RISKS OF HOSPITALIZATION FOR UPPER GASTROINTESTINAL BLEEDING IN SELECTIVE SEROTONIN REUPTAKE INHIBITORS USERS AFTER *HELICOBACTER PYLORI* ERADICATION THERAPY: A PROPENSITY SCORE MATCHING ANALYSIS

Running title: UGIB risk of SSRI

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SUMMARY

Background: Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for depression but there is a concern on the risk of upper gastrointestinal bleeding (UGIB). Past studies, however, are largely confounded by the presence of *Helicobacter pylori* (HP).

Aims: To evaluate the UGIB risk of SSRI users after treatment for HP.

Methods: This was a propensity score (PS) matched cohort study with patients who used SSRI after receiving HP eradication therapy from the Hong Kong territory-wide healthcare database. The primary outcome was hospitalization for non-variceal UGIB. PS matching analysis with a ratio of 1:2 plus Cox regression model was used to compute the hazards ratios (HR) and 95% confidence intervals (CI) of UGIB risk.

Results: In this study, 3,358 SSRI users and 57,906 non-users were included. The median follow-up duration was 7.74 (interquartile range 5.32-10.42) years. The overall crude incidence of hospitalization for UGIB was 3.98 (95% CI 3.80-4.16) per 1000 person-years. In the PS matching analysis of 3,358 SSRI users with 6,716 non-users, SSRI was associated with a higher risk of UGIB than non-users (HR 1.95, 95% CI 1.41-2.70). This result was consistent in sensitivity analysis with 1:1 PS matching (HR 2.13, 95% CI 1.50-3.02) and multivariable analysis with 1-month intervals (HR 1.81, 95% CI 1.34-2.45) or 3-month intervals (HR 1.61, 95% CI 1.20-2.17). After stratifying by age, the increased risk of SSRI was only significant among patients >50 years.

Conclusion: SSRI users have a higher risk of hospitalization for non-variceal UGIB after treatment for HP, particularly among older patients.

Keywords: upper gastrointestinal bleeding, selective serotonin reuptake inhibitors, *Helicobacter pylori* eradication

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are currently recommended as the first-line treatment for depression and one of the most commonly prescribed antidepressants.[1,2] SSRIs are generally considered safe with few serious adverse effects.[3] However, there is still concern on the increased bleeding risk associated with SSRIs, especially severe upper gastrointestinal bleeding (UGIB).[4,5] The potential biological mechanism could be due to the inhibition of serotonin uptake in platelets by SSRIs which decrease the serotonin level in platelets, as serotonin plays a key role in platelets aggregation.[6,7] SSRI users with other risk factors, such as concomitant users of aspirin, antiplatelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, or history of UGIB or peptic ulcer may have a further higher bleeding risk.[8]

Though many studies have evaluated the association between the risk of UGIB and SSRI use,[4,5] the potential confounding effects of *Helicobacter pylori* infection have not been addressed. In particular, *H. pylori* infection is an independent risk factor for UGIB, and could further increase the risk of UGIB among SSRI users.[9] On the other hand, it remains unknown whether eradiation of *H. pylori* could modulate the risk of SSRIs related UGIB.

In this study, we determined the risk of UGIB among new SSRI users who had *H. pylori* eradicated in a large territory-based cohort of *H. pylori*-infected patients.

METHODS

Data Source

The data in this study were retrieved from an electronic healthcare database (Clinical Data Analysis and Reporting System [CDARS]) of the Hong Kong Hospital Authority, which is the only public healthcare provider for health services and covers 87%–94% of all secondary and tertiary care in Hong Kong. This system is used to record key information of patients from both public hospital and clinics for both audit and research purposes including patients' demographics, diagnoses, prescriptions, hospitalization, and death. This details of the database has been described in previous territory-wide studies.[10-13] The coding system in this database is International Classification of Diseases, 9th Revision (ICD-9), of which the accuracy for GIB has been verified in previous study.[13] All data in CDARS and this study were anonymized, in which unique numeric identifiers were used to represent specific patients. This study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (Reference Number: UW 16-545).

