Cerebrovascular, Cardiovascular, and Mortality Events in New Users of Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors

A Propensity Score-Matched Population-Based Study

Christine Leong, BSc (Pharm), PharmD, Silvia Alessi-Severini, PhD,* Murray W. Enns, MD,† Yao Nie, MSc,‡ Jitender Sareen, MD,† James Bolton, MD,† Heather J. Prior, MSc,‡ and Dan Chateau, PhD‡*

Abstract:

Background: Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are widely prescribed for mood and anxiety disorders. However, it is not clear whether SNRIs are more strongly associated with cardiovascular and cerebrovascular events than SSRIs.

Methods: This was a propensity score–matched, population-based, cohort study of Manitobans who started an SSRI or SNRI between April 1, 1998, and March 31, 2014. The primary outcome was a composite of acute myocardial infarction (AMI), stroke, or cardiovascular-related hospitalization within 1 year of drug initiation. Each component of the primary outcome and death were analyzed separately in secondary analyses.

Results: A total of 225,504 and 54,635 patients initiated treatment on an SSRI and SNRI, respectively. After propensity score matching, a higher risk was observed for the primary outcome among SNRI users (weighted hazards ratio [HR], 1.13; 95% confidence interval [CI], 1.06–1.21). Secondary analyses showed that the risk of nonfatal stroke was higher among SNRI users (weighted HR, 1.20; 95% CI, 1.08–1.33). The risk of death was higher among SNRI users without mood and/or anxiety disorders (weighted HR, 1.17; 95% CI; 1.03–1.32). No differences were observed in the risk of AMI or fatal stroke between SSRI and SNRI use.

Conclusions: New SNRI use was associated with a higher risk of nonfatal stroke relative to SSRI use. Further investigation is warranted regarding the higher risk of death observed in our subgroup analysis among incident SNRI users without mood and/or anxiety disorders.

Key Words: cardiovascular events, cerebrovascular events, death, pharmacoepidemiology, serotonin norepinephrine reuptake inhibitors

(*J Clin Psychopharmacol* 2017;37: 00–00)

Mental health is prevalent in the general population, with depression occurring in as many as 30% of individuals with a history of cardiovascular or cerebrovascular disease.[1–3] Among the antidepressants used to treat mood and anxiety disorders, serotonin norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed.[4–9] Although both of these classes exhibit serotonergic activity, SNRIs also exhibit noradrenergic effects.[10] It is unclear whether these effects provide an advantage in their efficacy for mood and anxiety, but may account for the observed differences in the rates of hypertension, tachycardia, and cardiotoxic effects in high doses when compared with SSRIs.[10–17] The SNRI venlafaxine was found to have a relative fatal toxicity index that is 5 times higher than that of SSRIs and has been reported to be frequently involved in overdose deaths.[11] Previous studies have demonstrated higher sympathetic activity as a result of SNRI-induced norepinephrine elevation.[18–21] It is also well known that hypertension is a major risk factor for cardiovascular and cerebrovascular events.[22] However, the cardiovascular and cerebrovascular risk of a patient is not always considered before prescribing an SSRI or SNRI.

Serotonin reuptake inhibitors block platelet aggregation and induce vasospasm, which have been associated with both hemorrhagic and ischemic stroke in observational and case series studies.[23–30] By virtue of their mechanism of action, we hypothesized that SNRIs will have a higher risk for both cardiac and cerebrovascular events compared with SSRIs. Only a few studies in a restricted population have examined the risk of these events between the 2 classes of antidepressants in a population-based design.[31,32] On the basis of limited existing data, the risk of cardiovascular, cerebrovascular, and death events between SSRIs and SNRIs still remains unclear. One study found no difference in the risk of cardiovascular events between venlafaxine (SNRI) and sertraline (SSRI) in patients aged 65 years and older. Another study found an elevated risk of cerebrovascular events in those without depression. We aimed to determine whether our study population would demonstrate results consistent with the findings found in these previous studies. We carried out a large-scale, multiyear, population-based cohort study not restricted to age or indication using propensity score–based matching to compare the risk of cerebrovascular, cardiovascular, and mortality events between incident users of SNRIs and SSRIs.

METHODS

Setting and Design

This was a retrospective, population-based, cohort study that spanned for a period of 16 years (from April 1, 1998–March 31, 2014) in Manitoba, Canada using the administrative health care databases located at the Manitoba Centre for Health Policy (MCHP). Manitoba has one of the most comprehensive data sets to conduct pharmacoepidemiology research. These databases capture and link outpatient prescriptions and health care services for approximately 1.2 million Manitobans, without restrictions

From the *College of Pharmacy, Rady Faculty of Health Sciences, Apotex Centre; †Department of Psychiatry, and ‡Manitoba Centre for Health Policy; Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada.

Received August 29, 2016; accepted after revision February 17, 2017.

Reprints: Christine Leong, BSc (Pharm), PharmD, College of Pharmacy, Rady Faculty of Health Science, University of Manitoba, Room 222, Apotex Centre, 750 McDermot Ave, Winnipeg, MB, Canada R3E 0T5 (e-mail: christine.leong@umanitoba.ca).

This study was funded by the University of Manitoba Start-Up Funds.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000701

of age or insurance coverage. This study was approved by the University of Manitoba Human Research Ethics Board and the Health Information Privacy Committee.

Data Sources

The Drug Program Information Network was used to obtain prescription records dispensed to all Manitobans outside of hospitals and personal care homes using Anatomical Therapeutic Chemical codes to identify specific drugs. The Drug Program Information Network accurately captures information on the date of dispensation, strength, quantity, and anticipated number of days' supply for a specific drug provided and has been used in previous research.[32] Health service use and diagnostic information were identified using *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (*ICD-9-CM* or equivalent *International Statistical Classification of Diseases*, *10th Revision, Canada* [ICD-10-CA]) codes from hospital abstracts and medical services physician billings. Emergency department visits in Winnipeg, Manitoba were obtained through Admission, Discharge, and Transfer, E-Triage and Emergency Department Information System. Vital statistics included information on the cause and date of death. The Manitoba Registry database included demographic information for the population.

