisson distribution.

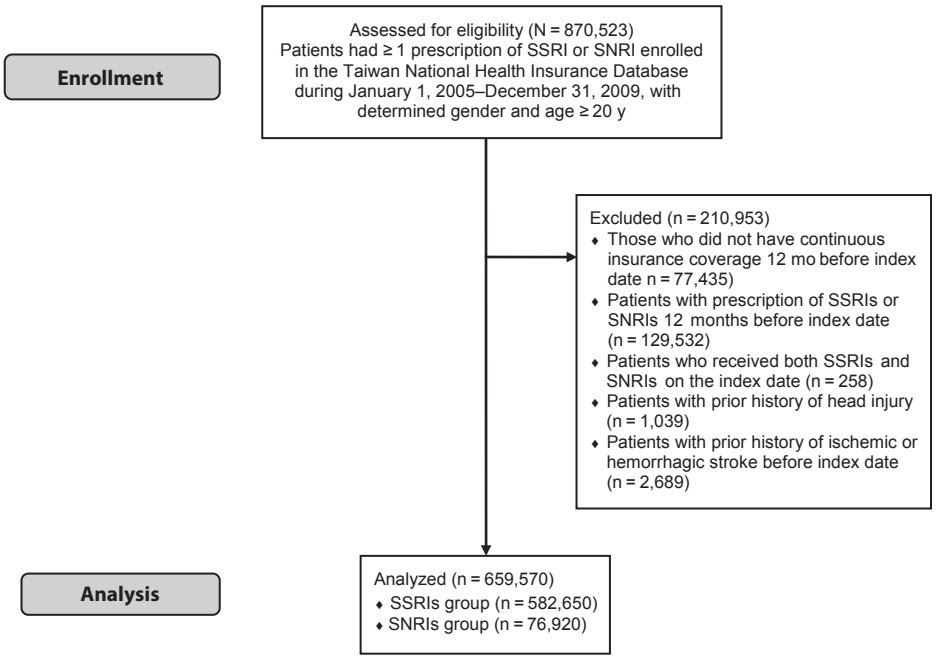
A Cox proportional hazards regression model, stratified by baseline propensity score quintiles, was used to calculate the hazard ratios (HRs) of ischemic stroke or intracranial hemorrhage and their 95% CIs using SSRIs as the reference group. Separate models were conducted to estimate the HR of ischemic stroke and intracranial hemorrhage.

In the sensitivity analyses testing of the robustness of our results, we investigated whether effect estimates changed substantially by (1) adjusting for mean daily dosage (≥ 0.5 or < 0.5 DDD) estimated from the first SNRI or SSRI prescription; (2) allowing a grace period of 7 days between study drug discontinuation and outcome occurrence; and (3) restricting to exclusive users who remained on the initial treatment. Meanwhile, stratified analyses were performed to evaluate potential effect modifications. Participants were further stratified according to (1) age (< 60 or ≥ 60 years), (2) sex, (3) the presence/absence of hypertension, and (4) the presence/absence of a depressive disorder. Confidence intervals between subgroups were compared, and a significant interaction was suggested if they did not overlap. A 2-sided P value < .05 was considered statistically significant. All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 582,650 SSRI initiators and 76,920 SNRI initiators were included in the analysis (Figure 1). As shown in Table 1, initiators of both types of drugs were similar in terms of most baseline characteristics and medication use, including antiplatelet agents, anticoagulants, and nonsteroidal anti-inflammatory drugs. However, SNRI initiators had a lower proportion of hypertension but a higher percentage of depressive and anxiety disorders. Other risk

Figure 1. Flowchart of Study Cohort Assembly



Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

factors for stroke were evenly distributed between the 2 treatment groups.

After an average follow-up period of 3.2 years, there were a total of 9,194 ischemic strokes and 1,787 intracranial hemorrhages in the SSRI group and 1,028 ischemic strokes and 208 intracranial hemorrhages in the SNRI group. In the SSRI group, the total event numbers for death, ischemic stroke, and intracranial hemorrhage were 36,111, 9,194, and 1,789 among the 582,650 users, corresponding to crude incidences (95% CIs) of 52.8 (52.3–53.4), 13.4 (13.2–13.7), and 2.61 (2.49–2.73), respectively. In the SNRI group, the total event numbers for death, ischemic stroke, and intracranial hemorrhage were 4,569, 1,028, and 208 among the 76,920 users, corresponding to crude incidences of 52.0 (50.5–53.5), 11.7 (11.0–12.4), and 2.37 (2.04–2.69), respectively. In addition, SNRI initiators were more likely to switch to SSRIs (30.8% vs 10.1%), and the mean daily dosage of SNRI users was lower than that of SSRI initiators (0.75 DDD vs 0.97 DDD).