Study Design and Patients

In this retrospective territory-wide cohort study, we identified all adult *H. pylori*-infected patients, who had received a course of clarithromycin-containing triple therapy for *H. pylori* in all public hospitals in Hong Kong between Jan 2003 and Dec 2012. The details of this cohort had been described previously.[10,12] The clarithromycin-containing

triple therapy was defined as the co-prescription of clarithromycin with either amoxicillin or metronidazole and one proton pump inhibitors (PPI) with the same start date of prescriptions and overlapping duration of $\geqslant$7 days. Patients who had prior gastrointestinal cancer, coagulant deficiency, surgical excision of any gastrointestinal tract segment or esophageal varices were excluded. Patients who had used SSRIs before enrollment or failed initial *H. pylori* eradication were also excluded (**Figure 1**). *H. pylori* infection, both before and after eradication therapy, is confirmed either through urea breath test or endoscopy-based methods like rapid urease test, histology and culture. However, post-eradication *H. pylori* status was not recorded in this database and the success of treatment was inferred by subsequent needs of retreatment.[12]

The follow-up period commenced from 60 days after the *H. pylori* therapy until hospitalization for non-variceal UGIB, death or the end of the study (30 Jun 2016), whichever came first. The 60-day interval was chosen to allow for the healing of ulcers or gastritis after *H. pylori* eradication, which may spuriously increase the bleeding risk. Patients were divided into SSRI users and non-users according to the use statuses of SSRIs during the follow-up period. Exposure was time-varying SSRI prescription.

Outcome and Covariates

The primary outcome of this study was hospitalization for non-variceal UGIB, which was determined by ICD-9 codes (**Supplementary Table 1)**. For diagnosis with the

code of 578.x, the free text part of the record would be checked. If the free text described the specific bleeding location, the diagnosis would be updated. For other patients with an unspecified GIB, if there were new specified diagnoses within 30 days, the diagnosis would be renewed with the original index date unchanged.

Baseline characteristics, prior medical conditions and concurrent medications were all included as covariates. Baseline medical conditions before enrollment including history of UGIB/peptic ulcer, hypertension, ischemic heart disease, stroke (ischemic stroke, transient ischemic attack or systemic embolism), diabetes mellitus, renal disease, intracranial hemorrhage and liver cirrhosis were included as dichotomous covariates. Concurrent medication during the follow-up period were also included as binary variables (present/absent), which include gastroprotective agents (PPI and histamine type-2 receptor antagonists [H2RA]), aspirin, other antiplatelet drugs, NSAIDs, anticoagulants (warfarin and new oral anticoagulants), corticosteroids, bisphosphonate, serotonin-norepinephrine reuptake inhibitors (SNRIs) and other antidepressants (**Supplementary Table 2**). As the usage of medications could change over time, they were included as time-varying variables in regression models. To deal with these time-varying variables, the follow-up period was split into 1-month intervals and drug use was defined as more than 7-day use in each interval. Similar to concurrent medications, SSRI use was also included as a time-varying variable. Considering the indication bias, the prescription records of PPI and H2RA in the last 4 weeks before the index date of events or censoring were excluded.

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were presented as numbers and percentages. Crude incidence rates and corresponding 95% confidence intervals (CI) of hospitalization for UGIB during the observation period were calculated.

To balance the differences in baseline characteristics between SSRI users and non-users, propensity score (PS) matching analysis was performed. Logistic regression was used to estimate PS with baseline covariates, in which drug use statuses in the first 1-month interval were used to calculate the scores. PS matching was performed using the nearest-neighbor algorithm with a ratio of 1:2 and calipers of width equaling to 0.2. Absolute standardized differences (ASD) were used to assess the imbalance of baseline characteristics between groups.[14] An ASD $\geq$0.1 denotes imbalance of baseline characteristics. Cox proportional hazards regression model was then used to evaluate the UGIB risk of SSRIs, in which SSRI use was included as a time-varying variable. PS matching with a ratio of 1:1 were also performed as a sensitivity analysis.

In addition, a multivariable Cox proportional hazards regression model with time-varying variables was performed to compare the risk of UGIB in SSRI users with non-users, in which all medications, except SNRIs and other antidepressants, were included as time-varying variables based on 1-month intervals. Sensitivity analyses with 3-

month intervals or using SSRIs for more than 14 days in 1-month intervals as the user definition were also performed. To further evaluate the UGIB risk of SSRIs by reducing the potential effects of depression, a multivariable analysis adjusting for SNRIs and other antidepressants together with other covariates was performed. The hazards ratio (HR) and corresponding 95% CI were reported.

Tests with a two-sided *P* value of less than 0.05 were regarded as statistical significance. All statistical analyses in this study were performed using R software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria, 2018).

