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Original Article

Risk of Lower Gastrointestinal Bleeding in Nonsteroidal Anti-inflammatory Drug (NSAID) and Proton Pump Inhibitor Users Compared with NSAID-Only Users: A Common Data Model Analysis

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Background/Aims: Recent studies have shown an increased risk of lower gastrointestinal bleeding in patients who use both nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs). We analyzed the risk of lower gastrointestinal bleeding and compared this risk between NSAID+PPI users and NSAID-only users.

Methods: In this retrospective, observational study, data from five hospitals were analyzed using a common data model to determine the risk of lower gastrointestinal bleeding and compare this risk between NSAID+PPI users (target cohort) and NSAID-only users (comparative cohort). Cox proportional hazard models and the Kaplan-Meier estimations were employed after extensive propensity score matching.

Results: Among 24,530 individuals in the target cohort and 57,264 in the comparative cohort, 8,728 propensity score-matched pairs were analyzed. The risk of lower gastrointestinal bleeding was significantly higher in NSAID+PPI users than in NSAID-only users (hazard ratio [HR], 2.843; 95% confidence interval [CI], 1.998 to 4.044; p<0.001). Similar findings were also noted in elderly patients >65 years (HR, 2.737), males (HR, 2.963), and females (HR, 3.221). However, the risk of lower gastrointestinal bleeding was comparable between NSAID+mucoprotective agent users and NSAID-only users (HR, 2.057; 95% CI, 0.714 to 5.924; p=0.172).

Conclusions: The risk of lower gastrointestinal bleeding was higher in NSAID+PPI users than in NSAID-only users. However, the risk of lower gastrointestinal bleeding was comparable between NSAID+mucoprotective agent users and NSAID-only users. **(Gut Liver 2025;19:243-252)**

Key Words: Nonsteroidal anti-inflammatory drug; Hemorrhage; Proton pump inhibitors

INTRODUCTION

A population-based study in Spain showed that between 1996 and 2005, upper gastrointestinal (UGI) complications/100,000 persons decreased, whereas lower gastrointestinal (LGI) complications/100,000 persons increased.[1] The decreasing incidence of *Helicobacter pylori* infection and the widespread use of anti-secretory drugs have likely contributed to the decrease in UGI complications. However, LGI complications are likely to increase further because older age and the number of comorbidities are more strongly associated with LGI complications than with UGI complications.[1] The most common type of LGI complication is LGI bleeding, which is defined as bleeding that starts from areas beyond the ligament of Treitz.[2]

Proton pump inhibitors (PPIs) have been widely used to prevent UGI bleeding in those using nonsteroidal anti-inflammatory drugs (NSAIDs) and treat acid-related disorders, such as peptic ulcers and gastroesophageal reflux disease.[3] Recent clinical trials, however, have shown a higher incidence of small bowel injuries in those who use both NSAIDs and PPIs than those who use only NSAIDs.[4-6] A

recent meta-analysis of 12 studies encompassing 341,063 participants revealed that the combined use of PPIs and NSAIDs was associated with a higher risk of LGI bleeding than the use of NSAIDs alone (hazard ratio [HR], 6.55; 95% confidence interval [CI], 2.01 to 21.33).[7] Similarly, the combined use of aspirin and PPIs was associated with a higher risk of small bowel injury than the use of aspirin alone (odds ratio [OR], 2.04; 95% CI, 1.05 to 3.97).[8] Therefore, PPI use may be associated with an increased risk of LGI bleeding in NSAID or aspirin users. As the combined use of NSAIDs and PPIs has been increasing, determining the risk of LGI bleeding associated with these combinations is warranted. However, previous clinical studies were limited by small sample sizes[4,5] and a meta-analysis was limited by a variable definition of LGI bleeding between included studies.[7]

Therefore, we aimed to quantify the comparative risk of LGI bleeding between NSAID+PPI users and NSAID-only users in real-world practice using a common data model (CDM).

MATERIALS AND METHODS

1. Data source and ethics

The concept and detailed methodology of the CDM have been described in detail in our previous publications.[9,10] Electronic health record data from five hospitals that transitioned to the CDM database were analyzed: Kyung Hee University Hospital at Gangdong (n=920,281), Kangdong Sacred Heart Hospital (n=1,240,471), Kyung Hee University Medical Center (n=1,301,539), Gyeongsang National University Hospital (n=678,365), and Pusan National University Hospital (n=1,753,001). Detailed patient numbers, the study period, and NSAID or PPI use before and after propensity score matching (PSM) are shown in Table 1. The Institutional Review Board of Kyung Hee University Hospital at Gangdong approved the study (KHNMC IRB 2024-05-006), and the need for written informed consent was waived since the CDM database involved no data security risks.

2. Study design and cohort definition

This retrospective, observational, comparative cohort study analyzed the risk of LGI bleeding between NSAID+PPI users and NSAID-only users aged ≥18 years from five hospitals. NSAID users were defined as individuals taking any NSAIDs or aspirin. The target cohort comprised patients who took NSAIDs and PPIs for >90 consecutive days, while the comparative cohort comprised patients who took only NSAIDs for the same duration. Exclusion criteria included a history of any LGI bleeding prior to the study entry, any PPI use in the comparative cohort, age <18 years, chronic liver or kidney diseases, renal dialysis, and kidney transplantation. The study investigated all types of NSAIDs, PPIs, and mucoprotective agents (MPAs) available in the South Korean market (Supplementary Table 1). MPA users were defined as any users of MPA without PPI. Patients were considered eligible if they were consistently exposed from the index date through the prescribed duration until LGI bleeding, hospital discharge, or treatment termination. The study followed the time-at-risk from the day after the index date to the end of the observation or up to 455 days (90 days of prescription and 365 days of observation). Patient observation endpoints included a lack of follow-up prescriptions after the last prescription, a change in use of the cohort medication that was initially prescribed, death, or the end of data availability.

