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Original Article

Rebamipide Prevents the Hemoglobin Drop Related to Mucosal-Damaging Agents at a Level Comparable to Proton Pump Inhibitors

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Background/Aims: The effect of proton pump inhibitors (PPIs) on the lower gastrointestinal (GI) tract is uncertain, with potential to worsen damage. This study aimed to find the best method for protecting the entire GI tract from mucosal damage.

Methods: A retrospective cohort study at Samsung Medical Center (2002-2019) included 195,817 patients prescribed GI mucosa-damaging agents. The primary goal was to assess the effectiveness of GI protective agents in preventing significant hemoglobin drops (>2 g/dL), indicating overall GI mucosal damage. Self-controlled case series and landmark analysis were used to address biases in real-world data.

Results: The incidence rate ratios for rebamipide, PPI, and histamine-2 receptor antagonist (H2RA) were 0.34, 0.33, and 0.52, respectively. Rebamipide showed a significantly lower incidence rate than H2RA and was comparable to PPIs. Landmark analysis revealed significant reductions in hemoglobin drop risk with rebamipide and H2RA, but not with PPI.

Conclusions: Rebamipide, like PPIs, was highly effective in preventing blood hemoglobin level decreases, as shown in real-world data. Rebamipide could be a comprehensive strategy for protecting the entire GI tract, especially when considering PPIs' potential side effects on the lower GI tract. **(Gut Liver 2024;18:1026-1036)**

Key Words: Gastrointestinal bleeding; Rebamipide; Proton pump inhibitors; Mucosa-damaging agents; Anti-inflammatory agents, non-steroidal

INTRODUCTION

It is well known that antithrombotic agents such as aspirin, clopidogrel, warfarin, and direct oral anticoagulants, as well as nonsteroidal anti-inflammatory drugs (NSAIDs), may induce or aggravate mucosal damages in the gastrointestinal (GI) tract.[1-4]

Since the 2009 American College of Gastroenterology guidelines recommended the appropriate use of proton pump inhibitors (PPIs) and/or misoprostol based on the risk of GI bleeding and cardiac risk,[5] PPIs have been widely used and have shown clear benefits in improving the upper GI (UGI) symptoms and preventing UGI ulceration and bleeding.[6-8] However, recent studies have indicated that PPIs may not effectively prevent lower GI (LGI) tract damage caused by NSAIDs and could even potentially exacerbate them.

Misoprostol was also recognized for its GI protective effects,[9-11] but its use has been limited due to its common side effects such as abdominal cramping and diarrhea. In the Koren Journal of Gastroenterology guidelines, considering the side effects, misoprostol was excluded from the recommended list of protective agents (PAs).[12] Rebamipide has emerged as a potential alternative to misoprostol, offering GI mucosa protective effects and minimal side effects.[13,14]

According to a Spanish study, from 1996 to 2005, there

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has been a gradual decrease in UGI complications associated with NSAIDs, while LGI complications have shown a significant increase.[1] Additionally, there is a study indicating that the risk of bleeding in the LGI tract is approximately three times higher compared to the UGI tract in dual antiplatelet agents and PPI co-therapy.[2] To ensure effective protection of the entire GI tract against mucosa-damaging agents (DAs), it is essential to address both the UGI and LGI regions. Therefore, we compared and analyzed the effects of individual or combined therapies involving PPIs, histamine-2 receptor antagonist (H2RA), and rebamipide, using a comprehensive indicator of blood hemoglobin (Hb) decrease, which reflects the overall damage to the UGI and LGI tracts.

MATERIALS AND METHODS

1. Study population and data collection

We collected 195,817 patients who received mucosa-damaging drugs at Samsung Medical Center (SMC) between 1 January 2002 and 31 December 2019 (Fig. 1). We excluded those with the diseases that can affect significant hemoglobin drop (SHD); cancer (International Classification of Diseases, 10th Revision [ICD-10]; C00-C97), intracerebral/intraventricular hemorrhage (ICD-10; I60-I62), injuries of external causes to the head, neck, thorax, abdomen with pelvis, hip, thigh and multiple body regions (ICD-10, S00-S39, S70-S79, and T00-T09), advanced chronic kidney disease (stage 3 or higher) (ICD-10, N183-N185), decompensated liver cirrhosis (ICD-10, K74) with varices and ascites (ICD-10, I85 and R18), bleeding disorders (hereditary factor VIII/IX deficiency and other coagulation defects) (ICD-10, D66-D68). The following analyses were conducted on 144,276 patients. Data was extracted from DARWIN-C, the clinical data warehouse at SMC. This study protocol was reviewed and approved by the SMC Institutional Review Board (SMC IRB number: 2022-11-083). The study was conducted in accordance with the Helsinki Declaration, and only data from patients who consented to electronical medical record access were collected.