Population

All patients who received a new prescription for an SNRI or SSRI between April 1, 1998, and March 31, 2014, were included. The index date was defined as the date of first prescription for either drug classes during the study period, and individuals may enter the study more than once because new use was defined as no receipt of a prescription SNRI or SSRI in the year before the receipt of their first prescription. The SSRIs included paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram, and escitalopram, and SNRIs included venlafaxine, duloxetine, and desvenlafaxine. New users were defined as those who have not received a prescription for any antidepressant in the year before their first prescription for an SNRI or SSRI. Patients were followed for 1 year after the index date because effects have been found to occur early in treatment.[14,33–35] Individuals who have been hospitalized or visited the emergency department with a cardiovascular or cerebrovascular event in the year before the first prescription or used the alternate study class medication within 1 year of the first prescription were excluded. Patients who started taking any antidepressant other than an SSRI or SNRI after the incident prescription were censored.

Study Outcomes

Patients were followed until the first occurrence of the outcome, the end of the 1-year follow-up period, or the end of the study period (March 31, 2014). The primary outcome was a composite of hospital admission for AMI (*ICD-9-C*M 410 or *ICD-10-CA* I21, I22), fatal or nonfatal stroke (*ICD-9-CM* 430–438 or *ICD-10-CA* I60–I69), or other cardiovascular-related hospitalization (congestive heart failure [CHF, *ICD-9-CM* 428 or *ICD-10-CA* I50], cardiac arrest [*ICD-9-CM* 427 or *ICD-10-CA* I46], unstable angina [*ICD-9-CM* 411 or *ICD-10-CA* I20], and conduction disorder/arrhythmia [*ICD-9-CM* 426, 427.3, 427.4, 427.6–427.9 or *ICD-10-CA* I44, I45, I48, I49]). Secondary outcomes included each of the components of the primary outcome separately, cardiovascular-related death (AMI, CHF, arrest, unstable angina, conduction disorder/arrhythmia, fatal stroke), and all-cause death. Patients with nonischemic chest pain were excluded by limiting the outcome definition for AMI to patients who were hospitalized for at least 3 days or died in the hospital.[36–38] Case definitions used to identify events are available in Supplementary Table 1A, Supplemental Digital Content 1, http://links.lww.com/JCP/A433, and have been used in previous research.[39–41]

Statistical Analysis

Baseline characteristics (including age, sex, region of residence, income quintile, mean number of ambulatory, emergency, hospital visits, chronic prescription drug use in past year, Charlson comorbidity index, comorbidities [Supplementary Table 1B, Supplemental Digital Content 2, http://links.lww.com/JCP/A434, for case definitions used] in the past 3 years, and comedications in the past year) were reported for incident SNRI and SSRI users using descriptive statistics with unweighted and weighted standardized differences.

Inverse probability of treatment weighting with propensity score of baseline characteristics was used to determine the probability of receiving an SNRI and account for baseline differences between the 2 groups. Average treatment effect in the treated patients was used to compare the risk of outcome between those who received an incident prescription for an SNRI to an SSRI.[42,43] Time-to-event analyses with SSRI as a reference group was performed using weighted samples. Crude and weighted hazards ratios (HRs) with 95% confidence intervals (CIs) using Cox proportional hazards regression were estimated for all outcomes. Using a fitted model, survival curves for each treatment group were derived.

Stratification of outcomes between the 2 groups was carried out for those with and without mood and/or anxiety disorder, cardiovascular disease, and those aged older and younger than 40 years. We also carried out a sensitivity analysis of the crude and weighted HR for all outcomes by restricting to only those who filled at least 2 consecutive prescriptions for the SSRI or SNRI with a gap between the 2 prescription fills of less than 1.5 of the days' supply. The prescribed daily dose (PDD) was also determined for each SSRI and SNRI used in the 1-year observation period. The PDD is the average daily amount of drug in milligrams (mg) that is actually prescribed, which was calculated by multiplying the quantity of drug dispensed by the strength of drug dispensed divided by the number of users for that drug.[44]

RESULTS

A total of 225,504 and 54,635 patients initiated treatment on an SSRI and SNRI, respectively (Supplementary Figure 1, Supplemental Digital Content 3, http://links.lww.com/JCP/A435, for flowchart of cohort). These patients were followed for a mean (SD) of 346.4 (65.4) and 348.8 (58.9) days, respectively. Baseline characteristics between the 2 groups were similar (Table 1) with SNRI users being slightly older (mean, 44.0 years vs 42.9 years; age, 10–19 group; 5.0% vs 10.2%; age 50–59 group; 17.8% vs 13.0% in SNRI vs SSRI group, respectively). Approximately 80% of the patients had a history of anxiety and/or mood disorder diagnosis in the past 3 years. Most of the incident prescriptions for an SSRI or SNRI were written by a general practitioner (84.7%) and 7.4% by a psychiatrist. No meaningful differences in means of measured baseline covariates were observed after weighting because all standardized differences in the weighted sample were less than or equal to 0.05.

In the primary analysis, a significantly higher risk for the primary outcome was observed with the new use of SNRIs compared with SSRIs after weighting (weighted HR, 1.13; 95% CI, 1.06–1.21) (Table 2). Secondary analyses after weighting found no differences in the risk of AMI, fatal stroke, cardiovascular-related hospitalizations, death, and cardiovascular-related death between SSRIs and SNRIs. However, the risk of nonfatal stroke

TABLE 1. Baseline Characteristics in the Matched Cohort With an Incident Prescription for an SNRI Compared With an SSRI (N = 280,139)