The outcome cohort was identified using specific SNOMED-CT (Systematized Nomenclature of Medicine Clinical Terms) codes for patients with LGI bleeding and related treatments, which included gastrointestinal bleeding from the jejunum to the rectum (Supplementary Table 2). The definition of LGI bleeding could be more accurate, if it includes the drop of hemoglobin level and endoscopic hemostasis, however, coding for LGI bleeding is much more accurate than other disease codes, and it is widely

Table 1. Summary of Data Source after Propensity Score Matching

Database*	No. of participants	Study period	NSAID+PPI users (target group)	NSAID users (comparator group)	Target, day	Comparator, day
KHNMC	920,281	Jan 2006 to Dec 2023	1,351	1,351	1,012,068	899,530
KDH	1,240,471	Nov 1986 to Dec 2023	1,246	1,246	1,022,643	911,905
KHMC	1,301,539	Jun 2007 to Dec 2023	2,635	2,635	2,198,948	1,957,863
GNUH	678,365	Nov 2009 to Jan 2024	2,502	2,502	2,265,785	2,124,448
PNUH	1,753,001	Feb 2011 to Aug 2019	994	994	804,806	728,276
Total	5,893,657		8,728	8,728		

NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.
*Database from five hospitals: KHNMC, Kyung Hee University Hospital at Gangdong; KDH, Kangdong Sacred Heart Hospital; KHMC, Kyung Hee University Medical Center; GNUH, Gyeongsang National University Hospital; PNUH, Pusan National University Hospital.

used without an operational definition in claim-based study. Therefore, outcome cohort was defined with only SNOMED-CT codes for LGI bleeding and rectal bleeding in this study. To assess the risk of LGI bleeding, 1:1 PSM was employed based on logistic regression of the age, sex, and comorbidity score, using a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Post-matching balance was evaluated by the standardized mean difference (SMD), with values <10% considered acceptable.[11] Acceptable SMD after matching indicated that the matched groups were similar in terms of their covariates and that the matching process was of good balance between the groups. This means that any differences observed in the outcome were more likely to be due to medication effects than differences in baseline characteristics. Even though treatment periods were not matched in this study, the outcomes are unlikely affected by treatment periods as preventive medications of LGI bleeding in PPI and NSAID users are not recommended during study periods.

Table 2. Distribution of Baseline Characteristics in the Overall Population from the Five Hospitals between NSAID and PPI Users versus NSAID Users before and after PSM

Characteristic	Before PSM, No. (%)			After PSM, No. (%)		
	NSAID+PPI users (n=24,530)	NSAID users (n=57,264)	SMD	NSAID+PPI users (n=8,728)	NSAID users (n=8,728)	SMD
Age group						
<40 yr	2,108 (8.6)	3,777 (6.6)	0.075	451 (5.2)	582 (6.7)	0.064
40–49 yr	2,704 (11.0)	5,835 (10.2)	0.027	774 (8.9)	839 (9.6)	0.026
50–59 yr	6,190 (25.2)	13,549 (23.7)	0.037	2,018 (23.1)	1,990 (22.8)	0.008
60–69 yr	6,698 (27.3)	16,376 (28.6)	0.029	2,510 (28.8)	2,462 (28.2)	0.012
70–79 yr	4,941 (20.1)	13,051 (22.8)	0.065	2,171 (24.9)	2,068 (23.7)	0.028
≥80 yr	1,889 (7.7)	4,676 (8.2)	0.017	804 (9.2)	787 (9.0)	0.007
Female sex	12,430 (50.7)	25,725 (44.9)	0.015	4,117 (47.2)	4,115 (47.1)	<0.001
Medical history						
General						
Hypertensive disorder	3,426 (14.0)	16,233 (28.3)	0.358	2,032 (23.3)	1,978 (22.7)	0.015
Hyperlipidemia	2,057 (8.4)	8,653 (15.1)	0.210	1,139 (13.0)	1,102 (12.6)	0.013
Diabetes mellitus	1,527 (6.2)	6,301 (11.0)	0.171	826 (9.5)	831 (9.5)	0.002
Gastroesophageal reflux disease	1,584 (6.5)	892 (1.6)	0.252	353 (4.0)	366 (4.2)	0.007
Osteoarthritis	490 (6.1)	1,443 (2.5)	0.176	323 (3.7)	353 (4.0)	0.018
Visual system disorder	1,058 (4.3)	3,100 (5.4)	0.051	481 (5.5)	467 (5.4)	0.007
Neoplasms	1,139 (4.6)	2,499 (4.4)	0.013	564 (6.5)	605 (6.9)	0.019
Cardiovascular						
Heart disease	6,253 (25.5)	15,572 (27.2)	0.039	2,796 (32.0)	2,724 (31.2)	0.018
Ischemic heart disease	5,073 (20.7)	10,477 (18.3)	0.060	2,095 (24.0)	1,991 (22.8)	0.028
Cerebrovascular disease	1,134 (4.6)	4,627 (8.1)	0.142	672 (7.7)	661 (7.6)	0.005
Medication use						
Anti-inflammatory and antirheumatic products	20,764 (84.6)	46,826 (81.8)	0.077	7,594 (87.0)	7,582 (86.9)	0.004
Antithrombotic agents	12,446 (50.7)	45,798 (80.0)	0.646	6,635 (76.0)	6,388 (73.2)	0.065
Lipid-modifying agents	8,809 (35.9)	24,915 (43.5)	0.156	4,058 (46.5)	3,879 (44.4)	0.041
Agents acting on the RAS	4,583 (18.7)	20,020 (35.0)	0.374	2,578 (29.5)	2,528 (29.0)	0.013
Opioids	9,057 (36.9)	10,255 (17.9)	0.436	2,579 (29.5)	2,628 (30.1)	0.012
Calcium channel blockers	6,253 (25.5)	17,706 (30.9)	0.121	2,624 (30.1)	2,590 (29.7)	0.009
Beta blocking agents	3,813 (15.5)	13,773 (24.1)	0.215	2,051 (23.5)	1,999 (22.9)	0.014
Diuretics	5,008 (20.4)	10,186 (17.8)	0.067	1,751 (20.1)	1,741 (19.9)	0.003
Antibacterials for systemic use	5,941 (24.2)	7,387 (12.9)	0.294	1,921 (22.0)	1,941 (22.2)	0.006
Psycholeptics	5,750 (23.4)	10,117 (17.7)	0.143	2,122 (24.3)	2,067 (23.7)	0.015
Drugs for obstructive airway diseases	5,934 (24.2)	6,186 (10.8)	0.358	1,558 (18.0)	1,579 (18.3)	0.012
Drugs used in diabetes	3,715 (15.1)	11,433 (20.0)	0.127	1,567 (18.0)	1,563 (17.9)	0.001
Antiepileptics	4,451 (18.1)	6,665 (11.6)	0.184	1,281 (14.7)	1,321 (15.1)	0.013
Antidepressants	3,970 (16.2)	6,786 (11.9)	0.125	1,422 (16.3)	1,392 (15.9)	0.009
Antineoplastic agents	2,306 (9.4)	2,414 (4.2)	0.207	668 (7.7)	722 (8.3)	0.023
Psychostimulants, agent used for ADHD and nootropics	681 (2.8)	3,934 (6.9)	0.192	455 (5.2)	431 (4.9)	0.013