Table 2. Hazard Ratios of Ischemic Stroke and Intracranial Hemorrhage Comparing Use of SNRIs vs SSRIs

	Crude Hazard Ratio (95% CI)	*P*	Adjusted Hazard Ratio[a] (95% CI)	*P*
Main analyses				
SNRIs (n = 76,920) vs SSRIs (n = 582,650)				
Ischemic stroke	0.92 (0.83–1.02)	.12	1.01 (0.90–1.12)	.91
Intracranial hemorrhage	1.17 (0.91–1.48)	.22	1.24 (0.97–1.58)	.08
Sensitivity analyses				
Taking dosage into account[b]: SNRIs (n = 76,920) vs SSRIs (n = 582,650)				
Ischemic stroke	0.91 (0.82–1.02)	.10	1.00 (0.90–1.11)	.98
Intracranial hemorrhage	1.16 (0.91–1.48)	.23	1.24 (0.97–1.57)	.09
With grace period of 7 days: SNRIs (n = 76,920) vs SSRIs (n = 582,650)				
Ischemic stroke	0.92 (0.83–1.02)	.13	1.01 (0.91–1.12)	.82
Intracranial hemorrhage	1.10 (0.87–1.39)	.41	1.17 (0.93–1.48)	.18
Restricted to exclusive users: SNRIs (n = 53,210) vs SSRIs (n = 524,014)				
Ischemic stroke	1.00 (0.94–1.08)	.91	1.07 (0.99–1.14)	.08
Intracranial hemorrhage	1.10 (0.95–1.29)	.21	1.14 (0.98–1.34)	.09

[a]Stratified on baseline propensity score quintiles.
[b]Based on the dosage of the first SNRI/SSRI prescription.
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

The Cox regression model with time-varying study medication use analysis showed that use of SNRIs seemed to demonstrate a trend toward increasing the occurrence of intracranial hemorrhage compared to use of SSRIs (crude HR = 1.17; 95% CI, 0.91–1.48; *P* = .22). Risks associated with SNRI use became more obvious after taking baseline differences into consideration (adjusted HR = 1.24; 95% CI, 0.97–1.58; *P* = .08). In contrast, the risk of ischemic stroke was comparable in these 2 treatment groups (adjusted HR = 1.01; 95% CI, 0.90–1.12; *P* = .91) (Table 2, Main Analyses). Similar results were found in the sensitivity analyses of different analytic protocols (Table 2, Sensitivity Analyses), with HRs for intracranial hemorrhage ranging from 1.14 to 1.24. Of note, SNRI treatment was also associated with a borderline modestly increased risk of ischemic stroke among exclusive users (adjusted HR = 1.07; 95% CI, 0.99–1.14; *P* = .08).

In the subgroup analysis, we found that the risk of intracranial hemorrhage was comparable between SSRI and SNRI users in patients regardless of age, sex, or

Table 3. Subgroup Analysis of Hazard Ratios of Intracranial Hemorrhage Comparing Use of SNRIs vs SSRIs

	No. of Events	Crude Hazard Ratio (95% CI)	*P*	Adjusted Hazard Ratio[a] (95% CI)	*P*
Age ≥ 60 y (n = 172,006)	1,303	1.30 (0.97–1.75)	.08	1.31 (0.97–1.76)	.07
Age < 60 y (n = 487,564)	692	1.30 (0.85–1.99)	.22	1.27 (0.83–1.94)	.27
Men (n = 244,238)	1,006	1.12 (0.79–1.58)	.52	1.17 (0.83–1.65)	.39
Women (n = 415,332)	989	1.23 (0.87–1.73)	.24	1.34 (0.95–1.88)	.09
Patients with hypertension (n = 155,796)	1,106	1.23 (0.89–1.70)	.22	1.26 (0.91–1.75)	.16
Patients without hypertension (n = 503,774)	889	1.23 (0.85–1.77)	.27	1.25 (0.87–1.80)	.23
Patients with depressive disorder (n = 436,325)	1,147	0.96 (0.69–1.34)	.81	1.03 (0.74–1.43)	.87
Patients without depressive disorder (n = 223,245)	848	1.65 (1.16–2.35)	.01*	1.63 (1.14–2.32)	.01*