			Standardized Difference*	
Demographic	**SSRI (n = 225,504)**	**SNRI (n = 54,635)**	**Crude**	**Weighted**
Age, mean (SD), y	42.9 (19.8)	44.0 (17.3)	0.058	0.004
Age, n (%), y				
<10	1497 (0.7)	83 (0.2)	0.080	Trimmed
10–19	22,931 (10.2)	2708 (5.0)	0.198	0.005
20–29	41,340 (18.3)	9885 (18.1)	0.006	0.012
30–39	44,044 (19.5)	10,978 (20.1)	0.014	0.004
40–49	41,531 (18.4)	11,887 (21.8)	0.083	0.016
50–59	29,374 (13.0)	9740 (17.8)	0.133	0.025
60–69	16,381 (7.3)	4339 (7.9)	0.026	0.003
70–79	14,122 (6.3)	2765 (5.1)	0.052	0.017
≥80	14,284 (6.3)	2250 (4.1)	0.100	0.020
Female, n (%)	148,980 (66.1)	35,510 (65.0)	0.023	0.001
Urban, n (%)	144,139 (63.9)	31,631 (57.9)	0.124	0.029
Income quintile (urban)				
U1 (lowest)	32,593 (14.5)	6793 (12.4)	0.059	0.012
U2	29,482 (13.1)	6720 (12.3)	0.023	0.008
U3	28,375 (12.6)	6444 (11.8)	0.024	0.008
U4	25,659 (11.4)	5808 (10.6)	0.024	0.008
U5 (highest)	24,589 (10.9)	5448 (10.0)	0.030	0.008
Income quintile (rural)				
R1 (lowest)	15,321 (6.8)	4169 (7.6)	0.032	0.009
R2	16,294 (7.2)	4983 (9.1)	0.069	0.015
R3	16,856 (7.5)	4799 (8.8)	0.048	0.012
R4	16,447 (7.3)	4548 (8.3)	0.038	0.008
R5 (highest)	15,959 (7.1)	4406 (8.1)	0.037	0.008
Missing	3929 (1.7)	517 (1.0)	0.069	0.009
No. ambulatory visits, mean (SD)	13.2 (13.1)	13.6 (13.0)	0.032	0.011
No. emergency visits, mean (SD)	0.33 (1.1)	0.31 (1.0)	0.012	0.0003
No. hospitalizations, mean (SD)	1.5 (1.0)	1.5 (1.0)	0.015	0.002
No. chronic prescriptions, mean (SD)	3.0 (2.8)	2.9 (2.7)	0.053	0.017
Weighted sum of 17 Charlson comorbidity index, mean (SD)	0.44 (1.02)	0.45 (1.08)	0.002	0.001
Comorbidities in the Past 3 Years, n (%)				
Anxiety/mood	179,407 (79.6)	43,636 (79.9)	0.008	0.003
Cardiovascular disease	74,555 (33.1)	18,936 (34.7)	0.034	0.001
Diabetes	15,903 (7.1)	3979 (7.3)	0.009	0.002
Renal disease	12,452 (5.5)	2698 (4.9)	0.026	0.006
Coronary artery disease	10,919 (4.8)	2349 (4.3)	0.026	0.008
Dementia	10,608 (4.7)	1941 (3.6)	0.058	0.008
Stroke	5166 (2.3)	939 (1.7)	0.041	0.008
CHF	3583 (1.6)	655 (1.2)	0.033	0.005
Rheumatoid arthritis	2007 (0.9)	529 (1.0)	0.008	0.004
Arrhythmia/conduction	2078 (0.9)	398 (0.7)	0.021	0.003
Valvular heart disease	1396 (0.6)	247 (0.5)	0.023	0.004
Total respiratory morbidity†	65,944 (29.2)	16,080 (29.4)	0.004	0.005
Medications Used in the Past Year, n (%)				
ACEI/ARB	20,359 (9.0)	4942 (9.0)	0.001	0.003
Diuretic	17,096 (7.6)	3850 (7.0)	0.019	0.005
Statin	14,054 (6.2)	3740 (6.8)	0.025	0.003
β-blocker	11,678 (5.2)	2738 (5.0)	0.008	0.003
Calcium channel blocker	11,930 (5.3)	2621 (4.8)	0.022	0.005
Antiplatelet	6544 (2.9)	1418 (2.6)	0.017	0.002

Continued next page

TABLE 1. *(Continued)*

Demographic	SSRI (n = 225,504)	SNRI (n = 54,635)	Standardized Difference* Crude	Standardized Difference* Weighted
Warfarin	—	—	0.009	0.005
New oral anticoagulant	3847 (1.7)	629 (1.2)	0.009	0.003
Antiarrhythmic	2414 (1.1)	411 (0.8)	0.035	0.005
Aldosterone blocker	884 (0.4)	207 (0.4)	0.002	0.001
Oral NSAIDs	13,467 (6.0)	3662 (6.7)	0.030	0.003
Opioids	13,446 (5.7)	4450 (8.1)	0.069	0.019
Estrogen/progesterone	9292 (4.1)	2623 (4.8)	0.032	0.004
Antipsychotic‡	6994 (3.1)	1258 (2.3)	0.046	0.002
Oral corticosteroids	2943 (1.3)	713 (1.3)	0.0004	0.001
Gabapentin	1716 (0.8)	911 (1.7)	0.083	0.010
Cholinesterase inhibitor	1306 (0.6)	201 (0.4)	0.030	0.003
Tamoxifen	492 (0.2)	292 (0.5)	0.052	0.008
Domperidone	1471 (0.6)	340 (0.6)	0.004	0.001
Thiazolidinedione	873 (0.4)	243 (0.4)	0.009	0.002

*Standardized difference <0.1 indicates good balance between the cases and controls.

†Total respiratory morbidity is a measure of different types of respiratory illness used to overcome problems in diagnosis codes being used for the same underlying illness by different physicians. These include the following: bronchitis and bronchiolitis, emphysema, asthma, and chronic airway obstruction.

‡Second generation antipsychotics.

ACEI/ARB indicates angiotensin converting enzyme inhibitor/angiotensin receptor blocker; NSAIDs , nonsteroidal anti-inflammatory drug.

was higher among SNRI users (weighted HR, 1.20; 95% CI, 1.08–1.33). Among nonfatal stroke events, ischemic stroke was higher among SNRI users compared with SSRI users (weighted HR, 1.32; 95% CI, 1.15–1.51), and no difference was observed for nonfatal hemorrhagic stroke (weighted HR, 1.20; 95% CI, 0.84–1.71).