We reported covariates over 5% for the total patient population before propensity score matching (PSM).
NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SMD, standardized mean difference; RAS, renin-angiotensin system; ADHD, attention deficit hyperactivity disorder.

3. Covariates

To enhance large-scale PSM analysis between the target and comparative cohorts, a comprehensive set of 237 covariates, which included age, sex, index year, Charlson Comorbidity Index, various comorbidities, and medications prescribed within the 365 days prior to the index date, was used. Covariates >5% of the total patients prior to matching are shown in Table 2. The general medical history, neoplastic history, cardiovascular history, and medication history were matched between the target and comparative cohorts. The overall burden of comorbidities was assessed using the Charlson Comorbidity Index, the $CHADS_2$ score, and the CHA_2DS_2VASc score.

4. Statistical analysis

Data were displayed as the number (percentage) for categorical variables and the mean (standard deviation) for normally distributed continuous variables. The ATLAS platform (version 2.12.0) provided tools for initial CDM analysis. R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for Cox model analysis and Kaplan-Meier estimation. Cox proportional hazard models compared LGI bleeding in the matched cohorts with HR and 95% CI. The Kaplan-Meier curves, constructed using log-rank tests, illustrated the percentage of event-free patients over time, and tested the statistical significance of differences. Two-sided p-values <0.05 were considered statistically significant. Statistical heterogeneity was assessed using the chi-square test and I^2 statistics, with a fixed-effects model in the absence of heterogeneity ($p<0.05$, $I^2>50\%$) and a random-effects model otherwise.

RESULTS

A total of 24,530 NSAID+PPI users (target cohort) and 57,264 NSAID-only users (comparative cohort) met the eligible criteria before PSM. Patients included in both cohorts who had a history of LGI bleeding, were not ≥1 day at risk, and did not match the propensity score were excluded (Fig. 1). Finally, 8,728 propensity-matched pairs from both cohorts were analyzed. All SMDs were <0.1 after PSM in terms of age group, sex, medical history, cardiovascular disease history, and medication use (Table 2).