2. Variables of interest

1) Mucosa-DAs

Mucosa-DAs refer to a group of medications known to cause damage to the GI mucosa. This includes NSAIDs such as fenoprofen, ibuprofen, indomethacin, ketorolac, loxoprofen, mefenamic acid, meloxicam, morniflumate, nabumetone, naproxen, piroxicam, sulindac, talniflumate, and zaltoprofen; as well as antiplatelet agents and anticoagulants such as aspirin, clopidogrel, and direct oral anticoagulants like apixaban, rivaroxaban, warfarin, edoxaban, and dabigatran. The DA group was defined as patients who received the prescription for more than 30 days.[15,16]

2) Protective agents

PAs included anti-ulcer drugs, acid-suppressing agents, and mucosa-PAs. If the duration of medication was 7 days or longer, it was defined as the PA group.[17] PPIs included lansoprazole, esomeprazole, pantoprazole, and rabeprazole, while H2RAs included ranitidine, famotidine, cimetidine, and lafutidine. We examined several mucosa-PAs, including sodium alginate, rebamipide, ecabet sodium hydrate, polaprezinc, and Stillen (artemisiae argyi herba 95% ethanol extract). Among these agents, only rebamipide was included in this study because it has been extensively studied in the literature and the prescription frequency was high in this center.

3. Outcome of interest

We used the SHD as our primary outcome to assess how effectively GI protective drugs prevent mucosal damage, because blood Hb level decrease can be an indicator that clinically reflects overall GI mucosal damage.[18-20] The occurrence of SHD was declared if the blood Hb level decreases by more than 2 g/dL compared with the baseline level that is the average of the three most recent sequential measurements.

4. Study designs

We conducted a self-controlled case series (SCCS) analysis supplemented by a landmark analysis[21] to investigate the extent of reduction in the incidence of SHD when using various PAs.

1) Self-controlled case series

The SCCS is a case-only design that includes only individuals experiencing an event of interest (i.e., cases), and assesses the association between a transient exposure and the event by within-individual comparison.[22,23] Its major advantages are no requirement of independent controls and a natural control for all time-invariant confounding.

For each individual, PA-exposed periods are prespecified along with PA-non-exposed periods as self-controls. The occurrence rates of the events are compared between the exposed and non-exposed periods in within-individual manner.

For an SCCS analysis, we constructed the dataset as follows. First, we extracted patients from the cohort dataset, who had received concomitant prescriptions of DAs and PAs and experienced an SHD at least once (Fig. 1). The