Similar findings were found in our sensitivity analysis of patients (SSRI, 118,647; SNRI, 27,059) who received at least 2 consecutive prescriptions for an SNRI or SSRI (Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/JCP/A436). When stratified by ages younger than 40 years and 40 years or older, the rate of events was less frequent, and no differences in any of the end points were observed in the younger cohort (Fig. 1A), but a higher risk for the primary outcome, nonfatal stroke, and cardiovascular-related hospitalizations were observed among SNRI users in the older cohort (Fig. 1B).

When stratified by those with and without a history of mood and/or anxiety disorder in the past 3 years, the risk of nonfatal stroke was higher in both subgroups for SNRI users. However, the risk of all-cause and cardiovascular-related deaths were only significantly higher in the subgroup without a history of mood and/or anxiety disorders (Fig. 2, A and B). When stratified by those with and without a history of cardiovascular disease, the risk for the primary outcome and nonfatal stroke was higher among SNRI users compared with SSRI users in only the subgroup with a history of cardiovascular disease. There was also a higher risk of cardiovascular-related hospitalizations for the SNRI users compared with the SSRI users in this subgroup. No difference in any of the events was observed in those without cardiovascular disease (Fig. 3, A and B).

The median age in which patients experience the composite outcome is 77.3 years (interquartile range, 65.3–84.8 years). Citalopram was the most common SSRI used (42.2% of SSRI users), and venlafaxine was the most common SNRI used (94.0% of SNRI users) (Table 3). The mean PDDs for each antidepressant is shown in Table 3.

DISCUSSION

In this 16-year observational study, our primary analysis found a higher risk for the primary composite outcome of AMI,

TABLE 2. Cardiac, Cerebrovascular, and Death Events Among Incident Users of SNRI Compared With SSRI (n = 268,531)

Outcome	Events in SNRI (n = 52,803)	Events in SSRI (n = 215,728)	Crude HR (95% CI)	Weighted Events SNRI (n = 53,325.7)	Weighted Events SSRI (n = 212,771)	Weighted HR (95% CI)
Composite*	1061	5648	1.32 (1.23–1.41)	1066.1	4794.06	1.13 (1.06–1.21)
AMI	112	552	1.20 (0.97–1.48)	116.033	484.89	1.04 (0.84–1.28)
Fatal stroke	83	424	1.32 (1.03–1.68)	82.1084	336.169	1.08 (0.84–1.38)
Nonfatal stroke	474	2685	1.41 (1.28–1.56)	474.322	2231.79	1.20 (1.08–1.33)
Cardiovascular hospitalization	604	3136	1.28 (1.17–1.40)	604.961	2640.77	1.09 (1.00–1.20)
Death	903	4352	1.16 (1.08–1.25)	900.785	3744.04	1.02 (0.95–1.10)
Cardiovascular death	225	1173	1.16 (1.07–1.25)	223.585	891.216	1.02 (0.94–1.10)

*Composite of AMI, fatal, and nonfatal stroke, and cardiovascular-related hospitalization.