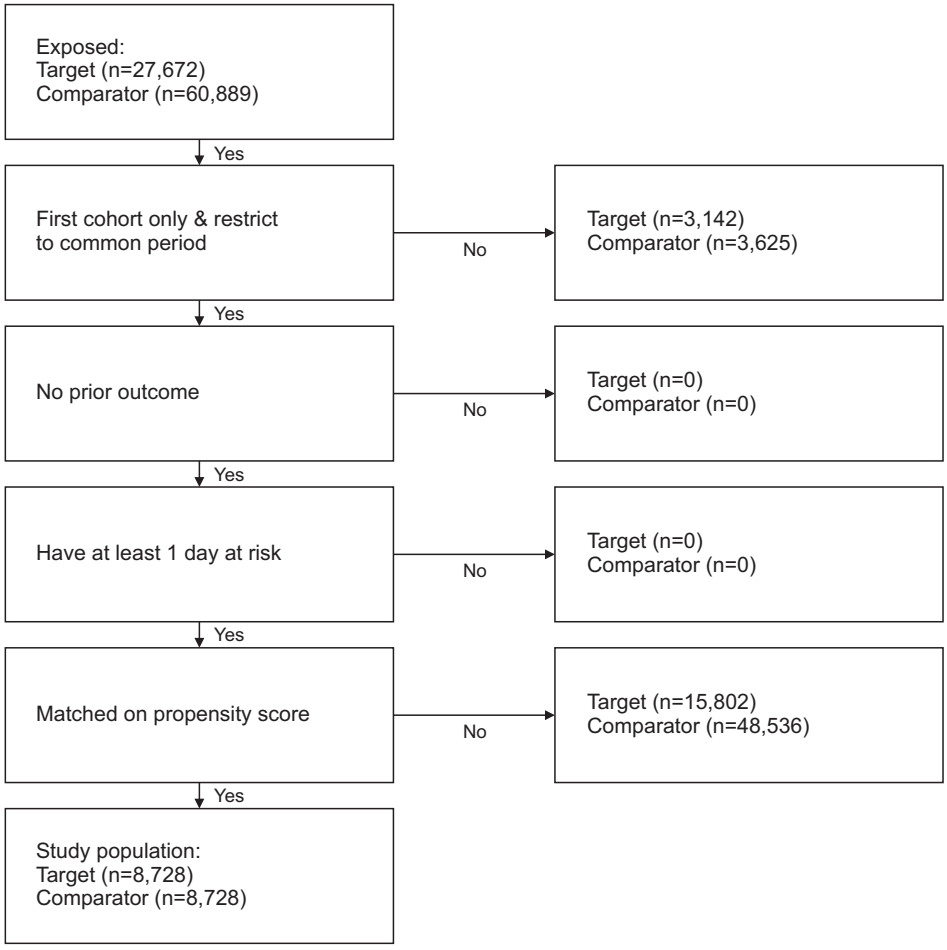


Fig. 1. Study flowchart of cohort data from the five hospitals. Patients in both cohorts with a history of lower gastrointestinal bleeding who did not have ≥1 day at risk and were not matched in terms of propensity score were excluded. Finally, 8,728 propensity-matched pairs between nonsteroidal anti-inflammatory drug (NSAID)+protein pump inhibitor users (target cohort) and NSAID-only users (comparative cohort) were included in the analyses.

Among 16,975 and 21,788 individuals in the NSAID+MPA users and NSAID-only users, respectively, 5,638 propensity score-matched pairs were also analyzed (Table 3). These two cohorts were also well balanced as all SMDs were <0.1 after PSM.

1. Baseline characteristics of study subjects

After PSM between both cohorts, the proportion of NSAID+PPI users or NSAID-only users was highest in the age group 60–69 years (Table 2). The most common general medical history was hypertension, followed by hyperlipidemia and diabetes mellitus, and the most common cardiovascular disease history was heart disease, followed by ischemic heart disease. The most common medications prescribed before cohort entry were anti-inflammatory and antirheumatic products, followed by antithrombotic agents and lipid-modifying agents (Table 2). As PPIs are classified as drugs for acid-related disorders, drugs for acid-related disorders were not described in this study. Baseline characteristics of study subjects in Table 3 were very similar to those of Table 2 for distributions of age, sex, medical history, as well as medication use.

Table 3. Distribution of Baseline Characteristics in the Overall Population from the Five Hospitals between NSAID and MPA Users versus NSAID Users before and after PSM

Characteristic	Before PSM, No. (%)			After PSM, No. (%)		
	NSAID+MPA users (n=16,975)	NSAID users (n=21,788)	SMD	NSAID+MPA users (n=5,638)	NSAID users (n=5,638)	SMD
Age group						
<40 yr	1,878 (11.1)	1,530 (7.0)	0.141	364 (6.5)	358 (6.3)	0.004
40–49 yr	1,808 (10.7)	2,129 (9.8)	0.029	517 (9.2)	534 (9.5)	0.010
50–59 yr	4,055 (23.9)	4,981 (22.9)	0.024	1,352 (24.0)	1,316 (23.3)	0.015
60–69 yr	4,465 (26.3)	6,211 (28.5)	0.049	1,659 (29.4)	1,671 (29.6)	0.005
70–79 yr	3,493 (20.6)	5,147 (23.6)	0.073	1,342 (23.8)	1,308 (23.2)	0.014
≥80 yr	1,276 (7.5)	1,790 (8.2)	0.026	404 (7.2)	451 (8.0)	0.031
Female sex	8,548 (50.4)	10,671 (49.0)	0.028	2,789 (49.5)	2,779 (49.3)	0.004
Medical history						
General						
Hypertensive disorder	3,145 (18.5)	7,343 (33.7)	0.351	1,748 (31.0)	1,715 (30.4)	0.013
Hyperlipidemia	2,105 (12.4)	4,512 (20.7)	0.225	1,135 (20.1)	1,139 (20.2)	0.002
Diabetes mellitus	1,226 (7.2)	2,018 (9.3)	0.074	587 (10.4)	570 (10.1)	0.010
Gastroesophageal reflux disease	1,165 (6.9)	465 (2.1)	0.230	233 (4.1)	254 (4.5)	0.018
Osteoarthritis	1,208 (7.1)	959 (4.4)	0.117	268 (4.8)	285 (5.1)	0.014
Neoplasms	564 (3.3)	540 (2.5)	0.050	208 (3.7)	192 (3.4)	0.015
Cardiovascular						
Heart disease	3,377 (19.9)	3,860 (17.7)	0.056	1,379 (24.5)	1,399 (24.8)	0.008
Ischemic heart disease	2,576 (15.2)	2,629 (12.1)	0.091	1,055 (18.7)	1,065 (18.9)	0.005
Cerebrovascular disease	1,449 (8.5)	1,989 (9.1)	0.021	479 (8.5)	484 (8.6)	0.003
Medication use						
Anti-inflammatory and antirheumatic products	15,044 (88.6)	19,292 (88.5)	0.003	5,088 (90.2)	5,076 (90.0)	0.007
Antithrombotic agents	9,599 (56.5)	15,197 (69.7)	0.276	3,953 (70.1)	3,931 (69.7)	0.009
Lipid-modifying agents	6,269 (36.9)	7,639 (35.1)	0.039	2,258 (40.0)	2,278 (40.4)	0.007
Agents acting on the RAS	3,972 (23.4)	6,728 (30.9)	0.169	1,644 (29.2)	1,654 (29.3)	0.004
Opioids	4,655 (27.4)	4,118 (18.9)	0.203	1,446 (25.6)	1,482 (26.3)	0.015
Calcium channel blockers	3,954 (23.3)	6,260 (28.7)	0.124	1,617 (28.7)	1,610 (28.6)	0.003
Beta blocking agents	2,802 (16.5)	3,732 (17.1)	0.017	1,078 (19.1)	1,102 (19.5)	0.011
Diuretics	2,382 (14.0)	3,028 (13.9)	0.004	893 (15.8)	902 (16.0)	0.004
Antibacterials for systemic use	2,859 (16.8)	2,584 (11.9)	0.142	969 (17.2)	978 (17.3)	0.004
Psycholeptics	3,029 (17.8)	3,847 (17.7)	0.005	1,143 (20.3)	1,184 (21.0)	0.018
Drugs for obstructive airway diseases	3,003 (17.7)	2,600 (11.9)	0.163	931 (16.5)	949 (16.8)	0.009
Drugs used in diabetes	2,190 (12.9)	3,877 (17.8)	0.136	964 (17.1)	968 (17.2)	0.002
Antiepileptics	2,720 (16.0)	3,140 (14.4)	0.045	870 (15.4)	854 (15.1)	0.008
Antidepressants	2,799 (16.5)	3,380 (15.5)	0.027	1,026 (18.2)	1,018 (18.1)	0.004
Antineoplastic agents	1,729 (10.2)	1,069 (4.9)	0.201	410 (7.3)	391 (6.9)	0.013
Psychostimulants, agent used for ADHD and nootropics	834 (4.9)	2,407 (11.0)	0.228	459 (8.1)	475 (8.4)	0.010