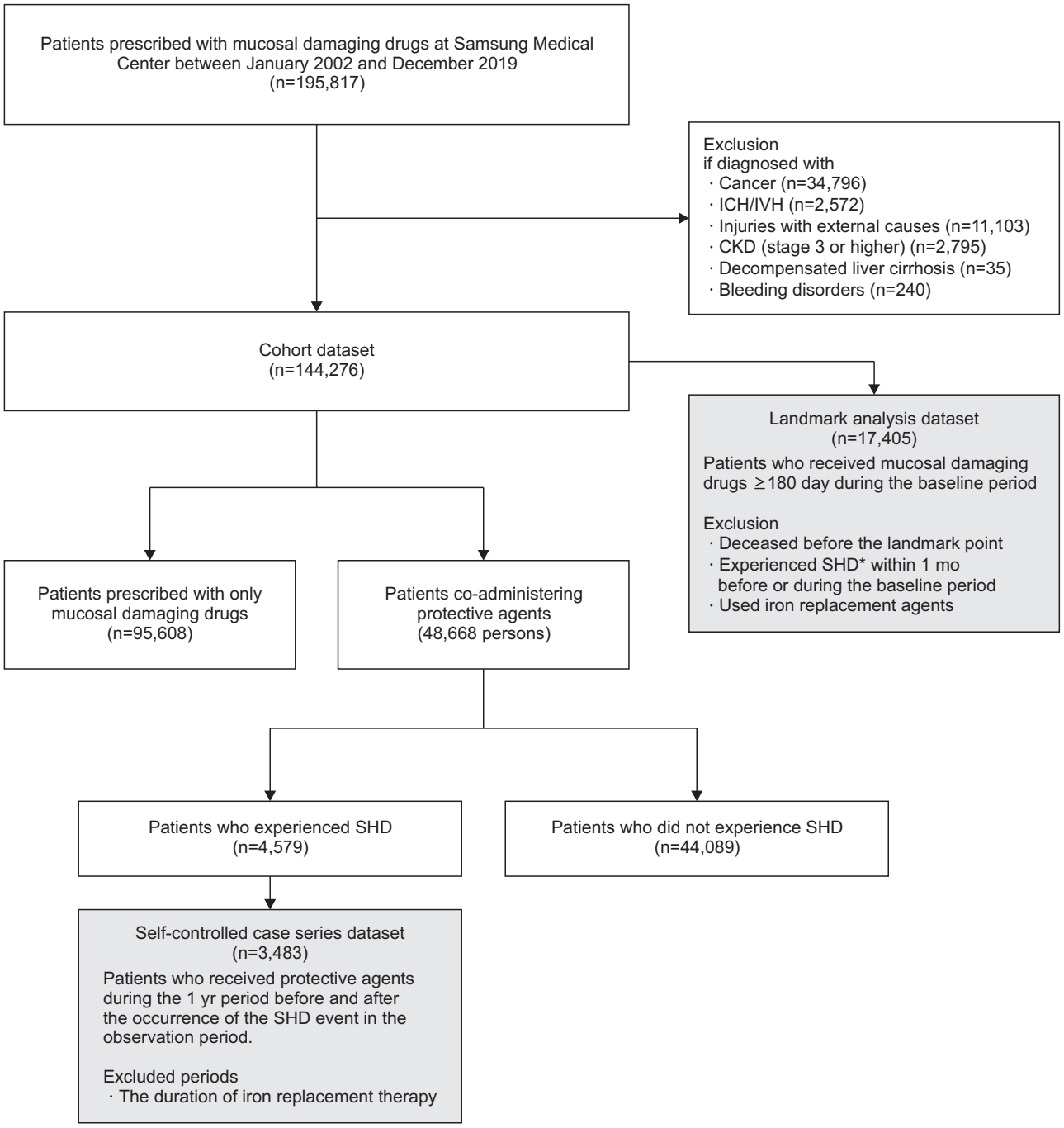


Fig. 1. Study population flowchart. ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; CKD, chronic kidney disease; SHD, significant hemoglobin drop. *SHD: the occurrence of an SHD event is declared if hemoglobin decreases by >2 g/dL compared with the baseline hemoglobin.

date of SHD occurrence was used as the index date. Then, the SCCS dataset comprised of only those patients who received PAs within the period of 1 year before and after the index date.

The SCCS design used in this study is illustrated in Fig. 2. For a drug, "continuous" prescriptions were defined as consecutive ones if the interval between the end of the previous prescription and the start of the next prescription was not greater than 7 days. A "latent period" was defined as additional 7 days after termination of a prescription to account for potential lingering effects of the drugs even after discontinuation by considering various drug half-lives commonly used in drug design.[24-26] Then, we defined an "observation period" was defined as the total duration

of continuous prescriptions of the DAs plus a latent period (Fig. 2A). All observation periods were identified and constituted the whole study period for each patient. A "PA period" was an exposed period in which a patient is exposed to PAs within an observation period. It was defined as the total duration of continuous prescriptions of either single PA agent or a combination of PA agents plus a latent period. All the remaining time within the observation period constitutes "non-PA periods," and used as non-exposed periods (i.e., controls) in within-patient comparison of SHD occurrence rates.

"Outcome periods" were defined as 30-day period following the occurrence of a SHD (Fig. 2B).[27,28] If outcome periods of multiple SHD events overlapped, we considered them as a single outcome period that started after the first SHD and lasted until 30 days after the last SHD. All outcome periods were excluded from the analysis evaluating the protective effect of the PAs since PAs prescribed during these periods are likely intended to prevent immediate further bleeding. In other words, the preceding SHD could influence both the exposure to PAs and the occurrences of subsequent SHDs within these periods.

During the observation periods, we excluded all periods from the analysis, within which patients received iron replacement therapy because it directly affects blood Hb levels. All observation periods for analysis were restricted within 1 year before and after the index date to minimize potential confounding due to time-varying confounders (Fig. 2C).

2) Retrospective cohort design for landmark analysis

Additional landmark analysis of DA users was planned to verify the consistency of the results derived from the SCCS. The landmark method was developed to adjust for the immortal time bias inherent when comparing cumulative incidence rates (CIRs) of time-to-event outcomes between exposure and non-exposure groups determined not at the baseline but during the follow-up.[29] It provides unbiased estimates for CIRs by using group memberships determined at a specific time point, called as a landmark

