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Use of SSRI, But Not SNRI, Increased Upper and Lower Gastrointestinal Bleeding

A Nationwide Population-Based Cohort Study in Taiwan

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Abstract: Selective serotonin receptor inhibitor (SSRI) and serotonin-noradrenaline reuptake inhibitor (SNRI) users have been reported to have an increased risk of upper gastrointestinal bleeding (UGIB), but their association with lower gastrointestinal bleeding (LGIB) is less studied. This study aimed to analyze the incidence of UGIB and LGIB among SSRI users, SNRI users, and controls.

Using the National Health Insurance Research Database of Taiwan, 9753 subjects who were taking serotonin reuptake inhibitors (8809 with SSRIs, and 944 with SNRIs), and 39,012 age, sex, and enrollment time-matched controls were enrolled at a 1:4 ratio. The log-rank test was used to analyze differences in the cumulative hazard of UGIB and LGIB between groups. Cox proportional hazard regression analysis was used to evaluate the independent risk factors for UGIB and LGIB.

During the 10-year follow-up period from 2000 to 2010, SSRI users, but not SNRI users, had significantly higher incidences of UGIB and LGIB than the controls ($P < 0.001$; log-rank test). The use of SSRIs, but not SNRIs, was independently associated with an increased risk of UGIB (hazard ratio [HR]:1.97; 95% confidence interval [CI]: 1.67–2.31) and LGIB (HR: 2.96, 95% CI: 2.46–3.57) after adjusting for age, sex, underlying comorbidities, and medications.

The long-term use of SSRIs significantly increased the risk of UGIB and LGIB, and caused more LGIB than UGIB in the general population after adjusting for possible confounding factors, but the association between SNRIs and GIB is insignificant. Further prospective studies are needed to clarify this important issue.

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Abbreviations: ASA = acetylsalicylic acid, CAD = coronary artery disease, COX = cyclooxygenase, DDD = defined daily dose, GIB/UGIB/LGIB = gastrointestinal bleeding/upper gastrointestinal bleeding/lower gastrointestinal bleeding, LHID = Longitudinal Health Insurance Database, NHIRD = National Health Insurance Research Database, NSAID = nonsteroidal anti-inflammatory drug, PUD = peptic ulcer disease, SNRI = serotonin-noradrenaline reuptake inhibitor, SSRI = selective serotonin receptor inhibitor.

INTRODUCTION

Selective serotonin receptor inhibitors (SSRIs) are recommended as the first-line pharmacotherapy in treating depression and are approved for the treatment of various psychogenic disorders, mainly based on their favorable safety profile.[1] However, the inhibition of serotonin uptake into platelets by SSRIs may increase the risk of bleeding including gastrointestinal bleeding (GIB), genitourinary bleeding, and intracranial hemorrhage.[2] The concern for upper GIB (UGIB) has led to a large number of studies, especially when the use of SSRIs/SNRIs is combined with ulcerogenic medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antiplatelet agents.[2–8] A recent meta-analysis suggests that SSRIs are associated with only a modest increase of UGIB with a number need to harm of 3177 in low-risk and 881 in high-risk patients.[9] However, the association between serotonin-noradrenaline reuptake inhibitors (SNRIs) and UGIB is still controversial: some authors suggest SNRIs carry more risk for UGIB while others claim only SSRIs have a higher possibility of causing UGIB.[5,10] Literature about the association between antidepressants usage and LGIB is relatively few with inconsistent results.[11–14]

This nationwide cohort study aimed to compare the incidence of UGIB and LGIB among controls, SSRI and SNRI users and to identify the risk factors for UGIB, LGIB in all enrollees and in SSRI users after adjustments for possible confounding factors such as age, sex, underlying comorbidities, and some medication.