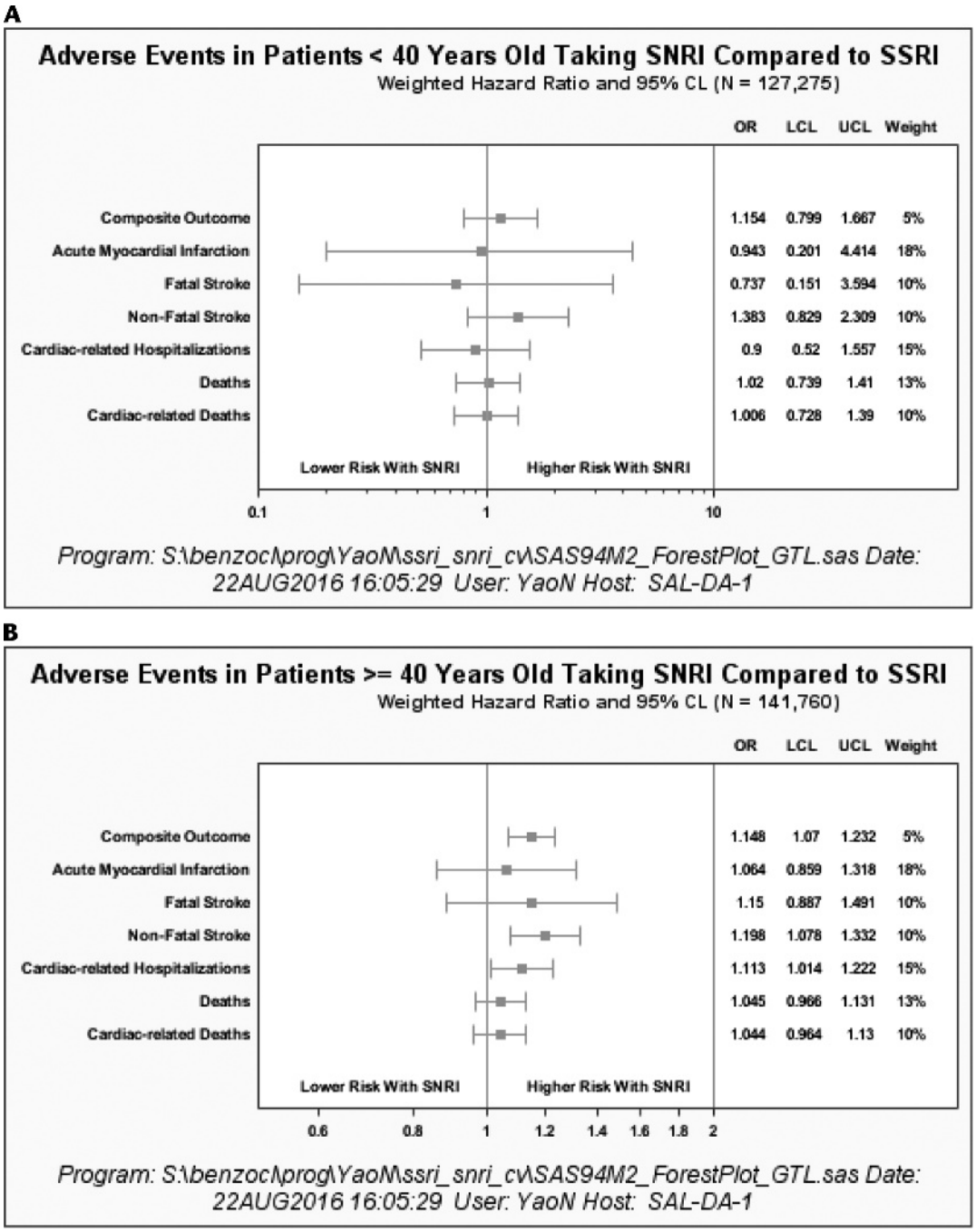

FIGURE 1. A, Weighted HR and 95% CI of cardiac, cerebrovascular, and death events among incident users of SNRI compared with SSRI, aged younger than 40 years (n = 127,275). B, Weighted HR and 95% CI of cardiac, cerebrovascular, and death events among incident users of SNRI compared with SSRI, aged 40 years or older (n = 141,760).

stroke, and cardiovascular-related hospitalizations in new SNRI users compared with new SSRI users. Of note, the risk of nonfatal stroke was the only component of this composite outcome that was found to be significantly higher. The risk of nonfatal stroke remained significant after restricting to those who filled a second prescription for their SNRI or SSRI and in those who were aged 40 years or older. No difference in the risk of death events was observed in the primary analysis. A higher risk for cardiovascular-related hospitalization was also observed in those who were aged 40 years or older starting an SNRI.

Some of our findings were consistent with previous studies examining the risk of cardiac and cerebrovascular events between SNRIs and SSRIs. Ho et al[31] also found no difference in the risk of AMI and CHF between new users of venlafaxine and sertraline over a 1-year period in patients aged older than 65 years old in Ontario, Canada. We were able to add to these findings by expanding the age group to include younger patients and by including other SSRIs and SNRIs in the analysis of events.

The higher risk of nonfatal stroke found in the current study will also add to the findings by Lee et al, which was set in

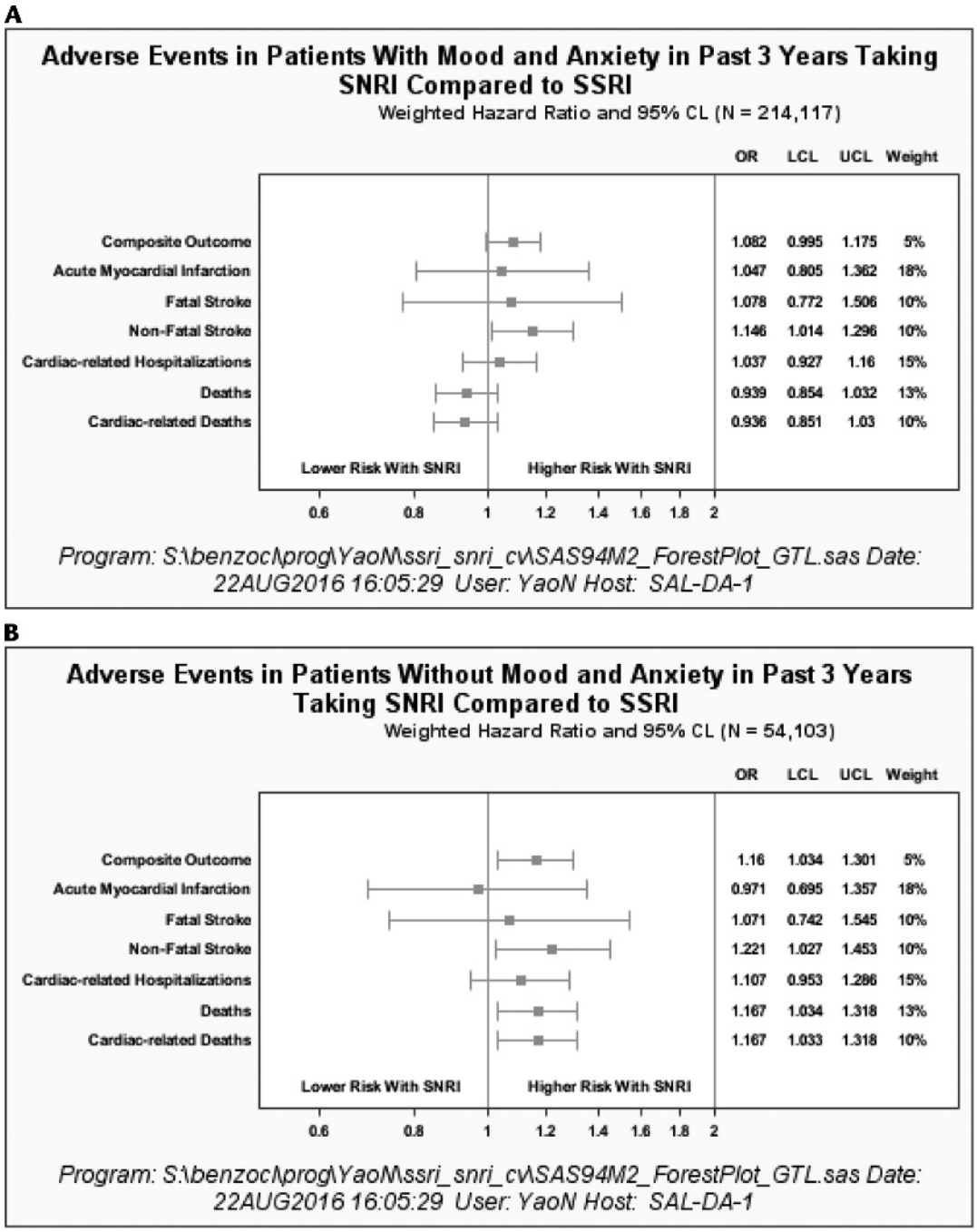

FIGURE 2. A, Weighted HR and 95% CI of cardiac, cerebrovascular, and death events among incident users of SNRI compared with SSRI, with mood/anxiety disorders (n = 214,117). B, Weighted HR and 95% CI of cardiac, cerebrovascular, and death events among incident users of SNRI compared with SSRI, without mood/anxiety (n = 54,103).