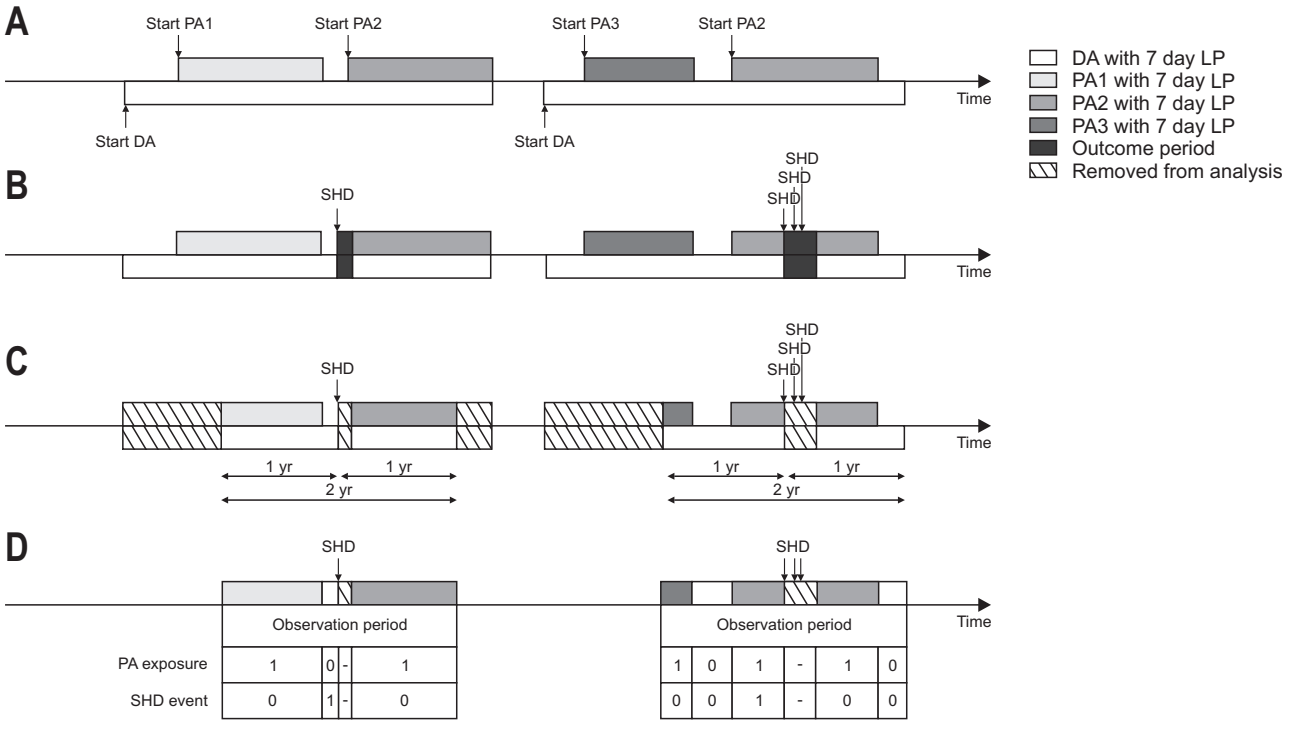


Fig. 2. Pictorial representation of the self-controlled case series design used in the study. (A) The observation period is defined as the total duration of consecutive prescriptions of the mucosa-damaging agents (DAs). We added the 7-day latent period (LP) following the termination of the DA prescriptions considering any lingering effects. Protective agent (PA) periods are defined as the total duration of consecutive prescription of the PAs, either singly or in combination of proton pump inhibitor, histamine-2 receptor antagonist, or rebamipide, with a 7-day LP. We only considered PA periods in the observation period. (B) The initiation of an outcome period is the date of significant hemoglobin drop (SHD) occurrence. If SHD events occur multiple times within one outcome period, they are considered as a single SHD event, and the outcome period is extended until 30 days after the last SHD event. (C) For each SHD event, we analyzed 1 year before and after the event to assess the association between PA use and SHD prevention within the entire observation period. The outcome period additionally was not considered in the analysis. (D) We investigated the duration of the PA periods or non-PA periods. We also examined the occurrence of an event during the exposure interval. Accordingly, the Poisson incidence rates can be computed with each interval. Finally, we estimated the incident rate ratios using the conditional Poisson log-likelihood

point, and thus allows for a proper comparison of the CIRs.

In this study, patients started PA use not always at the initiation of DA use but at various times after starting DAs, and their memberships of PA-exposure group varied across time points during the follow-up. If a conventional analytic method was used with no consideration on time-variable group memberships, the PA-exposure group earns a period free from SHD events until the initiation of PA use. This may lead to the immortal time bias, due to which the association between the PA-exposure and bleeding prevention could be overestimated.

To use a landmark method for the bias correction, we constructed a SHD-free cohort that consists of 1-year sub-cohorts. Each sub-cohort for each year from 2003 to 2019 was constructed as follows (Fig. 3). First, the important dates and periods were defined: the baseline date was set as January 1; the landmark point was defined as January 1 of the next year (i.e., 1 year after the baseline date); the baseline period was defined as the period from the baseline date until the landmark point; and the follow-up period was defined as the 1-year period after the landmark point. Second, we used the baseline period to assess the eligibility of patients and to determine their group memberships of the PA exposure. The use of an agent was declared when a patient received it for 180 days or more during the baseline period. We included patients who used DAs; were alive during the baseline period; and did not experience SHD within 1 month before or during the baseline period (Fig. 1). Patients who used iron replacement agents were excluded. The PA-exposure group consisted of patients who used DAs and PAs with concomitant prescriptions whereas the non-exposure group consisted of those who used DAs alone. Finally, all sub-cohorts constituted the SHD-free cohort for the landmark analysis.

5. Statistical analysis

All data processing and statistical analyses were performed using R software (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was declared with two-sided p-values less than 0.05.

1) SCCS analyses

Conditional Poisson regression models were used to estimate and compare the incidence rate ratios (IRRs) of SHD occurrence and their 95% confidence intervals (CIs). By conditioning on the marginal total number of SHD events that occurred in a patient, these models provided within-patient comparison of incidence rates between PA-exposed and unexposed periods with implicit adjustment for all time-invariant patient-level risk factors and potential confounders (Fig. 2D).

In cases where multiple SHD events occurred within an observation period, we assumed them to be independent since we excluded outcome periods to avoid the influence of a preceding outcome on the subsequent outcomes, and performed separate analyses on each individual outcome. To address a potential bias due to possible non-independence between multiple SHD events, a sensitivity analysis followed by analyzing only the first SHD event.