METHODS

Data Sources

All data were collected from the Taiwan National Health Insurance Research Database (NHIRD) (http://www.nhri.org.tw/nhird/en/index.htm). This database is derived from a mandatory single-payer social health insurance system initiated by the Taiwanese government in 1995. By 2014, over 23 million residents, corresponding to approximately 99% of the population of Taiwan, were covered by this health insurance system.[15]

The present study analyzed data from the Longitudinal Health Insurance Database (LHID2000) of the NHIRD that includes a cohort dataset of 1,000,000 randomly sampled individuals who were traced retrospectively to 1996 and followed up to 2010. There were no statistically significant differences in age, sex, and healthcare cost distribution between patients in the LHID2000 and the original NHIRD. The comprehensive healthcare dataset included enrollment files, registry for drug prescription (i.e., dose, frequency, starting and ending dates, and administration route), claims data, and catastrophic illness files.[11]

In the cohort dataset, each patient's primary identification number was encrypted for privacy. Therefore, as this cohort dataset consisted of deidentified secondary data released to the public for research purposes, the study did not require informed consent from the patients. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

Study Group

Patients who took serotonin reuptake inhibitors (SSRIs or SNRIs) with an average dose of 28 defined daily doses (DDD) within an every 12-week interval after January 2000 were considered for enrollment into the study group. SSRI users were defined as those taking at least 28 DDD within 12 weeks of an SSRI (fluvoxamine, fluoxetine, paroxetine sertraline citalopram, or escitalopram) without using an SNRI (milnacipran, venlafaxine, duloxetine) during the SSRI administration period. SNRI users were defined as those taking at least 28 DDD within 12 weeks of an SNRI without using any SSRI during the SNRI administration period. SSRI users who had discontinued SSRIs for more than 1 year and switched to SNRIs thereafter could be enrolled as SNRI users for the period 2000 to 2010. SNRI users who had discontinued SNRIs for more than 1 year and switched to SSRIs thereafter could be enrolled as SSRI users for the period 2000 to 2010. Patients were excluded if they were taking less than 28 DDD within 12 weeks in the follow-up, until they were eligible again. After excluding the patients with alcohol-related disease (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes: 291.xx, 303.xx, 305.xx, 571.0, 571.1, 571.2, 571.3), malignancy of the GI tract (150.xx, 151.xx, 152.xx, 153.xx, 154.xx), inflammatory bowel disease (556.x, 555.x), bleeding of the GI tract (530.7, 530.82, 531.0, 531.00, 531.01, 531.2,531.2x, 531.4, 531.4x, 531.6,531.6x, 532.0, 532.00, 532.01, 532.2,532.2x, 532.4, 532.4x, 532.6,532.6x, 533.0, 533.00, 533.01, 533.2,533.2x, 533.4, 533.4x, 533.6,533.6x, 534.0, 534.00, 534.01, 534.2,534.2x, 534.4, 534.4x, 534.6,534.6x, 535.X1, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.x, 537.84, 537.85, 569.86) before January 1, 2000, 8809 SSRI users and 944 SNRI users were identified from the LHID2000. While 102 SSRI users who discontinued SSRI for more than 1 year and started SNRI later were enrolled and followed in the SSRI group at first and in the SNRI group later, 137 SNRI users who ceased to take SNRI for more than 1 year and started to take SSRI were enrolled and followed in the SNRI group at first and in the SSRI group later in this study cohort. Subjects with a history of uncomplicated peptic ulcer disease (PUD) (ICD-9-CM codes: 531.30, 531.70, 531.90, 532.30, 532.70, 532.90, 533.30, 533.70, and 533.90) were included.

Control Group

Using the same exclusion criteria (alcoholic disease, GI bleeding and malignancy, inflammatory bowel disease) as the study group, a control group of 39,012 subjects who had not taken SSRIs or SNRIs before and after enrollment during the period 2000 to 2010 were selected from the same cohort dataset at a 1:4 ratio (SSRI+SNRI: control). They were matched with the study group in terms of age, sex, and time of enrollment.