[a]Stratified on quintiles of baseline propensity score.
*$P < .05$.
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

comorbidities, with or without hypertension (Table 3). However, a significantly increased risk of intracranial hemorrhage was observed in SNRI users without a previous depressive disorder (adjusted HR = 1.63; 95% CI, 1.14–2.32; $P = .01$), although the confidence interval overlapped with that of the subgroup of patients with previous depressive disorder, suggesting no significant effect modification. In addition, a trend toward a borderline increase of intracranial hemorrhage was observed in patients 60 years or older (adjusted HR = 1.31; 95% CI, 0.97–1.76; $P = .07$).

DISCUSSION

Our results demonstrated that the use of SNRIs was not associated with an increased risk of either ischemic stroke or intracranial hemorrhage, compared to SSRIs, in patients with depression or anxiety. This finding was consistent in the sensitivity analyses and even for the more susceptible groups, such as patients with a past history of hypertension, men, and the elderly. However, the use of SNRIs was associated with an increased risk of intracranial hemorrhage in the subgroup of patients without depression.

It has been previously documented that the use of SSRIs was associated with an increased risk of intracerebral hemorrhage and all types of stroke.[7,15] Our finding that the cerebrovascular risk was comparable between SSRI and SNRI users further suggested that serotonin might play a major role in this adverse effect. Serotonergic drugs may influence the risk of bleeding by inhibiting collagen-induced platelet aggregation and activation.[16,17] Concomitant use of drugs such as antiplatelet agents, nonsteroidal anti-inflammatory drugs, and antipsychotics also increases the risk of bleeding.[18]

SNRIs elevate norepinephrine levels in neuronal synapses and result in increased sympathetic activities.[10] Recent studies showed that use of duloxetine (one example of an SNRI) increased the frequency of tachycardia, palpitations, and hypertension.[19,20] In addition, the use of SNRIs in patients with either depression or anxiety was associated with decreased vagal activity and increased blood pressure.[21,22] Venlafaxine posed a significant sympathomimetic reaction on the cutaneous blood vessels through α-adrenergic receptor stimulation, which was assessed by the vasoconstrictor responses of the dorsal hand vein.[23,24] Furthermore, the sequential changes in the plasma concentration of norepinephrine might differ between users of SSRIs and SNRIs.[25] However, the effect of sympathetic activation of SNRIs did not seem to correlate with an increased cerebrovascular risk in our analyses. The results did not support the hypothesis that the sympathomimetic effects of SNRIs further significantly increased the risk of ischemic stroke or intracranial hemorrhage over SSRIs.

The only exception was that there was likely an increased risk of intracranial hemorrhage with the use of SNRIs as compared to SSRIs in the subgroup of patients without depression. These patients were mostly diagnosed with anxiety disorder and might include a portion of patients with fibromyalgia. A recent review including information regarding the pharmacology and pharmacokinetics of duloxetine in the management of fibromyalgia suggested that this drug must be used with caution in patients with a bleeding risk and should be avoided in patients with bleeding tendencies when used to manage fibromyalgia.[26] The findings that appear to associate SNRI use with a higher risk of intracranial hemorrhage but not ischemic stroke suggest that the increased sympathetic activation in combination with decreased serotonergic effect on platelet aggregation will synergistically impose a greater impact on intracranial hemorrhage, in particular among those with lower baseline cerebrovascular risks. However, the results from a subgroup analysis might be due to type I error arising from multiple comparison analyses and should be interpreted cautiously and conservatively.

In our study, we found that the drug switch rate was higher in SNRI users than SSRI users. Regarding the adverse effects of antidepressants, adults taking SNRIs were significantly more likely to have symptoms of nausea or vomiting, irritability, insomnia, dysuria in men, and cardiovascular responses compared with adults taking SSRIs.[27] We speculated that the relatively high incidence rate of the norepinephrine-related side effects of SNRIs may partly contribute to the higher switch rate. The differential switching to other study drug between 2 comparison groups may bias the risk estimates associated with SNRIs toward the null. In this study, we conducted analyses with time-varying medication use in order to take study drug switching into consideration.