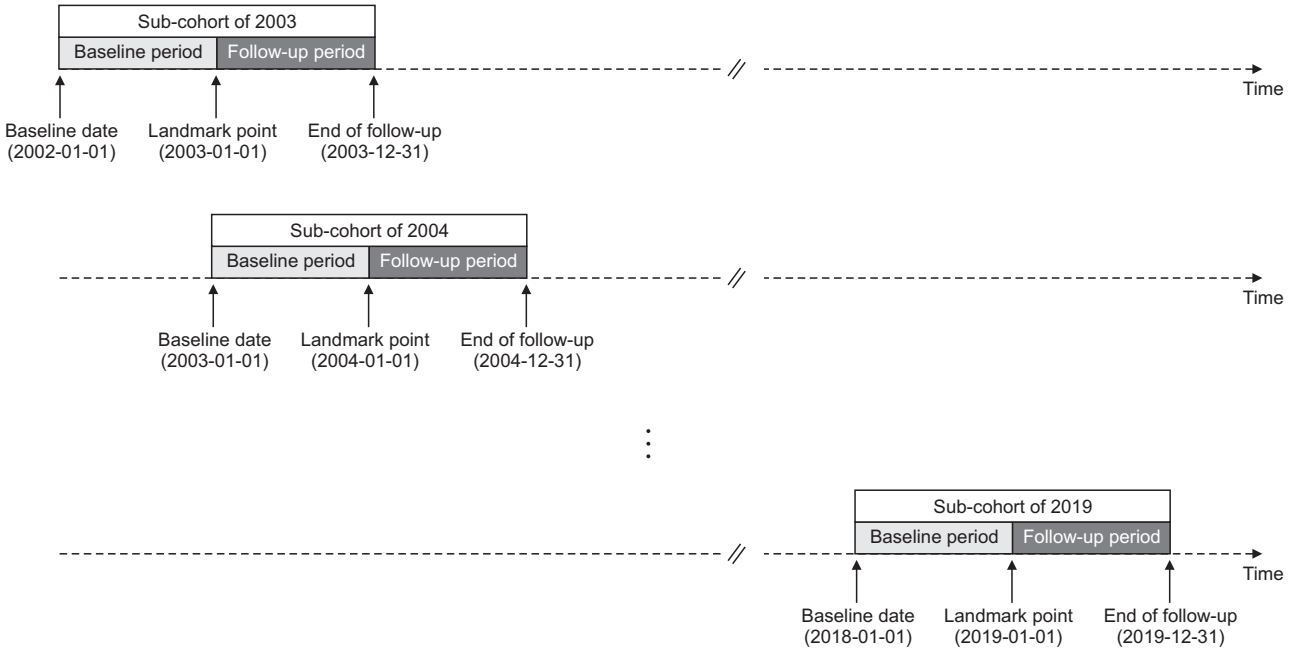


Fig. 3. Pictorial representation of retrospective cohort design for the landmark analysis.

2) Landmark analysis

Kaplan-Meier method and log-rank tests were used to estimate and compare CIRs. We employed multivariable conditional Cox proportional hazards models to estimate hazard ratios (HRs) with 95% CIs adjusted with age, sex, and number of SHD incidences prior to the baseline date. Because a patient can belong to multiple sub-cohorts, we added the cluster effect into the models to reflect the within-patient variation. While the above main analyses were conducted with the first SHD event within each follow-up period, a recurrent survival analysis of the multiple SHD events was additionally performed using the shared frailty model. The proportional hazard assumption and multicollinearity were verified using the Schoenfeld residual method and no severe violation was found.

RESULTS

A total of 144,276 patients were included in the whole cohort dataset (Fig. 1). The median age was 59 years (interquartile range, 49 to 68 years), and 52.1% were males (Table 1). Aspirin, NSAIDs, and clopidogrel were prescribed to 65.6%, 25.4%, and 24.5% of all patients, respectively. Among the patients prescribed with DAs, 44.3% received PAs additionally. The SCCS dataset contains 3,483 patients, out of which 55.0%, 41.5%, and 16.8% were respectively in H2RA, PPI, and rebamipide monotherapy groups whereas 4.7%, 2.6%, and 2.8% belonged respectively to the PPI-H2RA, H2RA-rebamipide, and PPI-rebamipide combination therapy groups.

1. IRR of SHD according to various PAs uses in the SCCS

In comparison to the DA-only period, the IRRs of SHD significantly decreased in all periods of PA monotherapies and two-PA combination therapies (Table 2). In the rebamipide, PPI, and H2RA groups, the IRRs were 0.34 (95% CI, 0.28 to 0.42), 0.33 (95% CI, 0.28 to 0.38), and 0.52 (95% CI, 0.45 to 0.59), respectively. Through further analysis, we confirmed that the IRR of Rebamipide was significantly lower than that of H2RA, and there was no significant difference when compared to PPI. The two-PA combination therapies exhibited IRRs similar to those of PA monotherapies, but with fewer incidences of SHD, resulting in a wider CI. We had consistent results when considering only the first incidence of SHD in each observation period (Table 2).