Comorbidities and Medications

Other recorded covariates included age, sex, preexisting hypertension (ICD-9-CM codes 401.xx-405.xx), diabetes mellitus (ICD-9-CM codes 250.xx), CAD (ICD-9-CM codes 411.xx-414.xx), chronic obstructive pulmonary disease (ICD-9-CM codes 491.xx, 492.xx, 494.xx, and 496.xx), chronic renal disease (ICD-9-CM codes 585, 586, 588.8,588.9, 250.4, 274.1, 403.x1, 404.x2, 404.x3, and 440.1), liver cirrhosis (ICD-9-CM codes 571.2, 571.5, and 571.6), uncomplicated PUD (ICD-9-CM codes 531.30, 531.70, 531.90, 532.30, 532.70, 532.90, 533.30, 533.70, and 533.90), and dyslipidemia (ICD-9-CM codes 272.0, 272.01, 272.3, 272.4).

Medication (acetylsalicylic acid [ASA] [low-dose]), NSAIDs [oral or parenteral], selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), steroids [oral or parenteral], clopidogrel, ticlopidine, and warfarin were identified and classified by the National Drug Code and the Anatomic Therapeutic Chemical Code, which is an internationally accepted classification system of drugs coordinated by the World Health Organization Collaborating Center for Drug Statistics Methodology.[16] Use of medications was defined as prescription of these medications for more than 6 weeks within 12 weeks before the index date. Censoring occurred when study subjects withdrew from national health insurance for reasons including mortality, or were prescribed an SSRI or SNRI with less than 28 DDD within every 12-week period, respectively, met the exclusion criteria during the study period, or reached the endpoints.

ENDPOINTS

The primary endpoint of this study was the occurrence of GIB as the main diagnosis during hospitalization after enrollment. GIB included UGIB (ICD-9-CM codes 530.7, 530.82, 531.0, 531.00, 531.01, 531.2,531.2x, 531.4, 531.4x, 531.6,531.6x, 532.0, 532.00, 532.01, 532.2,532.2x, 532.4, 532.4x, 532.6,532.6x, 533.0, 533.00, 533.01, 533.2,533.2x, 533.4, 533.4x, 533.6,533.6x, 534.0, 534.00, 534.01, 534.2,534.2x, 534.4, 534.4x, 534.6,534.6x, 535.X1, 537.83, 537.84, 578.0) and LGIB (ICD-9-CM 562.02, 562.03, 562.12, 562.13, 569.86, 569.3, 569.85, 578.1). The 2 endpoints were followed and analyzed respectively and independently.

Statistical Analysis

All data were expressed as frequency (percentage) or mean ± standard deviation. Parametric continuous data between the study and control groups were compared by one-way analysis of variance (ANOVA), while categorical data were compared using the χ^2 test and Yates' correction or Fisher's exact test, as appropriate. Cumulative hazard was assessed using Kaplan–Meier analysis, with significance based on the log-rank test.

Multiple regression analysis was conducted using Cox proportional hazard regression analysis to identify the risk factors for UGIB and LGIB. Statistical significance was considered a 2-sided P value of less than 0.05. Microsoft SQL Server 2005 was used for data management and computing. All statistical analyses were performed using the SPSS software package (Version 15.0, SPSS Inc, Chicago, IL).

TABLE 1. Baseline Characteristics of the Study Population Among SSRI Users, SNRI Users, and Controls