RESULT

Patient characteristics

A total of 61,264 patients (median age 54 years; male 46.9%) were included in this analysis, including 3,358 SSRI users (**Figure 1**). The median follow-up duration was 7.74 (IQR 5.32-10.42) years. The baseline characteristics of these patients are presented in **Table 1**. The SSRI exposure duration accounted for 25.1% of total observational person-years (7263.1/28883.5) among SSRI users. After PS matching, 3,358 SSRI users were matched with 6,716 non-users. Imbalance was detected in several variables among overall patients, which was improved after matching with all ASDs less than 0.1.

Risk of hospitalization for UGIB in SSRI users

The overall crude incidence rate of hospitalization for UGIB was 3.98 (95% CI 3.80-4.16) per 1000 person-years, and the corresponding incidence rate for SSRI users and non-users was 3.19 (95% CI 2.60-3.87) and 4.03 (95% CI 3.85-4.21) per 1000 person-years. However, in the Cox model with 1:2 PS matching, SSRI users was associated with a higher risk of hospitalization for UGIB than non-users (HR1.95, 95% CI 1.41-2.70). The result was consistent in sensitivity analysis with 1:1 PS matching (HR 2.13, 95% CI 1.50-3.02). After adjusting for age, sex, comorbidities, concurrent medications except SNRIs and other antidepressants, the finding was also consistent in multivariable analysis with 1-month intervals (HR 1.81, 95% CI 1.34-2.45; Multivariable model 1) and 3-month intervals (HR 1.61, 95% CI 1.20-2.17; Multivariable model 3, **Table 2**). The result was also similar when >14 days of SSRI uses in 1-month intervals was used as the definition of users (HR 1.71, 95% CI 1.24-2.34; Multivariable model 4). In the multivariable model involving SNRIs and other antidepressants, the result was also comparable (HR 1.79, 95% CI 1.46-2.21; Multivariable model 2). However, the increased risk of UGIB was not observed in users of SNRIs (HR 1.49, 95% CI 0.62-3.60) and other antidepressants (HR 1.13, 95% CI 0.85-1.50).

In the subgroup analyses using multivariable Cox model with 1-month intervals (Multivariable model 1), increased UGIB risk was only significant among SSRI users >50 years old (HR 1.99, 95% CI 1.45- 2.73), but not in younger patients (**Table 3**). However, increased bleeding risk of SSRIs was observed in both male (HR 1.71, 95% CI 1.03-2.83) and female (HR 1.86, 95% CI 1.28-2.70). Patients without history

of UGIB or peptic ulcer had a significantly increase in risk of UGIB (HR 1.77, 95% CI 1.25-2.50), but patients with history UGIB or peptic ulcer history had a borderline risk only (HR 1.80, 95% CI 0.98-3.27). In addition, in both gastroprotective agent users (HR 1.71, 95% CI 1.25-2.33) and non-users (HR 3.01, 95% CI 1.21-7.52), SSRIs were associated with a significantly increased risk of in UGIB.

In the multivariate model, significant interactions between SSRIs and other concomitant drugs, like aspirin, other antiplatelet drugs, NSAIDs, anticoagulants, corticosteroids and bisphosphonate were not observed, and hence they were not included in the final model.

Other risk factors associated with hospitalization for UGIB

In the multivariable Cox model with 1-month intervals (Multivariable model 1), other covariates that increased the risk of hospitalization for UGIB included older age (HR 1.06, 95% CI 1.05-1.06), male patients (HR 1.31, 95% CI 1.19-1.44), history of UGIB or peptic ulcer (HR 3.21, 95% CI 2.91-3.55), hypertension (HR 1.23, 95% CI 1.08-1.46), diabetes mellitus (HR 1.25, 95% CI 1.07-1.46), renal disease (HR 1.60, 95% CI 1.23-2.06), cirrhosis (HR 2.52, 95% CI 1.55-4.08), concomitant use of aspirin (HR 1.95, 95% CI 1.67-2.28), other antiplatelet drugs (HR 2.04, 95% CI 1.46-2.54), NSAIDs (HR 1.80, 95% CI 1.46-2.22), anticoagulants (HR 2.36, 95% CI 1.76-3.16) and corticosteroids (HR 3.54, 95% CI 2.87-4.37). In contrast, concomitant use of gastroprotective agents significantly reduced the risk of UGIB (HR 0.54, 95% CI 0.47-

0.63, **Table 4**).