We reported covariates over 5% for the total patient population before propensity score matching (PSM).
NSAID, nonsteroidal anti-inflammatory drug; MPA, mucoprotective agent; SMD, standardized mean difference; RAS, renin-angiotensin system; ADHD, attention deficit hyperactivity disorder.

2. LGI bleeding between NSAID+PPI users and NSAID-only users

Cox proportional hazard analyses were conducted to compare the risk of LGI bleeding between NSAID+PPI users and NSAID-only users after PSM (Fig. 2). The risk of LGI bleeding was significantly higher in NSAID+PPI users than in NSAID-only users (HR, 2.843; 95% CI, 1.998 to 4.044; p<0.001). LGI bleedings occurred after median of 288.5 days (interquartile range, 139.8 to 523.5 days) in NSAID+PPI users and median of 362 days (interquartile range, 178 to 568 days) in NSAID-only users.

3. LGI bleeding between two cohorts in older patients

Fig. 3 shows the Kaplan-Meier plots for LGI bleeding between NSAID+PPI users and NSAID-only users in older patients aged >65 years. In older patients, the risk of LGI bleeding was significantly higher in NSAID+PPI users than in NSAID-only users (HR, 2.737; 95% CI, 1.178 to 4.202; p<0.001).

4. LGI bleeding between two cohorts according to sex

Fig. 4 shows the Kaplan-Meier plots for LGI bleeding between NSAID+PPI users and NSAID-only users according to sex. The risk of LGI bleeding was significantly higher in NSAID+PPI users than in NSAID-only users in both males (HR, 2.963; 95% CI, 1.952 to 4.499; p<0.001) (Fig. 4A) and females (HR, 3.221; 95% CI, 1.909 to 5.434; p<0.001) (Fig. 4B).

5. LGI bleeding between NSAID+MPA users and NSAID users

In comparing the risk of LGI bleeding between NSAID+MPA users and NSAID-only users after PSM, the use of PPIs was excluded from both cohorts. The risk of LGI bleeding was comparable between NSAID+MPA

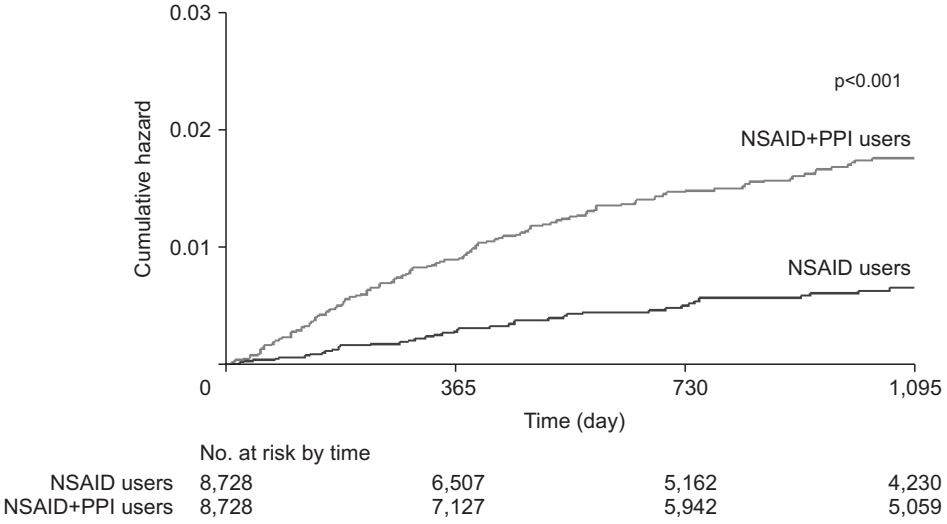


Fig. 2. Kaplan-Meier plots for lower gastrointestinal bleeding between nonsteroidal anti-inflammatory drug (NSAID)+protein pump inhibitor (PPI) users (target cohort) and NSAID-only users (comparative cohort). The risk of lower gastrointestinal bleeding was significantly higher in NSAID+PPI users than in NSAID-only users (hazard ratio, 2.843; 95% confidence interval, 1.998 to 4.044; p<0.001).