	Controls N = 39,012	SSRI Group N = 8809	SNRI group N = 944	*P* Value
Age, years	50.36 ± 17.33	50.44 ± 17.44	49.85 ± 16.51	0.609
Male, n (%)	14,964 (38.36)	3378 (38.35)	363 (38.45)	0.998
Hypertension, n (%)	6828 (17.50)	1790 (20.32)	191 (20.23)	<0.001
Diabetes, n (%)	3424 (8.78)	852 (9.67)	95 (10.06)	0.014
Coronary artery disease, n (%)	3905 (10.01)	1255 (14.25)	148 (15.68)	<0.001
Chronic obstructive pulmonary disease, n (%)	3747 (9.60)	1004 (11.40)	113 (11.97)	<0.001
Chronic renal disease, n (%)	1262 (3.23)	319 (3.62)	37 (3.92)	0.109
Uncomplicated peptic ulcer disease, n (%)	6623 (16.98)	2077 (23.58)	278 (29.45)	<0.001
Cirrhosis, n (%)	324 (0.83)	79 (0.90)	12 (1.27)	0.303
Dyslipidemia, n (%)	5636 (14.45)	1480 (16.80)	169 (17.90)	<0.001
Medication				
ASA, n (%)	2849 (7.30)	807 (9.16)	66 (6.99)	<0.001
NSAIDs, n (%)	11,066 (28.37)	2552 (28.97)	307 (32.52)	0.013
COX-2 inhibitors, n (%)	1667 (4.27)	447 (5.07)	50 (5.30)	0.002
Steroids, n (%)	2484 (6.37)	531 (6.03)	50 (5.30)	0.223
Clopidogrel, n (%)	313 (0.80)	89 (1.01)	15 (1.59)	<0.008
Ticlopidine, n (%)	124 (0.32)	67 (0.76)	2 (0.21)	<0.001
Warfarin, n (%)	192 (0.49)	78 (0.89)	8 (0.85)	<0.001
Upper gastrointestinal bleeding	672 (1.72)	196 (2.22)	10 (1.06)	0.001
Lower gastrointestinal bleeding	396 (1.02)	161 (1.83)	4 (0.42)	<0.001

Data are mean ± SD, one-way analysis of variance and χ^2 test were used for continuous variables and categorical variables, respectively. ASA = acetyl salicylatic acid, COX = cyclooxygenase, NSAIDs = nonsteroidal anti-inflammatory drugs; SNRIs = serotonin-noradrenaline reuptake inhibitors, SSRIs = selective serotonin receptor inhibitors.

RESULTS

Demographic and Clinical Data

In all, 8809 SSRI users and 944 SNRI users were enrolled in the study, including 8570 pure SSRI users, 705 pure SNRI users, 102 SSRI-SNRI cross-over users, and 137 SNRI-SSRI cross-over users. There were no significant differences between the groups in terms of age, sex, rate of chronic renal disease, cirrhosis, and the use of steroids. However, the SSRI and SNRI groups had significantly higher rates of hypertension, diabetes, CAD, chronic obstructive pulmonary disease, uncomplicated PUD, dyslipidemia, and use of COX-2 inhibitors, clopidogrel, and warfarin. More SSRI users used aspirin and ticlopidine, while more SNRI users used NSAIDs (Table 1).

Cumulative Hazard for UGIB and LGIB

During the 10-year follow-up period (median, 5.06 years; range, 0.01–11.01 for UGIB; median, 5.08 years, range, 0.01–11.01 for LGIB), 878 (1.80%) of the 48,765 patients developed UGIB, 561 (1.15%) developed LGIB (Table 1). The cumulative hazard of UGIB and LGIB using Kaplan–Meier analysis showed that the SSRI group, but not the SNRI group, had a significantly higher hazard for UGIB and LGIB than the control group (all $P < 0.001$, Figures 1 and 2).

Risk Factors for UGIB and LGIB in the Whole Study Population

After adjusting for age, sex, presence of hypertension, diabetes, CAD, chronic obstructive pulmonary disease, chronic renal disease, uncomplicated PUD, cirrhosis, dyslipidemia, and the use of ASA, NSAIDs, COX-2 inhibitors, steroids, clopidogrel, ticlopidine, and warfarin, use of SSRI was an independent risk factor for UGIB (hazard ratio [HR]: 1.97, 95% confidence interval [CI]: 1.67–2.31) and LGIB (HR: 2.96, 95% CI: 2.46–3.57). However, the use of SNRIs did not increase the risk of UGIB and LGIB (Tables 2 and 3). Cox proportional hazard regression analysis showed no association