Taiwan.[32] Lee et al found a nonsignificant trend toward the risk for intracranial hemorrhage with the new use of SNRIs compared with SSRIs (adjusted HR, 1.24; 95% CI, 0.97–1.58; $P = 0.08$). These findings were only significantly higher in the subgroup of patients without depression (adjusted HR, 1.63; 95% CI, 1.14–2.32), which may be because depression can also affect the risk for these events. No difference in ischemic stroke was observed in this study. In our study, the risk of nonfatal stroke with the use of SNRIs was higher than for SSRIs in those with and without a history for mood and/or anxiety. However, the risk of all-cause and cardiovascular-related deaths were only higher in the SNRI group compared with the SSRI group in those without a history of mood and/or anxiety disorders. Moreover, the risk of nonfatal stroke and cardiovascular-related events were higher among incident SNRI users with a history of cardiovascular disease but not in those without cardiovascular disease. Like Lee et al,[32] the findings in our study would also suggest precaution in using SNRIs in patients without a history of mood and/or anxiety disorders, but also in patients with a history of cardiovascular disease. The fact that our study found a higher risk in nonfatal

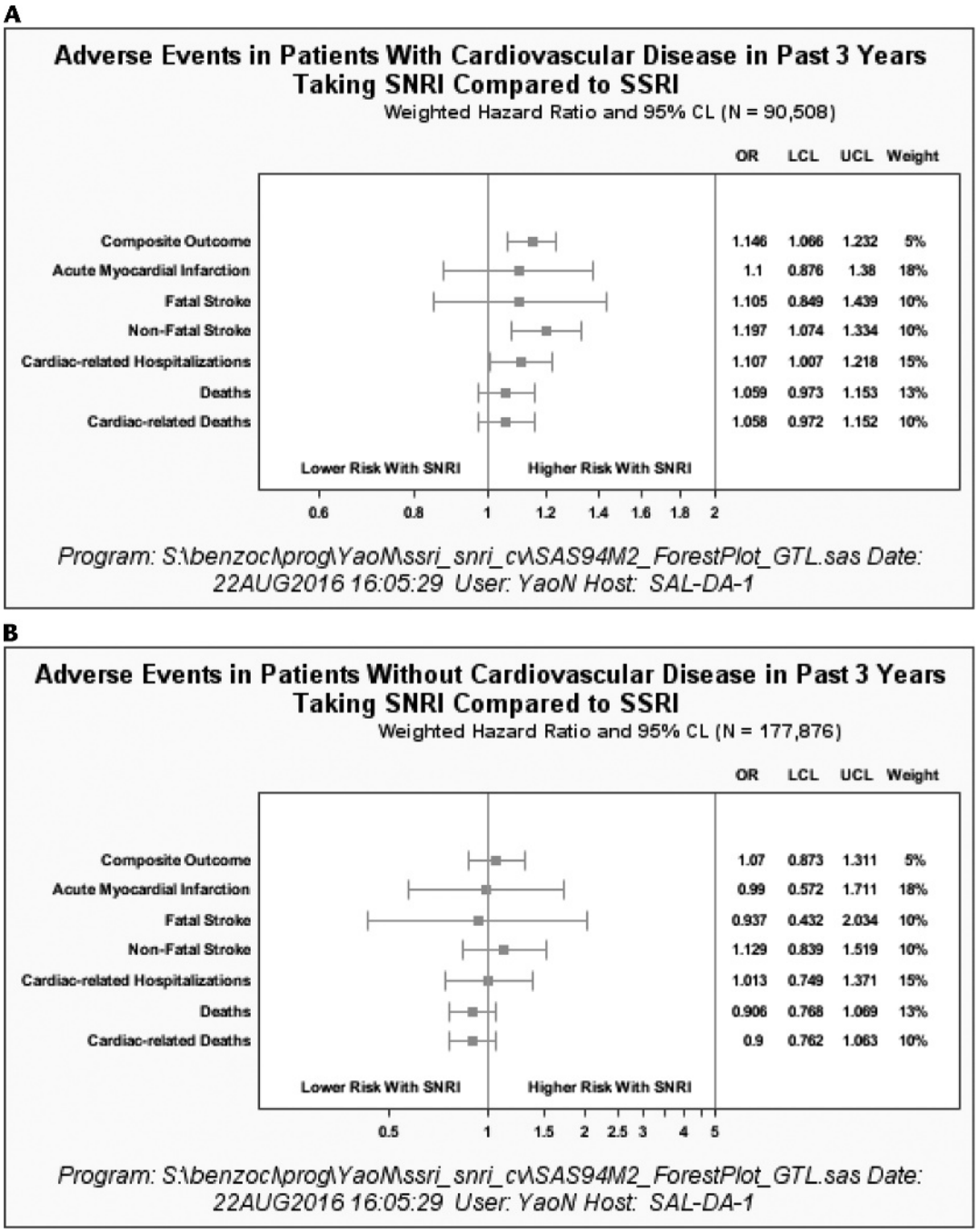

FIGURE 3. A, Weighted HR and 95% CI of cardiac, cerebrovascular, and death events among incident users of SNRI compared with SSRI, with cardiovascular disease (n = 90,508). B, Weighted HR and 95% CI of cardiac, cerebrovascular, and death events among incident users of SNRI compared with SSRI, without cardiovascular disease (n = 177,876).

ischemic rather than hemorrhagic stroke might be explained by the inherent differences in the population and setting in which the study was conducted in. Previous studies found a higher risk of new and recurrent stroke with the use of tricyclic antidepressants compared with other antidepressants.[29,45]