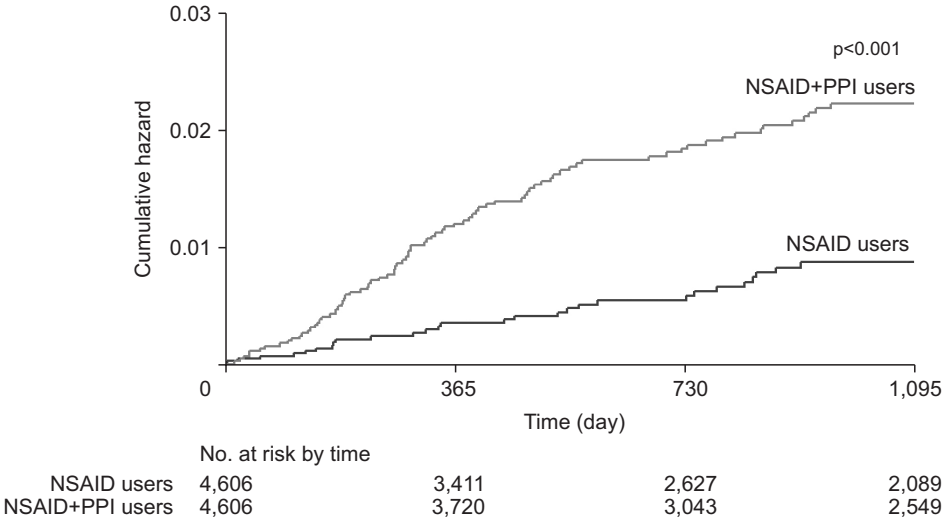
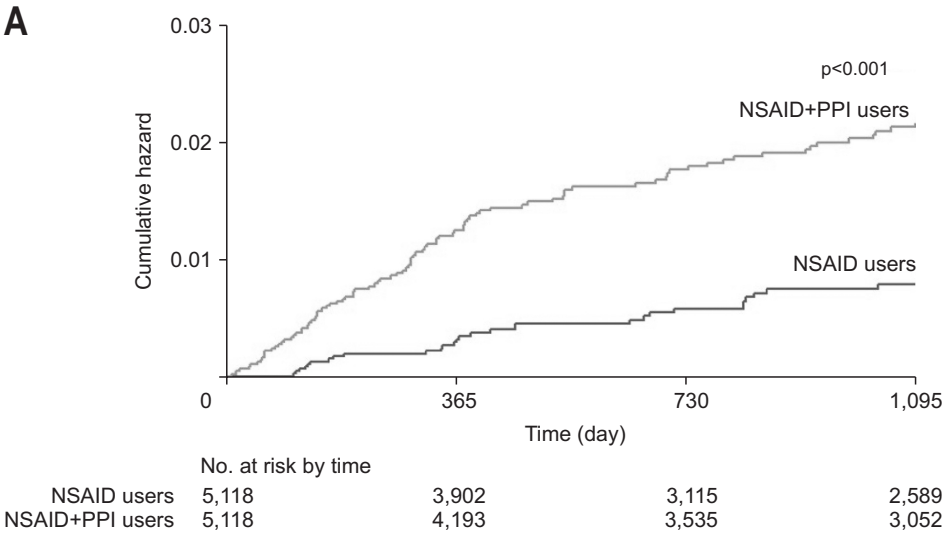


Fig. 3. Kaplan-Meier plots for lower gastrointestinal bleeding between nonsteroidal anti-inflammatory drug (NSAID)+protein pump inhibitor (PPI) users and NSAID-only users in older patients (age >65 years). The risk of lower gastrointestinal bleeding was significantly higher in NSAID+PPI users than in NSAID-only users (hazard ratio, 2.737; 95% confidence interval, 1.178 to 4.202; p<0.001).