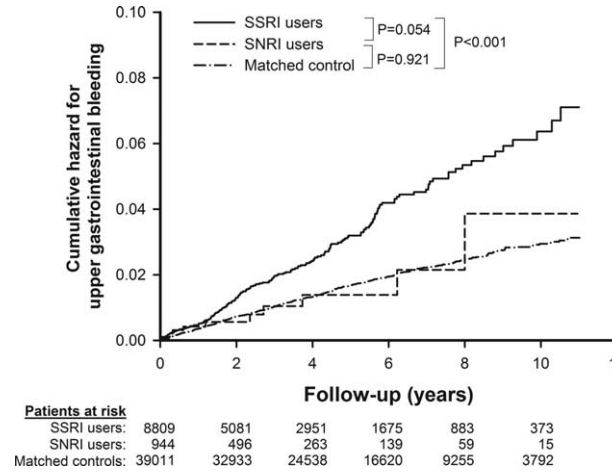

FIGURE 1. Kaplan–Meier estimates of cumulative hazard of upper gastrointestinal bleeding of the patients categorized by selective serotonin reuptake inhibitors (SSRI) users, serotonin-noradrenaline reuptake inhibitor (SNRI) users, and the matched controls ($P < 0.001$ between the SSRI group and control group by the log-rank test).

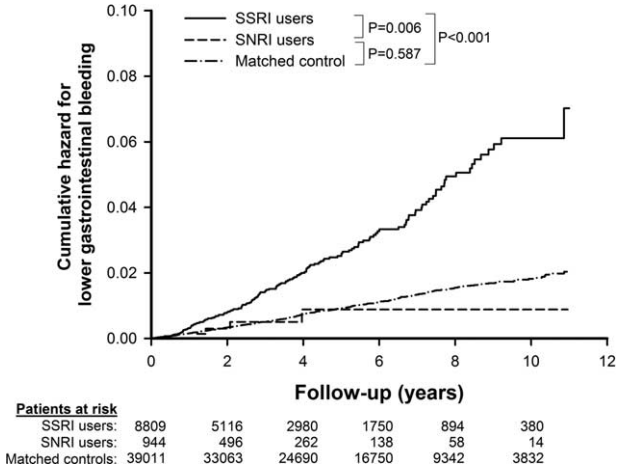

FIGURE 2. Kaplan–Meier estimates of cumulative hazard of lower gastrointestinal bleeding of the patients categorized by selective serotonin reuptake inhibitors (SSRI) users, serotonin-noradrenaline reuptake inhibitor (SNRI) users, and the matched controls ($P < 0.001$ between the SSRI group and control group by the log-rank test).

TABLE 2. Independent Predictors of Upper Gastrointestinal Bleeding Among All the Enrollees by Cox Regression Analysis

	Hazard Ratio (95% CI)	*P* Value
Age	1.06 (1.06–1.07)	<0.001
Male	1.69 (1.48–1.93)	<0.001
Hypertension	1.01 (0.86–1.19)	0.901
Diabetes	1.00 (0.81–1.23)	0.987
Coronary artery disease	0.98 (0.82–1.17)	0.814
Chronic obstructive pulmonary disease	1.08 (0.90–1.29)	0.428
Chronic renal disease	1.90 (1.51–2.39)	<0.001
Uncomplicated peptic ulcer disease	1.29 (1.10–1.51)	0.002
Cirrhosis	3.02 (2.07–4.40)	<0.001
Dyslipidemia	0.84 (0.69–1.01)	0.064
Medication		
ASA	1.51 (1.28–1.79)	<0.001
NSAIDs	1.64 (1.43–1.89)	<0.001
COX-2 inhibitors	1.44 (1.17–1.76)	<0.001
Steroids	1.43 (1.15–1.77)	0.001
Clopidogrel	1.24 (0.83–1.86)	0.289
Ticlopidine	0.48 (0.18–1.27)	0.138
Warfarin	0.97 (0.52–1.80)	0.911
SSRIs	1.97 (1.67–2.31)	<0.001
SNRIs	1.09 (0.58–2.04)	0.786

ASA = acetyl salicylatic acid, COX = cyclooxygenase, NSAIDs = nonsteroidal anti-inflammatory drugs, SNRIs = serotonin-noradrenaline reuptake inhibitors, SSRIs = selective serotonin receptor inhibitors. Each variable was adjusted for every other variable listed.