The strength of our study is the enrollment of a nationally representative cohort of a large sample size. We used a new-user design and restricted our study participants to

antidepressant initiators with depressive or anxiety disorders to reduce confounding by indication. Furthermore, the use of covariates including underlying diseases, medication use, and health care utilization prior to antidepressant initiation as proxies for the presence or severity of cerebrovascular and psychiatric disorders was combined into a summary propensity score for confounding adjustment.

Some limitations of the study should be considered. First, residual confounding, such as the duration or severity of depressive and anxiety disorders and cardiovascular comorbidities, blood pressure levels, obesity, smoking, and physical inactivity, may potentially exist. However, our observation of a marginal increased risk of intracranial hemorrhage associated with SNRI use may underestimate the true risk, as SNRI initiators had a lower proportion of hypertension in our study population. Second, adherence to antidepressant therapy was low, and the treatment duration was short in Taiwan. Thus, we are not able to examine the long-term cerebrovascular effect of SSRI use. Third, this study only assessed risk in patients with depressive or anxiety disorders, and our findings may not be generalizable to those without these diagnoses. Fourth, growing evidence has attributed bleeding events to SSRI use, including spontaneous bleeding in the genitourinary, respiratory, and gastrointestinal tracts.[28–31] Our analysis was not designed to detect a potential detrimental effect of concomitant use of SSRIs and antiplatelet agents or anticoagulants. Thus, the additive or synergic effects on the occurrence of intracranial hemorrhage should be further examined.[32] Fifth, since both SSRIs and SNRIs are, to some extent, heterogeneous groups that contain individual drugs having various effects on neurotransmitter reuptake, it would be too complicated to compare the outcome differences between individual drugs. We therefore grouped these medications into SSRIs (paroxetine, sertraline, fluoxetine, citalopram, escitalopram, fluvoxamine) and SNRIs (venlafaxine, duloxetine, milnacipran). However, this grouping might underestimate the risk of either ischemic stroke or intracranial hemorrhage on some specific drugs. Future large-scale study focusing on individual SSRIs or SNRIs is needed to clarify the cerebrovascular effects of specific class of drugs. Sixth, even though we applied a time-varying Cox regression model to study the exposure and doses of study medications in the analysis, the doses of individual class of SNRIs used by patients in the clinical practice might not be pharmacodynamically equivalent to the SSRI doses in terms of effects on serotonin or norepinephrine reuptake. Our results may not fully reflect the pharmacodynamics effects of SNRI and SSRI on the central cerebrovascular system.

In conclusion, our results showed that the use of SNRIs was not associated with an increased risk of either ischemic stroke or intracranial hemorrhage compared to the use of SSRIs in adult patients with either depression or anxiety. However, SNRIs should be cautiously used in patients without depression due to the potential risk of intracranial hemorrhage.

Submitted: July 19, 2014; accepted January 5, 2015.

Drug names: citalopram (Celexa and others), digoxin (Lanoxin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), milnacipran (Fetzima and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author contributions: Study concept and design: Lee YC, Lin CH, Chang CH, Lin JW. Acquisition of data: Chang CH, Lin JW. Analysis and interpretation of data: Lin CH, Lee YC, Chang CH, Lin JW. Drafting of the manuscript: Lin CH, Lee YC, Chang CH, Lin JW. Critical revision of the manuscript for important intellectual content: Lin CH, Lin MS, Lin JW. Statistical analysis: Lu Y. Obtained funding: Chang CH. Study supervision: Lin JW, Chang CH.

Potential conflicts of interest: None reported.

Funding/support: This study was supported in part by the Taiwan National Science Council (grant NSC 101-2314-B-002 -127 -MY2).

Role of the sponsor: The sponsor played no role in the study design; collection, analysis, and interpretation of data; report writing; or the decision to submit the paper for publication.

Disclaimer: The corresponding authors have full access to all data from the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by the National Health Research Institutes. The interpretation and conclusions contained here do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

Acknowledgments: The authors thank the subjects who participated in the study.

Additional information: The Taiwan National Health Insurance (NHI) Database can be found at http://nhirdnew.nhri.org.tw/en/Data_Subsets.html. The NHI Database used in this study is maintained by The Collaboration Center of Health Information Application (CCHIA), Ministry of Health and Welfare, Executive Yuan, R.O.C. CCHIA was established to promote the application of value-added health information, for the purpose of enhancing statistics-based decision support and further capacity for academic research. Utilization and publicizing of any information by the CCHIA have been in accordance with The Freedom of Government Information Law, Personal Information Protection Act, and other related regulations.