2. Kaplan-Meier analysis and HR for SHD according to various PAs uses in the landmark analysis

A total of 17,405 patients received DAs for 180 days or more during the baseline periods (Fig. 1). The total follow-up was 53,843 person-years. We observed 1,563 SHD events for all patients, out of which 70 patients experienced more than one event. Compared to the DA-only group,

Table 1. Baseline Characteristics of Patients with Mucosa-DAs

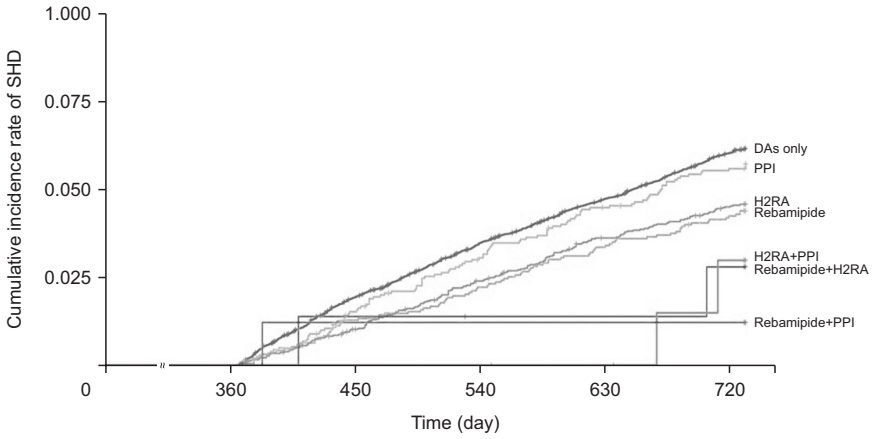
Variable	Cohort dataset (n=144,276)	SCCS dataset (n=3,483)
Age, median (IQR), yr	59 (49–68)	65 (55–74)
Sex, No. (%)		
Female	69,104 (47.9)	1,433 (41.1)
Male	75,172 (52.1)	2,050 (58.9)
Mucosa-DAs, No. (%)		
Aspirin	94,643 (65.6)	2,567 (73.7)
Clopidogrel	35,306 (24.5)	1,315 (37.8)
Warfarin	14,169 (9.8)	908 (26.1)
NSAIDs	36,693 (25.4)	387 (11.1)
DOAC	7,719 (5.4)	337 (9.7)
PAs co-administered with DAs, No. (%)		
Rebamipide	15,064 (10.4)	586 (16.8)
PPI	27,310 (18.9)	1,446 (41.5)
H2RA	40,872 (28.3)	1,916 (55.0)
PPI + rebamipide	1,772 (1.2)	99 (2.8)
H2RA + rebamipide	2,679 (1.9)	91 (2.6)
PPI + H2RA	3,562 (2.5)	164 (4.7)
PPI + H2RA + rebamipide	277 (0.2)	7 (0.2)

DA, damaging agent; SCCS, self-controlled case series; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; DOAC, direct oral anticoagulant; PA, protective agent; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist.

Table 2. Associations of PA Uses with SHD Occurrences in the SCCS Analyses

Exposure period	No. of SHD incidences	IRR (95% CI)	p-value
All SHD events			
Mucosa-DA use alone	5,048	Reference	
Rebamipide	334	0.34 (0.28–0.42)	<0.001
PPI	465	0.33 (0.28–0.38)	<0.001
H2RA	736	0.52 (0.45–0.59)	<0.001
PPI + rebamipide	14	0.34 (0.18–0.64)	0.001
H2RA + rebamipide	15	0.36 (0.19–0.67)	0.001
PPI + H2RA	18	0.51 (0.29–0.90)	0.020
PPI + H2RA + rebamipide	0	-	-
First SHD event only			
Mucosa-DA use alone	4,338	Reference	
Rebamipide	309	0.35 (0.28–0.44)	<0.001
PPI	407	0.32 (0.28–0.38)	<0.001
H2RA	654	0.51 (0.45–0.59)	<0.001
PPI + rebamipide	14	0.36 (0.19–0.68)	0.002
H2RA + rebamipide	13	0.37 (0.19–0.73)	0.004
PPI + H2RA	16	0.50 (0.27–0.92)	0.027
PPI + H2RA + rebamipide	0	-	-

PA, protective agent; SHD, significant hemoglobin drop; SCCS, self-controlled case series; IRR, incidence rate ratio; CI, confidence interval; DA, damaging agent; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist.



No. at risk						
DAs only	19,138	19,138	18,740	18,420	18,155	17,888
Rebamipide	2,027	2,027	2,000	1,981	1,958	1,939
PPI	1,902	1,902	1,869	1,837	1,808	1,786
H2RA	4,099	4,099	4,048	3,988	3,932	3,893
Rebamipide+H2RA	82	82	81	81	81	81
Rebamipide+PPI	72	72	71	70	70	69
H2RA+PPI	69	69	69	69	68	65

Fig. 4. Cumulative incidence rate of significant hemoglobin drop (SHD). DA, damaging agent; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist.