Although this study used a new user design and used data from a comprehensive database not restricted by age or drug coverage, there were a few limitations worth noting. First, the indication for antidepressant therapy was not identified, but we did identify almost 80% of patients with a history of mood or anxiety disorder in the past 3 years, and we stratified the population based on the presence of this diagnosis. Second, certain risk factors for the primary outcome, such as smoking status, were not captured in administrative data and, as such, the baseline differences in these factors could not be determined. However, we did incorporate total respiratory morbidity into the propensity score, which is a measure of different types of respiratory illness including asthma, bronchitis, emphysema, and chronic airway destruction. Third, only new users were included in this study where the doses of some of these agents may have been low on average. Noradrenergic events may be

TABLE 3. Type of SSRI and SNRI and Dose Intensity Used at Index Date in Weighted Matched Population (n = 268,531)

Baseline Demographic	SSRI (n = 215,728)	SSRI PDD*/User/D, mg	SNRI (n = 52,803)	SNRI PDD*/User/D, mg
SSRI, n (%)				
Citalopram	91,037 (42.2)	22.7	N/A	N/A
Paroxetine	58,451 (27.1)	21.7	N/A	N/A
Sertraline	33,289 (15.4)	64.9	N/A	N/A
Fluoxetine	21,681 (10.1)	24.4	N/A	N/A
Escitalopram	5,910 (2.7)	14.4	N/A	N/A
Fluvoxamine	5,360 (2.5)	92.8	N/A	N/A
SNRI, n (%)				
Venlafaxine	N/A	N/A	49,629 (94.0)	88.9
Duloxetine	N/A	N/A	2,396 (4.5)	53.7
Desvenlafaxine	N/A	N/A	778 (1.5)	62.4

*Prescribed Daily Dose (PDD).

present at higher doses for some of the SSRIs and for venlafaxine, and we were not able to identify differences in cytochrome P450 polymorphism, which can affect the metabolism rate for some of these agents.[46] However, a new user design was deemed the most appropriate design for a study of this kind to reduce the risk of prevalent user bias. Therefore, to avoid selecting for those who have survived events, we excluded prevalent users and described the PDDs for each drug used by the patients in this study. Fourth, channeling bias and other unmeasured confounders are limitations to observational studies using administrative claims data. It should also be noted that while this study compared 2 classes of antidepressants, most of SNRI users received venlafaxine (94%), and citalopram was used by most of the SSRI users (42%). Future directions will include investigating the risk of events by dose of drug and drug type further.

CONCLUSIONS

Incident SNRI use was associated with a higher risk for nonfatal stroke, but not for AMI or nonfatal stroke relative to SSRIs. Those with cardiovascular disease who received an SNRI were at higher risk compared with incident SSRI users with cardiovascular disease. Further study is warranted to investigate the higher risk of death observed among incident SNRI users in the subgroup without mood and/or anxiety disorders.

ACKNOWLEDGMENTS

The authors acknowledge the MCHP for use of data contained in the Population Health Research Data Repository under project number 2013/2014 (HIPC number 2013/2014-39). The results and conclusions are those of the authors and no official endorsement by the MCHP, Manitoba Health, Manitoba Health, Seniors and Active Living, or other data providers is intended or should be inferred.

AUTHOR DISCLOSURE INFORMATION

The authors have no conflicts of interest to report.

REFERENCES

1. Patten SB, Wang JL, Williams JV, et al. Descriptive epidemiology of major depression in Canada. *Can J Psychiatry*. 2006;51:84–90.
2. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289:3095–3105.
3. Paolucci S. Epidemiology and treatment of post-stroke depression. *Neuropsychiatr Dis Treat*. 2008;4:145–154.
4. Top Therapeutic Classes by U.S. Spending. *IMS National Sales Perspectives, IMS Health*. Available at: http://www.imshealth.com/files/web/Corporate/News/Top-Line%20Market%20Data/Top_Therapy_Classes_by_Sales.pdf. Updated February 23, 2012 Accessed July 18, 2016.
5. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry*. 2009;66:848–856.
6. Pratt LA, Brody DJ, Gu Q. *Antidepressant Use in Persons Aged 12 and Over*. Washington, DC: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2011:2005–2008.
7. Arora N, Knowles S, Gomes T, et al. Interprovincial variation in antipsychotic and antidepressant prescriptions dispensed in the Canadian pediatric population. *Can J Psychiatry*. 2016;Published online ahead of print May 12, 2016. Available at: http://cpa.sagepub.com.uml.idm.oclc.org/content/early/2016/05/12/0706743716649190.long. Accessed August 8, 2016.
8. Abbing-Karahagopian V, Huerta C, Souverein PC, et al. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. *Eur J Clin Pharmacol*. 2014;70:849–857.
9. OECD. Health at a Glance 2015: OECD Indicators. OECD Publishing. Available at: http://dx.doi.org/10.1787/health_glance-2015-en. Accessed July 5, 2016.
10. Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. *Arch Gen Psychiatry*. 2000;57:503–509.
11. Hawton K, Bergen H, Simkin S, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. *Br J Psychiatry*. 2010;196:354–358.
12. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med*. 2011;155:772–785.
13. Debonnel G, Saint-André É, Hébert C, et al. Differential physiological effects of a low dose and high doses of venlafaxine in major depression. *Int J Neuropsychopharmacol*. 2007;10:51–61.
14. Johnson EM, Whyte E, Mulsant BH, et al. Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. *Am J Geriatr Psychiatry*. 2006;14:796–802.
15. Wernicke J, Lledó A, Raskin J, et al. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo- controlled studies. *Drug Saf*. 2007;30:437–455.