DISCUSSION

In this territory-wide cohort study of more than 60,000 *H. pylori* infected patients who had received clarithromycin-based triple therapy, we determined the risk of hospitalization for UGIB in new SSRI users. Unlike previous studies that comprised of a heterogenous group of *H. pylori* infected and non-infected subjects, this study focused on patients after eradication of *H. pylori*, a major etiological agent of UGIB. We found that SSRI was associated with an almost 2-fold increase in the risk of hospitalization for UGIB as compared to SSRI non-users. This risk was significantly increased in older patients.

This was consistent with previous studies and meta-analyses that SSRI was associated with a higher risk of UGIB.[4,5] However, most of the previous studies are case-control studies and the SSRI user status was included as unchanging variable. In the real-world setting, SSRIs and other concomitant drugs user statuses could change during the follow-up period. When introducing these factors as constant variables over time, bias would be introduced, e.g. immortal time bias due to inappropriate assignment/exclusion of immortal person-time, which would decrease/increase the risk.[15,16] In our study, in both PS matching and multivariable regression analyses, SSRIs and other concomitant drugs were included as time-varying covariates to reduce these potential biases.

Notably, the crude incidence rate of UGIB in this study was apparently lower for SSRI users than non-users (3.19 [95% CI 2.60-3.87] vs 4.03 [95% CI 3.85-4.21] per 1000 person-years). However, the crude incidence rate could not reflect the real bleeding risk as SSRI exposure duration only accounted for 25.1% of total observational person-years in SSRI users. Therefore, adjusted HR in model with time-varying variables was a better indicator of the bleeding risk.

In contrast, Laursen et al.[17] found that SSRI was not associated with increased risk of endoscopy-refractory peptic ulcer bleeding. The discrepancy may be accounted by the use of different primary outcome of endoscopy-refractory bleeding ulcer, which is the most severe end of the bleeding spectrum. It is therefore likely that SSRI still increase the overall risk of all UGIB but may be not associated with refractory ulcer bleeding.

We also found that SNRIs and other antidepressants were not associated with the increased risk of UGIB, which was consistent with the study of Cheng et al.[18] The inclusion of these two control medications also addressed the concern that patients with depression may have a higher risk of peptic ulcer disease and hence the risk of UGIB rather than due to SSRIs use.[19]

Significant interactions between SSRIs and other concomitant drugs like aspirin,[20,21] NSAIDs[4,5] or antiplatelet drugs[4], were not detected in our study, and thus were not included in the final multivariable model. The non-significant results in our study may

be caused by the small number patients who concurrently used both SSRI and these medications. In addition, the improvement of gastric inflammation after *H. pylori* eradication may also affect the potential interactions between SSRIs and these concomitant medications on risks of UGIB. For instance, *H. pylori* could impair the gastric adaptation of the mucosa to aspirin treatment and eradication of *H. pylori* would restore this process and decrease the risk of UGIB,[22] which may also weaken the interaction between SSRIs and aspirin. Moreover, a high proportion (>45%) of our patients were taking gastroprotective agents, which may also affect the potential interactions. Similar findings were also reported in previous studies which did not report any significant interactions between SSRIs and other drugs[18,23].

The results of other risk factors for UGIB in multivariable regression model was consistent with previous studies on SSRIs and UGIB.[23] Though SSRIs increased the bleeding risk in gastroprotective agent users in our study (HR 1.71, 95% CI 1.25-2.33), the HR seems to be lower than non-users of gastroprotective agents (HR 3.01, 95% CI 1.21-7.52). Similarly, the protective effective of gastroprotective agents were not observed in the study of Walraven et al.[23] In contrast, Dall et al.[20] reported that the increased bleeding risk of SSRIs was only significant in PPI non-user. It was also consistent with the meta-analysis of Jiang et al.[4] that concurrent use of SSRIs and acid-suppressing drugs did not reduce the risk of UGIB (odds ratio [OR] 0.81, 95% CI 0.43–1.53). Therefore, further studies are needed to confirm the role of gastroprotective agents in the prevention of UGIB among SSRI users. However, gastroprotective agents

may still be considered in high-risk patients with concomitant use of aspirin or NSAIDs, as well as older patients.[24]