Supplementary material: See accompanying pages.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Helen Lavretsky, MD, MS, at hlavretsky@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Comparison of the Effects of Serotonin-Norepinephrine Reuptake Inhibitors Versus Selective Serotonin Reuptake Inhibitors on Cerebrovascular Events

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DOI Number: 10.4088/JCP.14m09394

List of Supplementary Material for the article

1. **eTable 1** ICD-9-CM codes and ATC codes used in this study

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. ICD-9-CM codes and ATC codes used in this study

Comorbidities	ICD-9-CM codes	Medication	ATC codes
Diabetes	250	COX-2 nonselective NSAIDs	M01A (exclude M01AH, M01AX05)
Hypertension	401-404	COX-2 selective NSAIDs	M01AH
Cardiovascular disease	410-414, 428	Angiotensin-converting enzyme inhibitors	C09AA
Ischemic heart disease	410-414	Angiotensin receptor blockers	C09CA
Myocardial infarction	410, 412	Alpha-blockers	C02CA
Angina	413	Beta-blockers	C07A
Arrhythmia	427	Calcium channel blockers	C08
Atrial fibrillation	427.31	Diuretics	C03
Heart failure	428	Other anti-hypertensive agents	C02A, C02B, C02CC, C02D
Transient cerebral ischemia	435	Insulin	A10A
Migraine	346	Sulfonylurea	A10BB
Peripheral arterial disease	440.2, 440.4, 443.81, 443.9	Metformin	A10BA02
Hemorrhagic stroke	430, 431, 432 (exclude 800, 801, 802, 803, 804, 850, 851, 852, 853, 854 ,V57)	Thiazolidinediones	A10BG02, A10BG03
Ischemic stroke	433, 434, 436 (exclude 800, 801, 802, 803, 804, 850, 851, 852, 853, 854 ,V57)	Glinides	A10BX02, A10BX03
Chronic renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13,	Alpha-glucosidase inhibitors	A10BF

	404.92, 404.93, 585, V45.1, V56.0, V56.8		
Chronic liver disease	070.2x, 070.3x, V02.61, 070.41, 070.44, 070.51, 070.54, V02.62, 571.0, 571.1, 571.2, 571.3, 571.4, 571.5, 571.6	Anticoagulants	B01AA03
Chronic lung disease	490-496, 500-508	Aspirin	B01AC06, N02BA01
Rheumatoid arthritis	710,714,720	Non-aspirin antiplatelet agents	B01AC04, B01AC05
Osteoarthritis	715	Histamine-2 receptor blockers	A02BA
Osteoporosis	733.0	Proton pump inhibitors	B02BC
Gastritis or peptic ulcer disease	531-535	Nitrate	C01DA
Cancer	140-208	Statins	C10AA
Gout	274	Fibrates	C10AB
Thyroid disease	244.9	Anti-arrhythmics Class I and III	C01B
Seizure	345,780.3	Digitalis	C01AA
Dementia	290.0-290.4,291.2,294.1,331.0-331.2, 290.10-290.13,290.20,290.21,290.40-290.43,294.10,294.11,331.11,331.19,331.82	Estrogen	G03C
Depressive disorder	296.2,296.3,298.0,300.4,309.0,309.1, 293.83,296.90,309.28,296.82, 311	1st generation anti-psychotics	N05AD03, N05AD05, N05AA01, N05AF03, N05AC02,N05AA03, N05AF05, N05AB03, N05AC01, N05AD01, N05AF01,N05AG02, N05AB02, N05AG03
Anxiety disorder	300.0-300.3,300.5-300.9	2nd-generation anti-psychotics	N05AH02,N05AH03,N05AX08,N05AH04,N05AE04,N05AL01,N05AL05
Psychotic disorder	290.8,290.9,780.1, 295,297-299	Tri-cyclic anti-depressants	N06AA

Bipolar disorder	296.0,296.1,296.4- 296.9	Anxielytics	N05B
		Dopaminergic agents	N04B
		Anti-epileptics	N03
		Thyroid therapy	H03
		Anti-gout preparations	M04A
		Paroxetine	N06AB05
		Sertraline	N06AB06
		Fluoxetine	N06AB03
		Citalopram	N06AB04
		Escitalopram	N06AB10
		Fluvoxamine	N06AB08
		Venlafaxine	N06AX16
		Duloxetine	N06AX21
		Milnacipran	N06AX17