16. Licht CM, de Geus EJ, Seldenrijk A, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. *Hypertension*. 2009;53:631–638.
17. Licht CM, de Geus EJ, van Dyck R, et al. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biol Psychiatry*. 2010;68:861–868.
18. Abdelmawla AH, Langley RW, Szabadi E, et al. Comparison of the effects of venlafaxine, desipramine, and paroxetine on noradrenaline- and methoxamine-evoked constriction of the dorsal hand vein. *Br J Clin Pharmacol*. 1999;48:345–354.
19. Siepmann T, Ziemssen T, Mueck-Weymann M, et al. The effects of venlafaxine on autonomic functions in healthy volunteers. *J Clin Psychopharmacol*. 2007;27:687–691.
20. Blier P, Saint-André E, Hébert C, et al. Effects of different doses of venlafaxine on serotonin and norepinephrine reuptake in healthy volunteers. *Int J Neuropsychopharmacol*. 2007;10:41–50.
21. Hallbäck I, Hägg S, Eriksson AC, et al. In vitro effects of serotonin and noradrenaline reuptake inhibitors on human platelet adhesion and coagulation. *Pharmacol Rep*. 2012;64:979–983.
22. NIH National Heart, Lung, and Blood Institute. *Who is at risk for a stroke?*. Available at: https://www.nhlbi.nih.gov/health/health-topics/topics/stroke/atrisk. Updated June 22, 2016.
23. Andrade C, Sandarsh S, Chethan KB, et al. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry*. 2010;71:1565–1575.
24. Maurer-Spurej E, Pittendreigh C, Solomons K. The influence of selective serotonin reuptake inhibitors on human platelet serotonin. *Thromb Haemost*. 2004;91:119–128.
25. Padma LRR, Rohini ST. Selective serotonin reuptake inhibitors and the risk of bleeding. *Int J Basic Clin Pharmacol*. 2013;2:272–274.
26. Ramasubbu R. Cerebrovascular effects of selective serotonin reuptake inhibitors: a systematic review. *J Clin Psychiatry*. 2004;65:1642–1653.
27. Singhal AB, Caviness VS, Begleiter AF, et al. Cerebral vasoconstriction and stroke after use of serotonergic drugs. *Neurology*. 2002;58:130–133.
28. Chen Y, Guo JJ, Li H, et al. Risk of cerebrovascular events associated with antidepressant use in patients with depression: a population-based, nested case-control study. *Ann Pharmacother*. 2008;42:177–184.
29. Bak S, Tsiropoulos I, Kjaersgaard JO, et al. Selective serotonin reuptake inhibitors and the risk of stroke: a population-based case-control study. *Stroke*. 2002;33:1465–1473.
30. Wang MT, Chu CL, Yeh CB, et al. Antidepressant use and risk of recurrent stroke: a population-based nested case-control study. *J Clin Psychiatry*. 2015;76:e877–e885.
31. Ho JM, Gomes T, Straus SE, et al. Adverse cardiac events in older patients receiving venlafaxine: a population-based study. *J Clin Psychiatry*. 2014;75:e552–e558.
32. Lee YC, Lin CH, Lin MS, et al. Comparison of the effects of serotonin-norepinephrine reuptake inhibitors versus selective serotonin reuptake inhibitors on cerebrovascular events. *J Clin Psychiatry*. 2016;77:e1–e7.
33. Kozyrskyj AL, Mustard CA. Validation of an electronic population-based prescription database. *Ann Pharmacother*. 1998;32:1152–1157.
34. Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. *J Clin Psychiatry*. 1998;59:502–508.
35. Oslin DW, Ten Have TR, Streim JE, et al. Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. *J Clin Psychiatry*. 2003;64:875–882.
36. Martens P, Browness M, Au W, et al. *Health Inequities in Manitoba: is the socioeconomic gap in health widening or narrowing over time?* MBL Manitoba Centre for Health Policy: Winnipeg, MB; 2010;Available at: http://mchp-appserv.cpe.umanitoba.ca/reference/Health_Ineq_final_WEB.pdf Accessed August 8, 2016.
37. Fransoo R, Martens P, Prior H, et al. *Adult obesity in Manitoba: prevalence, associations and outcomes*. Winnipeg, MB: Manitoba Centre for Health Policy; 2011;Available at: http://mchp-appserv.cpe.umanitoba.ca/reference/MCHP-Obesity_Report_WEB.pdf Accessed August 8, 2016.
38. Tu JV, Austin PC, Filate WA, et al. Outcomes of acute myocardial infarction in Canada. *Can J Cardiol*. 2003;19:893–901.
39. Fransoo R, Martens P, The Need to Know Team, et al. *The 2013 RHA Indicators Atlas*. Winnipeg, MB: Manitoba Centre for Health Policy; : 2013. Available at: http://mchp-appserv.cpe.umanitoba.ca/reference/RHA_2013_web_version.pdf. Accessed August 8, 2016.
40. Brownell M, Martens PJ, Kozyrskyj A, et al. *Assessing the Health of Children in Manitoba: A Population-Based Study*. Winnipeg, MB: Manitoba Centre for Health Policy and Evaluation; 2001;Available at: http://mchp-appserv.cpe.umanitoba.ca/reference/child_pdf_one_document.pdf. Accessed August 8, 2016.
41. Lix L, Yogendran M, Mann J. *Defining and Validating Chronic Diseases: An Administrative Data Approach. An Update with ICD-10-CA*. Winnipeg, MB: Manitoba Centre for Health Policy, University of Manitoba; 2008; Available at: http://www.umanitoba.ca/faculties/health_sciences/medicine/units/mchp/projects/media/ICD10_Final.pdf. Accessed August 8, 2016.
42. Deb S, Austin PC, Tu JV, et al. A review of propensity-score methods and their use in cardiovascular research. *Can J Cardiol*. 2016;32:259–265.
43. Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. *Stat Methods Med Res*. 2015;Published online ahead of print April 30, 2015. Available at: http://smm.sagepub.com.uml.idm.oclc.org/content/early/2015/04/30/0962280215584401.long. Accessed August 6, 2016.
44. Manitoba Centre for Health Policy. Dose intensity. *Manitoba Centre for Health Policy*. Available at: http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?printer=Y&conceptID=1122#PDD. Accessed: August 1, 2016.
45. Lee YC, Lin CH, Lin MS, et al. Effects of selective serotonin reuptake inhibitors versus tricyclic antidepressants on cerebrovascular events: a nationwide population-based cohort study. *J Clin Psychopharmacol*. 2013;33:782–789.
46. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metab Rev*. 2009;41:89–295.