There are several limitations of our study. First, successful *H. pylori* eradication, which was not available in this database, was defined by the use of a single course of *H. pylori* eradication therapy without the need of retreatment. Some patients who failed *H. pylori* eradication may not receive further therapy and could be included in this study. In one of our previous studies by using the same data set, we performed a validation analysis of 51 bleeding patients from our centre who had been retested for *H. pylori* and found that the failure rate of the initial course of clarithromycin-based eradication was very low (3.9%).[10] In addition, a prospective study conducted in Hong Kong during the same period reported that the intention-to-treat success rate of clarithromycin-based triple therapy was 87.2%,[25] which was comparable with the observed success rate in our cohort 88.7%. Second, only UGIB that resulted in hospitalization were considered as the outcome. Some patients with minor bleeding may not be hospitalized and this result may be more applicable to patients with more severe bleeding. Third, continuous use of SSRI would be better to evaluate the UGIB risk of SSRIs, though time-varying variable was used in this study to reduce the time-dependent bias. As patients with long-term continuous use of SSRIs were limited, a large cohort would be needed to achieve this analysis. Lastly, information of some risk factors of UGIB (eg, smoking, alcohol consumption) could not be obtained from the electronic database and were not included in this analysis.

CONCLUSION

SSRI users have about two-fold increase in the risk of hospitalization for UGIB when compared to non-users after treatment for *Helicobacter pylori*. Older age, history of UGIB or ulcer, comorbid illnesses and concurrent use of other medications also increased the UGIB risk.

Funding and Conflict of Interest

Declaration of personal interests: WKL has received speaker fee from Eisai, Ipsen and honorarium for attending advisory board for Janssen and Pfizer. ICKW have received grant from Janssen, Pfizer, Bayer, Amgen and Novartis but not related with the present study. EWC has received honorarium from the Hong Kong Hospital Authority and funding from The Hong Kong Research Grants Council, The Research Fund Secretariat of the Food and Health Bureau, Narcotics Division of the Security Bureau of HKSAR, Hong Kong; Wellcome Trust, United Kingdom; National Natural Science Fund of China, China; Bayer, Bristol-Myers Squibb, Pfizer and Takeda, for work unrelated to this study. Other authors have no conflict of interest to declare.

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Authorship Statement

Guarantor of the article: Wai K. Leung

Specific author contribution: CGG and WKL were responsible for the conception and design of this study. LC and CGG were involved in data collection. CGG and FZ were involved in data analysis and interpretation. CGG and WKL drafted the manuscript. KSC, FZ, EWC, LC, and IW assisted in data interpretation and provided critical reviews of the manuscript. All authors approved the final version of the article.

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Table 1 Characteristics of SSRI users and non-users before and after propensity score matching

	Before matching			After matching		
	SSRI users	Non-users	ASD [a]	SSRI users	Non-users	ASD
Patients, n	3358	57,906		3358	6716	
Age, year (IQR)	53 (45-65)	54 (45-64)	0.030	53 (45-65)	54 (45-66)	0.020
Male, n (%)	1039 (30.9)	27709 (47.9)	0.351	1039 (30.9)	2096 (31.2)	0.006
Person-years of follow-up	28,883.5	448,004.8	-	28,883.5	52,629.7	-
Person-years of exposure duration	7263.1	-	-	7263.1	-	-
Baseline conditions, n (%)						
UGIB or ulcer	303 (9.0)	8388 (14.5)	0.170	303 (9.0)	605 (9.0)	0.001
Ischemic heart disease	182 (5.4)	2556 (4.4)	0.047	182 (5.4)	364 (5.4)	<0.001
Stroke	106 (3.2)	1690 (2.9)	0.014	106 (3.2)	237 (3.5)	0.021
Hypertension	340 (10.1)	4791 (8.3)	0.064	340 (10.1)	679 (10.1)	<0.001
Diabetes	233 (6.9)	3266 (5.6)	0.054	233 (6.9)	489 (7.3)	0.013
Renal disease	41 (1.2)	787 (1.4)	0.012	41 (1.2)	77 (1.1)	0.007
Intracranial hemorrhage	13 (0.4)	255 (0.4)	0.008	13 (0.4)	32 (0.5)	0.014
Cirrhosis	8 (0.2)	233 (0.4)	0.029	8 (0.2)	21 (0.3)	0.014
Medications, n (%) [b]						
Gastroprotective agents	1595 (47.5)	26,233 (45.3)	0.044	1595 (47.5)	3171 (47.2)	0.006
Aspirin	325 (9.7)	4716 (8.1)	0.054	325 (9.7)	687 (10.2)	0.018
Other Antiplatelet drugs	44 (1.3)	595 (1.0)	0.026	44 (1.3)	85 (1.3)	0.004
NSAIDs	211 (6.3)	2276 (3.9)	0.107	211 (6.3)	429 (6.4)	0.004
Anticoagulants	18 (0.5)	294 (0.5)	0.004	18 (0.5)	43 (0.6)	0.014
Corticosteroids	46 (1.4)	720 (1.2)	0.011	46 (1.4)	117 (1.7)	0.030
Bisphosphonate	13 (0.4)	102 (0.2)	0.040	13 (0.4)	26 (0.4)	<0.001

ASD, absolute standardized difference; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; UGIB, upper gastrointestinal bleeding.