Table 3. Effects of PA Uses on SHD Occurrences in the Landmark Analyses

Exposure group	No. of patients	SHD incidences		Landmark analysis		Recurrent analysis	
		No.	Per 100 person-years (95% CI)	HR (95% CI)	p-value	HR (95% CI)	p-value
Mucosa-DA alone	19,138	1,175	3.13 (2.96–3.31)	Reference		Reference	
Rebamipide	2,027	89	2.22 (1.81–2.73)	0.71 (0.57–0.88)	0.002	0.70 (0.56–0.88)	0.002
PPI	1,902	107	2.86 (2.37–3.45)	0.83 (0.68–1.02)	0.073	0.83 (0.67–1.02)	0.069
H2RA	4,099	187	2.31 (2.01–2.66)	0.73 (0.62–0.85)	<0.001	0.74 (0.63–0.87)	<0.001
PPI + rebamipide	82	1	0.61 (0.09–4.33)	0.19 (0.03–1.41)	0.104	0.20 (0.03–1.42)	0.107
H2RA + rebamipide	72	2	1.40 (0.35–5.56)	0.45 (0.12–1.76)	0.252	0.45 (0.11–1.82)	0.262
PPI + H2RA	69	2	1.46 (0.37–5.78)	0.38 (0.09–1.58)	0.185	0.40 (0.10–1.66)	0.206
PPI + H2RA + rebamipide	1	0	-	-	-	-	-

PA, protective agent; SHD, significant hemoglobin drop; HR, hazard ratio; CI, confidence interval; DA, damaging agent; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist.
The Cox models were adjusted with age, sex, and number of SHD incidences prior to the baseline date.

the PA monotherapy exposure groups showed a lower CIR (p<0.001) (Fig. 4). The number of SHD incidences was 3.13 per 100 person-year in the DA-only group whereas it was lowered to 2.22 in the rebamipide group and to 2.86 in the PPI group (Table 3).

The HR of SHD for each PA-exposure group was estimated against the DA-only group (Table 3). The rebamipide and H2RA groups exhibited significant reductions in SHD risk, but the reduction in the PPI group was not significant.

The HRs were 0.71 (95% CI, 0.57 to 0.88) for the rebamipide group, 0.73 (95% CI, 0.62 to 0.85) for the H2RA group, and 0.83 (95% CI, 0.68 to 1.02) for the PPI group. There was no statistical difference among the three drugs. In the results of the recurrent survival analysis, rebamipide was consistently shown to be significantly more protective compared to mucosa-DA alone (HR, 0.70; 95% CI, 0.56 to 0.88), and no significant difference was observed compared to PPI (Table 3).

DISCUSSION

In order to protect the entire GI mucosa from the mucosa-DAs, both the UGI and LGI tracts should be considered. Our study suggested that the use of rebamipide was not inferior to PPI for overall GI mucosal protection in that this showed the lowest IRR for SHD.

When mucosa-DAs render the mucosa vulnerable in the stomach and duodenum, gastric acid acts as an additional key offending factor to exacerbate damage and cause ulcers. Conversely, in the small intestine where the gastric

acid has already been neutralized, bile acids, pancreatic proteases, intestinal bacteria, and toxins can act as supplementary offending factors.[30-33]

The effect of PPIs in preventing UGI bleeding by protecting the UGI tract is already well established.[34] However, reports are increasing that suggest PPI may not prevent LGI bleeding and might even exacerbate it.[2,35-37] One hypothesis explaining this phenomenon is that the decrease in gastric acid due to PPI use promotes dysbiosis in the small intestine, which in turn exacerbates intestinal mucosal damage caused by NSAIDs.[38,39] Normally, bacteria are diminished by gastric acid as they pass through the stomach, leading to lower bacterial counts in the small intestine. However, long-term use of acid-suppressing agents such as PPIs could lead to bacterial overgrowth in the small intestine and worsen NSAID-induced damage. Additionally, the increased microbial growth in the small intestine might lead to greater deconjugation of NSAIDs and bile acids, ultimately enhancing the enterohepatic circulation of NSAIDs and potentially raising their concentration in the small intestine.[1,38-41] Actually, the use of PPIs has a detrimental effect on the recovery from anemia caused by GI mucosa damage as well because it inhibit iron absorption in the GI tract.[42]

Given the increasing trend of LGI bleeding in association with mucosa-DAs while UGI bleeding is decreasing, the clinical concern of PPIs being ineffective in protecting LGI tract calls for alternative approaches. Rebamipide, a mucosal PA, has garnered attention as a suitable alternative for comprehensive GI mucosal protection.