TABLE 3. Independent Predictors of Lower Gastrointestinal Bleeding Among All the Enrollees by Cox Regression Analysis

	Hazard Ratio (95% CI)	*P* Value
Age	1.08 (1.07–1.09)	<0.001
Male	1.42 (1.21–1.68)	<0.001
Hypertension	1.04 (0.85–1.26)	0.737
Diabetes	1.25 (0.97–1.60)	0.080
Coronary artery disease	1.15 (0.92–1.42)	0.215
Chronic obstructive pulmonary disease	1.28 (1.04–1.59)	0.023
Chronic renal disease	1.72 (1.28–2.30)	<0.001
Uncomplicated peptic ulcer disease	1.11 (0.91–1.36)	0.303
Cirrhosis	3.94 (2.58–6.03)	<0.001
Dyslipidemia	0.70 (0.55–0.90)	0.005
Medication		
ASA	1.25 (1.01–1.54)	0.042
NSAIDs	1.29 (1.04–1.55)	0.035
COX-2 inhibitors	0.77 (0.57–1.06)	0.106
Steroids	1.47 (1.11–1.93)	0.007
Clopidogrel	1.33 (0.84–2.11)	0.228
Ticlopidine	1.64 (0.87–3.07)	0.125
Warfarin	1.97 (1.16–3.37)	0.013
SSRIs	2.96 (2.46–3.57)	<0.001
SNRIs	0.84 (0.32–2.27)	0.737

ASA = acetyl salicylatic acid, COX = cyclooxygenase, NSAIDs = nonsteroidal anti-inflammatory drugs, SNRIs = serotonin-noradrenaline reuptake inhibitors, SSRIs = selective serotonin receptor inhibitors. Each variable was adjusted for every other variable listed.

between different cumulative doses of SSRIs (SSRI: 28–140 DDD, 141–280 DDD, and >280 DDD) and the risk of UGIB and LGIB (Table 4).

Risk Factors for UGIB and LGIB in the SSRI Users

After adjusting for age, sex, presence of hypertension, diabetes, CAD, chronic obstructive pulmonary disease, chronic renal disease, uncomplicated PUD, cirrhosis, dyslipidemia, and the use of ASA, NSAIDs, COX-2 inhibitors, steroids, clopidogrel, ticlopidine, and warfarin, we found that age, male sex, use of ASA, and NSAIDs were independent risk factors for UGIB in SSRI users; age, male sex, chronic renal disease, and use of clopidogrel were independent risk factors for LGIB in SSRI users (Table 5).

DISCUSSION

In this study, we found that the long-term use of SSRIs, but not SNRIs, incurred a significantly higher risk of UGIB and LGIB in the general population after adjustments for age, sex, comorbidities (ie, hypertension, diabetes, CAD, chronic obstructive pulmonary disease, chronic renal disease, uncomplicated PUD, cirrhosis, and dyslipidemia), and medications (eg, ASA, NSAIDs, COX-2 inhibitors, steroids, clopidogrel, ticlopidine, and warfarin).

An increased risk of UGIB with the use of SSRIs has been found in population-based cohort studies and case-control

TABLE 4. The Hazard Ratio of Different Accumulation Dose of SSRIs for Upper and Lower Gastrointestinal Bleeding After Cox Multivariate Regression Analysis

	Hazard Ratio (95% CI)	*P* Value
Upper gastrointestinal bleeding		
SSRIs (28–140 DDD vs control)	2.39 (1.68–3.39)	<0.001
SSRIs (141–280 DDD vs control)	2.39 (1.82–3.13)	<0.001
SSRIs (>280 DDD vs control)	1.71 (1.39–2.10)	<0.001
Lower gastrointestinal bleeding		
SSRIs (28–140 DDD vs control)	3.77 (2.55–5.57)	<0.001
SSRIs (141–280 DDD vs control)	3.18 (2.30–4.40)	<0.001
SSRIs (>280 DDD vs control)	2.71 (2.15–3.41)	<0.001

DDD = defined daily doses, SSRIs = selective serotonin receptor inhibitors.