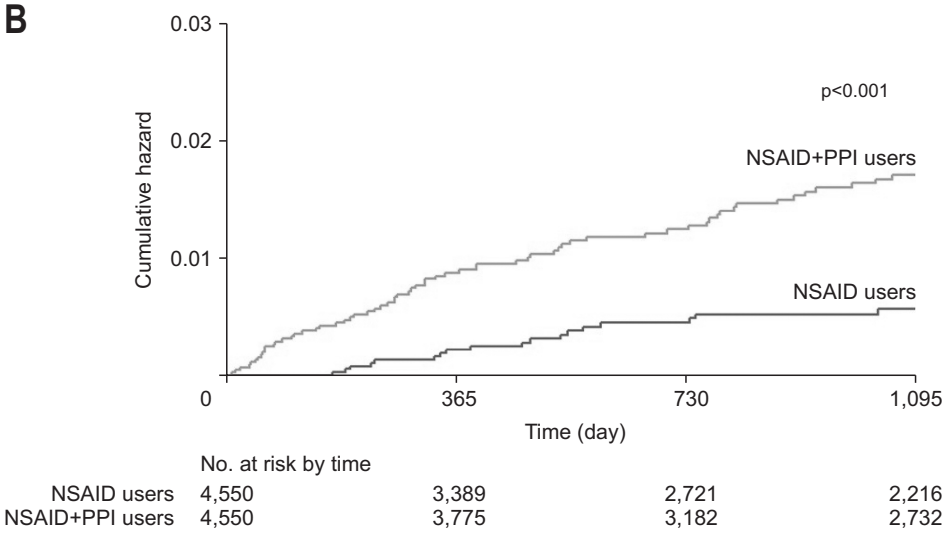


Fig. 4. Kaplan-Meier plots for lower gastrointestinal bleeding between nonsteroidal anti-inflammatory drug (NSAID)+protein pump inhibitor (PPI) users and NSAID-only users according to sex (A: male cohort; B: female cohort). The risk of lower gastrointestinal bleeding was significantly higher in NSAID+PPI users than in NSAID-only users in both males (hazard ratio [HR], 2.963; 95% confidence interval [CI], 1.952 to 4.499; p<0.001) and females (HR, 3.221; 95% CI, 1.909 to 5.434; p<0.001).

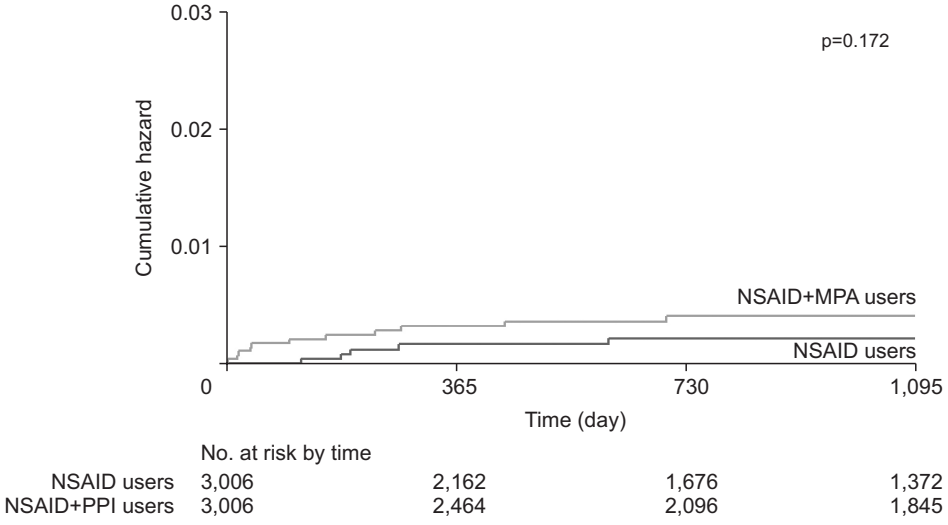


Fig. 5. Kaplan-Meier plots for lower gastrointestinal bleeding between nonsteroidal anti-inflammatory drug (NSAID)+mucoprotective agent (MPA) users and NSAID-only users. The risk of lower gastrointestinal bleeding was comparable between NSAID+MPA users and NSAID-only users (hazard ratio, 2.057; 95% confidence interval, 0.714 to 5.924; p=0.172).

users and NSAID-only users (HR, 2.057; 95% CI, 0.714 to 5.924; p=0.172) (Fig. 5). LGI bleedings occurred after median of 99 days (interquartile range, 27.5 to 256.5 days) in NSAID+MPA users and median of 196 days (interquartile range, 182 to 274 days) in NSAID-only users. As the most of the MPA prescriptions were eupatilin (*Artemisia argyi* leaf extract, 42898363) and rebamipide (43009008), these two medications were analyzed separately (Supplementary Fig. 1). The risk of LGI bleeding was not significantly different between NSAID+eupatilin users and NSAID-only users (HR, 1.103; 95% CI, 0.296 to 4.116; p=0.884) as well as between NSAID+rebamipide users and NSAID-only users (HR, 1.269; 95% CI, 0.510 to 3.158; p=0.607).

DISCUSSION

To the best of our knowledge, this is the first distributed network analysis using a CDM database to compare the risk of LGI bleeding between NSAID+PPI users and NSAID-only users. Our results showed that the risk of LGI bleeding was higher in NSAID+PPI users than in NSAID-only users. This increased risk was consistent across all demographics, including older patients aged >65 years and both sex cohorts. Our findings were consistent with previous clinical trials, which were limited by small sample sizes.[4,6,12] The strengths of this study are underscored by a large sample size with extensive PSM from a real-world setting, utilizing a CDM database across multiple substantial hospital databases, which markedly enhances the reliability and generalizability of our findings to routine clinical practice. The employment of the Cox proportional hazard models robustly quantifies the risk differences, elucidating the study's rigorous evaluation of outcomes. Additionally, the comprehensive inclusion of diverse patient demographics and meticulous control of confounding variables underscore the study's methodological rigor. Moreover, the investigation into MPAs, including eupatilin and rebamipide, as potential alternatives to an NSAID+PPI combination enriches the clinical implications of the study. These findings may suggest viable therapeutic options that could mitigate LGI bleeding risks associated with the NSAID+PPI therapy.