In terms of gastric mucosal protection, studies in patients taking NSAIDs demonstrated that rebamipide exhibited similar anti-ulcer effects to misoprostol while maintaining appropriate levels of drug compliance.[43] Furthermore, in studies targeting patients on low-dose aspirin alone or combined with clopidogrel, rebamipide reduced gastric mucosal damage.[44]

In terms of small intestinal mucosal protection, a randomized controlled trial targeting patients who had consumed aspirin or NSAIDs for over 3 months demonstrated that rebamipide reduced the occurrence of small bowel ulcers and erosions compared to placebo.[45] In patients concurrently using aspirin and omeprazole, additional rebamipide therapy significantly reduced the number of small intestinal mucosal breaks from baseline 4.0 to 2.0 after 8 weeks.[46] Furthermore, the side effects of rebamipide have been rarely reported.

The mechanisms for the mucosal protection, anti-inflammation, and tissue-repair effects of rebamipide involve the stimulation of prostaglandin and mucus glycoprotein synthesis, inhibition of reactive oxygen species, inflammatory cytokines, and chemokines, as well as suppression of neutrophil activation. In addition to its direct protective effects against intestinal mucosal damage, rebamipide has also been reported to induce lactobacillus proliferation, promoting the balance of intestinal microbiota.[47,48]

Edogawa *et al.*[14] emphasized that NSAIDs-induced small intestinal damage arises not solely from acid-dependent mechanisms but from various factors, including intestinal bacteria, bile acids, prostaglandin deficiency, impaired intestinal permeability, mitochondrial dysfunction, and endoplasmic reticulum stress. They proposed a strategy prioritizing the use of mucosa PAs for intestinal protection. Specifically, they suggested the solitary use of mucosal PAs for low-risk patients, and a combination of mucosa PAs and PPIs for patients with high risk factors of UGI complications such as a history of reflux esophagitis, peptic ulcers, or previous UGI bleeding events.[14]

In 2021, Zhang *et al.*[49] conducted a systemic review and meta-analysis concerning aspirin-related mucosal damage prevention. They presented data indicating that the combined use of omeprazole and rebamipide (92.96% cumulative percentage of reduction in GI injury rate) outperformed other groups such as ranitidine (87.91%) and omeprazole (84.21%). Based on these findings, they recommended the combined use of rebamipide and PPIs as a potentially preferred intervention for aspirin-induced mucosal protection.[49]

In retrospective studies dealing with massive real-world data, careful control of biases is crucial for deriving appropriate conclusions. In this study, to enhance reliability by mitigating biases, we adopted two systematic statistical techniques: the SCCS and landmark analysis. The SCCS controls potential time-invariant confounders like genetic background. It also effectively handles individual variations in exposure patterns, including varying durations of DA and PA use within a single patient. It also seamlessly adapts to transitions between different PA agents and irregular patterns of single or combination use of these agents. We performed the SCCS analysis for each DA separately. In the cases of NSAIDs and warfarin, the IRR was significantly lower in the rebamipide group compared to the PPI group, while in clopidogrel, the IRR was lower in the PPI group than in the rebamipide group, though not statistically significant. This suggests that rebamipide, when combined with certain DAs, may offer better protective effects than PPIs, indicating a need for future prospective studies to prove this.

In contrast, a retrospective cohort study offers a straightforward comparison between well-defined exposed and unexposed groups. A landmark analysis effectively minimizes immortal time bias by setting a specific assess-

ment time-point.

In the SCCS, the mucosal protective effect of rebamipide was found to be superior to that of H2RA, and there was no statistically significant difference when compared to PPI. Landmark analysis demonstrated a significant mucosal protective effect for rebamipide and H2RA, whereas this effect was not observed for PPI. However, no significant differences were observed among the three groups in both statistical methods. Despite numerical differences, further confirmation through large-scale prospective studies will be necessary for areas that are not statistically significant. Our study encompassed a large cohort of 144,276 individuals, examining a wide array of NSAID types and various antithrombotic agents, while the systemic review conducted by Watanabe *et al.*[46] focused solely on aspirin. Through recent advanced analysis techniques applied to a large-scale cohort across a diverse range of mucosa-DA groups, we have demonstrated the superiority of PPI and rebamipide combination therapy in providing overall GI protection, including the LGI tracts.

In conclusion, our study suggests that in patient populations consuming mucosa-DAs such as NSAIDs, aspirin, antiplatelet agents, and anticoagulants, the use of rebamipide can potentially serve as a comprehensive strategy throughout the entire GI tract, particularly in situations where concerns exist regarding the side effects of PPIs in the LGI tract. Future research, building upon our study's findings, need encompass large-scale prospective randomized controlled trials to establish guidelines for systematic preventive interventions.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Study concept and design: D.K.C. Data acquisition: J.E.K. Data analysis and interpretation: Y.C.L. Drafting of the manuscript: J.E.K. Critical revision of the manuscript for important intellectual content: T.S.K., E.R.K., S.N.H., Y.H.K. Statistical analysis: Y.C.L. Obtained funding: D.K.C. Administrative, technical, or material support; study supervision: K.K., D.K.C. Approval of final manuscript: all authors.

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly, given the privacy expectations of the individuals who participated in the study. The data will be shared upon reasonable request to the corresponding author.

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