[a] ASD $\geq$ 0.1 denotes imbalance;

[b] Drug using status in the first 1-month interval.

Table 2 The UGIB risk of SSRI in different models

Models	HR (95% CI)	*P* value
Cox model with 1:2 PS matching [a]	1.95 (1.41-2.70)	< 0.001
Cox model with 1:1 PS matching [a]	2.13 (1.50-3.02)	< 0.001
Multivariable Cox model 1 [b]	1.81 (1.34-2.45)	< 0.001
Multivariable Cox model 2 [c]	1.79 (1.46-2.21)	< 0.001
Multivariable Cox model 3 [d]	1.61 (1.20-2.17)	0.002
Multivariable Cox model 4 [e]	1.71 (1.24-2.34)	< 0.001

HR, hazards ratio; PS, propensity score.

[a] To calculate the propensity score, concurrent medications user statuses in the first 1-month interval were used. SSRI was included as time-varying variable, for which the 1-month intervals were used;

[b] Adjusting for age, sex, comorbidities and concurrent medications except SNRIs and other antidepressants, in which both SSRI and other medications were included as time-varying variables in terms of 1-month interval;

[c] Adjusting for all covariates, including SNRIs and other antidepressants, in which concurrent medications were included as time-varying variables in terms of 1-month interval;

[d] Using same covariates as multivariable Cox model 1 but using 3-month intervals instead;

[e] Using same covariates as multivariable Cox model 1 but SSRI use was defined as more than 14 days use in 1-month intervals.

Table 3 Stratified HR for the UGIB risk of SSRI in multivariable Cox model with 1-month intervals

Subgroups (Number of patients)	HR (95% CI) of SSRI	*P* value
Age		
<= 50 (24,906)	0.85 (0.27-2.74)	0.790
> 50 (36,358)	1.99 (1.45- 2.73)	< 0.001
Sex		
Male (28,748)	1.71 (1.03-2.83)	0.036
Female (32,516)	1.86 (1.28-2.70)	0.001
UGIB or ulcer history		
No (52,573)	1.77 (1.25-2.50)	0.001
Yes (8691)	1.80 (0.98-3.27)	0.056
Gastroprotective agents		
Non-users (10,192)	3.01 (1.21-7.52)	0.018
Users (51,072)	1.71 (1.25-2.33)	< 0.001

HR, hazards ratio; UGIB, upper gastrointestinal bleeding.

Table 4 Other risk factors of hospitalization for UGIB in multivariable Cox model with 1-month intervals

Variables	HR (95% CI)	*P* value
Age	1.06 (1.05-1.06)	< 0.001
Sex (male)	1.31 (1.19-1.44)	< 0.001
Baseline conditions		
UGIB or ulcer	3.21 (2.91-3.55)	< 0.001
Ischemic heart disease	0.92 (0.78-1.09)	0.338
Stroke	1.11 (0.93-1.34)	0.253
Hypertension	1.23 (1.08-1.41)	0.002
Diabetes	1.25 (1.07-1.46)	0.006
Renal disease	1.60 (1.23-2.06)	< 0.001
Intracranial hemorrhage	1.45 (0.96-2.18)	0.077
Cirrhosis	2.52 (1.55-4.08)	< 0.001
Medications		
Gastroprotective agents	0.54 (0.47-0.63)	< 0.001
Aspirin	1.95 (1.67-2.28)	< 0.001
Other antiplatelet drugs	2.04 (1.63-2.54)	< 0.001
NSAIDs	1.80 (1.46-2.22)	< 0.001
Anticoagulants	2.36 (1.76-3.16)	< 0.001
Corticosteroids	3.54 (2.87-4.37)	< 0.001
Bisphosphonate	1.38 (0.82-2.34)	0.225

HR, hazards ratio; NSAIDs, non-steroidal anti-inflammatory drugs; UGIB, upper gastrointestinal bleeding.

Figure Legends

Figure 1 Follow chart of the study