studies.[3,4,7,9] Our results also revealed that the use of SSRIs increased UGIB risk (Table 2). The possible mechanisms by which SSRIs increase the occurrence of UGIB include the inhibition of serotonin reuptake by platelets leading to depletion of serotonin, which impairs platelet aggregation;[17] increased gastric acid secretion and aggravation of NSAID-induced gastric mucosal injury.[18] Whether the use of SNRIs will increase the occurrence of UGIB is controversial, our result found the risk of UGIB was not associated with the use of SNRIs which was consistent with previous studies.[5,10,19,20] These findings support the notion that the occurrence of bleeding is strongly associated with high-affinity (SSRIs), rather than low-affinity (SNRIs), serotonin transporters.[21,22] In addition to SSRIs, age, male sex, chronic renal disease, uncomplicated PUD, cirrhosis, use of ASA, NSAIDs, COX-2 inhibitors, and steroids were also important risk factors for UGIB in all the enrollees.

Epidemiological data showed that men have a higher incidence of UGIB and LGIB respectively in the general population.[23,24] Men are more likely to have ulcer disease and more acidic gastric microenvironment which may account for the finding that male sex is a risk factor for UGIB.[25] Previous studies also have found that male sex was still a risk for UGI bleeding in patients taking serotonin receptor inhibitors.[10,26] This study revealed that male sex was a risk factor for both UGIB and LGIB in patients taking SSRIs. There are 2 possible explanations for the sex differences in the risk of GI bleeding after SSRI exposure. First, serotonin blood levels are lower in males than in females, because estradiol that is higher in female can stimulate serotonin uptake by platelets.[27] Second, estrogen can stimulate platelet aggregation, resulting in higher platelet aggregation activity in females compared with males.[28]

We knew that about one-fourth of the Taiwanese population with *Helicobacter pylori* infection[29] and *H. pylori* infection is a very important risk factor for ulcer bleeding and UGI bleeding. This epidemiologic study lacks information regarding the presence of *H. pylori* in this cohort and is therefore unable to assess this role of *H. pylori* in the UGI bleeding of SSRI/SNRI users. Wang's study showed that SSRI is an important risk factor for UGI bleeding regardless of *H. pylori* status in Taiwan,[26] whereas Dall's study showed that *H. pylori* infection increased the risk of SSRI-related serious UGI bleeding.[30] Though both the SSRI and SNRI users had significantly higher rates of previous PUD than controls (Table 1), which possibly implied that higher rates of *H. pylori* infection in the SSRI and SNRI groups. According to the guidelines of *H. pylori* eradication issued and covered by the Taiwan Bureau of National Health Insurance and previous publication,[24,31] it is reasonable to deduce that 80% patients with previous PUD have cured their *H. pylori* infection already. If that is true, both the SSRI and SNRI groups might not have higher rate of *H. pylori* infection. Interestingly, use of SSRI but not SNRI increased the risk of UGI bleeding in this study without adjustment of the status of *H. pylori* infection. Further study is needed to clarify the role of *H. pylori* for UGI bleeding in the SSRI/SNRI users.

Our cohort study also found that SSRIs are more strongly associated with LGIB (OR: 2.96) than UGIB (OR: 1.97) which is comparable with Wessinger's retrospective case control study.[14] Besides, age, male sex, chronic obstructive pulmonary disease, chronic renal disease, cirrhosis, use of ASA, NSAIDs, steroids, and warfarin were important risk factors for LGIB in our study cohort. These findings are consistent with previous studies showing that patients with chronic renal disease, renal failure, cirrhosis, and patients taking antiplatelets or NSAIDs had higher risks of UGIB and LGIB.[11,15,32] In addition, the finding that ASA use and NSAID use were independent risk factors for UGIB in SSRI users, and that use of clopidogrel was an independent risk factor for LGIB in SSRI users, coincides with previous findings that the risk of GIB is increased when SSRI users take NSAIDS or antiplatelets simultaneously.[3,4,7,9] Our results further found the use of SNRIs was not related to LGIB while SSRIs were strongly related to the occurrence of LGIB and supported the concept that agents that influence hemostasis have the potential to increase bleeding through the gastrointestinal tract.[14]