NSAIDs play a beneficial role by inhibiting cyclooxygenase and prostaglandin synthesis but can lead to gastrointestinal toxicities. Although prostaglandin deficiency is considered an important pathogenic factor of NSAID-induced gastropathy, gut microbiota also contributes to NSAID-induced enteropathy, as NSAIDs may lead to gut barrier destruction, gut dysbiosis, and bacterial translocation.[13] Meanwhile, PPIs and bile may contribute to the development of NSAID-induced enteropathy.[13] PPIs are powerful medications that significantly suppress gastric acid secretion, and long-term suppression of gastric acid with PPIs may lead to bacterial overgrowth in the small intestine as well as dysbiosis,[14,15] which may aggravate NSAID-induced enteropathy. A rodent experiment by Wallace *et al.*[16] revealed that PPIs may exacerbate small bowel injury by causing dysbiosis. Recently, the risk of LGI bleeding has been shown to increase with the combined use of PPIs and NSAIDs.[4,6,17] In a clinical trial using capsule endoscopy, 68% of healthy volunteers showed new pathology in the small bowel after 2 weeks of using NSAIDs and PPIs.[4] The most common lesions were mucosal breaks, reddened folds, petechiae, denuded mucosa, and blood in the lumen, which may potentially become a focus of LGI bleeding. In another clinical trial using capsule endoscopy, healthy subjects who used NSAIDs and PPIs for 2 weeks showed significantly more small bowel mucosal breaks than subjects who used a placebo (55% vs 7%, p<0.001).[12] A randomized, placebo-controlled trial also showed that NSAID+PPI users developed significantly more small bowel injuries than NSAID-only users (44.4% vs 16.7%, p=0.04).[6] Similarly, PPI use was identified as an independent risk factor for small bowel mucosal breaks (OR, 2.04; 95% CI, 1.05 to 3.97) in aspirin users.[8] However, these clinical trials were all limited by small sample sizes.[4,6,12] A recent meta-analysis of 12 studies encompassing 341,063 participants also demonstrated an association between PPI use and the risk of LGI bleeding in NSAID users (HR, 6.55; 95% CI, 2.01 to 21.33).[7] However, this meta-analysis was also limited by a variable definition of LGI bleeding and a variable study design. Therefore, the present study provides new evidence using large-size, real-world data.

The most effective method of preventing NSAID-induced enteropathy is to discontinue the use of NSAIDs, which would not be possible in patients with chronic pain or antiplatelet therapy.[18] Although several options for the prevention or treatment of NSAID-induced enteropathy have been suggested,[18] there is still little evidence. Our study showed that the risk of LGI bleeding was not significantly different between NSAID+MPA (specifically, eupatilin and rebamipide) users and NSAID-only users. Rebamipide has a gastroprotective effect by producing prostaglandins and mucus glycoproteins, blocking harmful reactive oxygen species and inflammatory cytokines, dampening neutrophil activation,[19] and improving dysbiosis by modulating the gut microbiota.[20,21] A meta-analysis showed that rebamipide has a preventive effect for NSAID-induced gastropathy (OR, 1.55; 95% CI, 1.02 to 2.36) as well as NSAID-induced small bowel damage (OR, 2.70; 95% CI, 1.02 to 7.16).[22] A randomized, double-

blinded study showed that rebamipide has a healing effect in patients with NSAID- and/or aspirin-induced small bowel injury.[23] In a recent adverse event reporting system from Japan, NSAID+rebamipide users had half the risk of LGI injury than NSAID-only users.[24] Eupatilin also has gastroprotective, anti-inflammatory, and analgesic effects.[25] In animal models, DA-9601, the main ingredient in eupatilin, has been shown to have an anti-inflammatory effect on NSAID-induced enteritis.[26] A recent analysis with national claim data compared the effect of various MPAs on aspirin-induced small bowel bleeding.[27] The multivariate analysis in this study demonstrated the risk of small bowel bleeding was higher with the concurrent use of aspirin and a PPI (HR, 2.85; 95% CI, 2.00 to 4.10; p<0.001) and lower with the concurrent use of aspirin and eupatilin (HR, 0.35; 95% CI, 0.15 to 0.80; p=0.013). Therefore, MPAs may have a preventive effect against LGI bleeding in NSAID/aspirin users.

Our study had several limitations. First, the inherent nature of a retrospective observational study, despite its extensive scope, cannot definitively establish causality and remains vulnerable to potential confounding. However, there have been no prospective studies on this issue, and extensive PSM was performed prior to the analysis to avoid potential bias. Second, variability in the operational definitions and diagnostic criteria for LGI bleeding may compromise the comparability of previous results with our study, which was also a limitation of a previous meta-analysis.[7] However, CDM-based studies have standardized data with the same structure across various medical institutions. Third, the relatively small sample sizes in certain subgroup analyses might have diminished the statistical power necessary to detect significant differences. Fourth, the latent period of taking NSAIDs and PPIs were not obtained in this study. As the target cohort was defined as NSAIDs and PPIs for >90 consecutive days, the minimum latent period from drug exposure to LGI bleeding was 90 days in this study. Fifth, this study did not perform a dose-response relationship analysis for PPI use. The PPI dosage analysis was not feasible due to the diverse types and doses of PPIs used. Sixth, rectal bleeding cases could not be completely excluded from LGI bleeding cases in coding-based definition and were analyzed together in this study. Therefore, further study is necessary for LGI bleeding definition excluding anorectal bleeding. Lastly, our study may be limited by the inclusion of only Korean patients, which may not adequately represent other ethnicities. It would be beneficial to analyze a more diverse range of ethnicities in future studies, as previous studies of MPA on LGI bleeding were mostly performed on Asian patients.[23,24,27]

In conclusion, this study demonstrated that the risk of LGI bleeding was higher with NSAID+PPI use than with NSAID-only use. However, NSAID+MPA (e.g., eupatilin, rebamipide) use was not associated with a higher risk of LGI bleeding. Further prospective studies are necessary to confirm these findings.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study concept and design: M.L., J.M.C. Data acquisition: M.L. Data analysis and interpretation: M.L., M.K. Manuscript drafting: M.L., J.M.C. Critical revision of the manuscript for important intellectual content: J.M.C. Statistical analysis: M.L., M.K. Study supervision: J.M.C. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl240247.

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