The important strength of this study is that it is a nationwide population-based cohort study with long-term follow-up and considering the important confounding factors including underlying comorbidity and medication. The Taiwan NHIRD encompasses all computerized information relevant to insurance claims. More than 99% of the 23 million residents in Taiwan are covered by the NHI, which is easily accessible and offers low copayments to the general population.[16] There are several limitations to this study. First, this was a cohort study with observations based on hospitalized patients with UGIB and

TABLE 5. Independent Risk Factors for Upper Gastrointestinal Bleeding and Lower Gastrointestinal Bleeding in SSRI Users by Cox Multivariate Regression Analysis

Upper Gastrointestinal Bleeding	Hazard Ratio (95% CI)	*P* Value
Age	1.05 (1.04–1.06)	<0.001
Male	1.70 (1.28–2.26)	<0.001
Use of ASA	1.66 (1.18–2.33)	0.004
Use of NSAIDs	1.61 (1.19–2.17)	0.002
Lower gastrointestinal bleeding	Hazard ratio (95% CI)	*P* value
Age	1.08 (1.07–1.09)	<0.001
Male	1.66 (1.21–2.26)	0.002
Chronic renal disease	1.80 (1.03–3.14)	0.038
Use of clopidogrel	2.39 (1.25–4.62)	0.009

ASA = acetyl salicylatic acid, NSAIDs = nonsteroidal anti-inflammatory drugs.

LGIB. Certain selection biases may exist and caution must be taken in extrapolating the results. Second, alcohol itself is a risk factor for UGIB even without cirrhosis.[33,34] Patients with mental disorders had 5-fold more alcoholic disorder than the general population in a hospital-based survey in Taiwan.[35] Though we excluded alcoholic cirrhosis and most alcohol-related diseases in the study and control groups, the influence of alcohol on GIB risk in this study cannot be totally excluded. Thus, the occurrence of UGIB and LGIB in SSRI/SNRI users could be overestimated. Third, acid-suppressing agents have been proven to reduce UGIB risk. Guidance and advice in the UK suggest all patients on an SSRI with 1 additional risk factor for UGIB should be additionally prescribed a proton pump inhibitor (PPI) for prophylaxis.[5] However, the use of PPIs in Taiwan is paid for by NHI only after endoscopic confirmation of peptic ulcer or reflux esophagitis. Data regarding the prophylactic use of PPI were not available in the NHIRD for both the study group and the control group.[11] Fourth, 20 to 30% of the general population use nonprescription medication and pain-relieving agents, which are responsible for about 10% of the nonprescription medications, and the use is even greater among psychiatric patients in Taiwan.[36] Because the use of nonprescription drugs is not documented in the NHIRD, its impact on the bleeding risk cannot be evaluated in this study. Fifth, though heparin/enoxaparin use and the procedure of percutaneous coronary interventions which are also risk factors for GIB are not included for analysis in the study, the use of dual antiplatelets (aspirin and clopidogrel) after percutaneous coronary interventions was included for analysis in this study. Sixth, the case number of SNRI group is much smaller than that of SSRI group. Whether taking SNRI is not a risk factor for GIB needs larger prospective studies to clarify it. Finally, despite the clear definition and corresponding ICD-9-CM code, some subjects with obscure GIB are indeed found in daily clinical practice. Misclassified coding occurs when an obscure GIB, usually in small bowels, does not have a corresponding ICD-9-CM code and when most subjects with an obscure GIB do not undergo capsule endoscopy or enteroscopy to explore the bleeding source.[32] However, it was impossible to have a validated system to verify the accuracy of diagnostic coding within the database due to deidentification of the study subjects.

In summary, the long-term use of SSRIs significantly increased the risk of UGIB and LGIB, and caused more LGIB than UGIB in the general population after adjusting for possible confounding factors, whereas the use of SNRIs did not increase. Accordingly, SNRIs might be a more appropriate choice than SSRIs for patients at risk of GI bleeding; however, further prospective studies are needed to clarify this important issue.

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