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Effect of Potassium-Competitive Acid Blockers on Upper Gastrointestinal Bleeding in Patients on Dual Antiplatelet Therapy After Percutaneous Coronary Intervention: A Nationwide Cohort Study

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Keywords: dual antiplatelet therapy | percutaneous coronary intervention | potassium-competitive acid blocker | proton pump inhibitor | upper gastrointestinal bleeding

ABSTRACT

Background and Aim: Proton pump inhibitors (PPIs) are the drug of choice to prevent upper gastrointestinal (UGI) bleeding in patients receiving dual antiplatelet therapy (DAPT); however, unmet needs remain. Potassium-competitive acid blockers (P-CABs) are novel acid-suppressive drugs that have emerged as potential alternatives. We evaluated the effectiveness of P-CAB in reducing the risk of UGI bleeding in patients receiving DAPT after percutaneous coronary intervention (PCI).

Methods: This retrospective cohort study included patients with PCI on DAPT between January 2019 and January 2023 using the Korean nationwide health claims database. The primary outcome was admission for UGI bleeding within 6 months of PCI. A multivariate Cox regression model was used to evaluate UGI bleeding risk based on PPIs and P-CAB use.

Results: Of the 210 447 patients who underwent PCI on DAPT (mean age, 65.5 years; 74.7% men), 4.6% and 47.5% patients were prescribed P-CABs and PPIs, respectively. Overall, 0.3% of patients experienced UGI bleeding within 6 months of PCI. P-CAB users had a reduced risk of UGI bleeding (adjusted hazard ratio, 0.59; 95% confidence interval, 0.38–0.92; $p = 0.019$) compared with patients not receiving P-CAB or PPI. No significant difference was observed between the P-CAB and PPI users ($p > 0.05$).

Conclusions: Among Korean patients undergoing PCI with DAPT, P-CABs reduced UGI bleeding comparably to PPIs. These findings suggest that P-CABs are potential alternatives to PPIs for preventing UGI bleeding.

1 | Introduction

Dual antiplatelet therapy (DAPT) in patients with coronary artery disease treated with percutaneous coronary intervention (PCI) is standard therapy, although it increases the risk of upper gastrointestinal (UGI) bleeding [1–3]. In these patients, proton pump inhibitors (PPIs) are effective in reducing the risk of UGI bleeding [4, 5]. Hence, coronary guidelines recommend the use of PPIs, especially in patients at high risk for bleeding [6–9]. Although PPIs have also been recommended as first-line

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HIRA, Health Insurance Review and Assessment Service; ICD, International Classification of Diseases; NHIS, National Health Insurance Service; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; P-CABs, potassium-competitive acid blockers; PPIs, proton pump inhibitors; PSM, propensity score matching; UGI, upper gastrointestinal.

acid-suppressive drugs for many acid-related UGI diseases [10,11], they have several limitations including slow onset of action, insufficient acid suppression, possible interaction with clopidogrel due to a shared metabolic pathway (CYP2C19), and potential long-term side effects [12]. These potential limitations are one of the main factor contributing to the underprescription of PPIs by cardiologists, even in patients at high risk for bleeding, despite the recommendation in coronary guidelines [13–15]. Consequently, they highlight the need for alternative acid-suppressive drugs that are superior to or at least similar in efficacy to PPIs.

Potassium-competitive acid blockers (P-CABs) are a new class of acid-suppressive drugs that competitively bind to the potassium binding site of the proton pump [16, 17]. Owing to their pharmaceutical properties, they provide a more potent and prolonged acid-inhibitory effect than that by PPIs, making it a potential alternative to PPIs [17–20]. Randomized trials for various acid-related UGI diseases have demonstrated the comparable efficacy of P-CABs and PPIs [19,21–24], with an excellent long-term safety profile [25, 26]. Considering the faster and stronger inhibition of acid, negligible CYP2C19 interaction, and long-term tolerability, P-CABs could be an alternative acid-suppressive drug for preventing UGI bleeding after PCI instead of PPIs.

In this study, we aimed to investigate the comparative effectiveness of P-CABs in preventing UGI bleeding in patients treated with DAPT after PCI using a nationwide population-based health claims database.

2 | Methods

2.1 | Data Source and Participants

This retrospective cohort study used data obtained from the Health Insurance Review and Assessment Service (HIRA) in Korea. It is mandatory for all Korean citizens to enroll in the National Health Insurance Service (NIHS), covering healthcare costs for the entire Korean population. The HIRA is a national organization that reviews all of the healthcare claims registered by the NIHS and validates the appropriateness of medical costs and healthcare service quality [27].

From the HIRA database, we selected adult (19 years and older) patients who had undergone PCI with a drug-eluting stent (DES) between January 2019 and January 2023. The inclusion criterion was admission with insurance claims for PCI (M6551-4, M6561-7, and M6571-2) and DES (J5083 and J8083). The index date was defined as the date of admission for PCI. The data for this study were available from January 2018; thus, there was at least a 1-year washout period for all patients.

Patients who were not prescribed DAPT after the index PCI were excluded. DAPT was defined as the combination of aspirin and a P2Y12 inhibitor, including clopidogrel, prasugrel, and ticagrelor. Clopidogrel was classified as a classic P2Y12 inhibitor, while prasugrel and ticagrelor as potent P2Y12 inhibitors. Patients with prior PCI or coronary artery bypass graft surgery before the index PCI, those treated with concomitant anticoagulants, those admitted for ≥ 30 days after the index PCI, or those followed up for < 30 days were excluded. We also excluded patients who were prescribed both PPIs and P-CABs.

2.2 | Comorbidities and Medications

We identified comorbidities and medications based on International Classification of Diseases (ICD)-10 diagnosis codes and Anatomical Therapeutic Chemical Classification System codes (Table S1). The use of a particular medication was defined as the prescription of the medication for at least 21 days in the 30 days following the index date of PCI.

In Korea, three P-CAB agents are currently commercially available and were investigated in this study: revaprazan (Yuhan Pharma, Seoul, Republic of Korea, 2005), tegoprazan (HK inno.N/RaQualia Pharma, Cheongju-si, Chungcheongbuk-do, Republic of Korea, 2019), and fexuprazan (Daewoong Pharma, Seoul, Republic of Korea, 2022). PPIs included esomeprazole, pantoprazole, lansoprazole, rabeprazole, omeprazole, ilaprazole, and dexlansoprazole. Patients were exclusively categorized into three groups according to the use of acid-suppressive drugs: (1) none, (2) PPI, and (3) P-CAB, which was the main variable in this study. Detailed information based on the claims data is provided in Table S1.

2.3 | Outcomes and Follow-Ups

Patients were followed up for 6 months after PCI [4]. The primary outcome was UGI bleeding identified on admission with a related primary diagnosis using ICD-10 codes (Table S1) [15]. The secondary efficacy outcomes included severe UGI bleeding and all types of GI bleeding. Severe UGI bleeding was defined as UGI bleeding accompanied by the receipt of red blood cell transfusion during admission. All types of GI bleeding were defined as admission with a primary diagnosis of upper or lower GI bleeding (Table S1). Secondary safety outcomes included the development of myocardial infarction and all-cause death. Myocardial infarction was defined as an admission with a primary diagnostic code and accordant claims for treatment (Table S1). After the index admission for PCI, the patients were followed up until either the development of the primary outcome, loss of NHIS eligibility due to emigration, death, end of the study period (July 31, 2023), or 6 months after the index date, whichever came first.

2.4 | Statistical Analyses

Differences between groups (none, PPI, and P-CAB) were evaluated using analysis of variance for continuous variables and the chi-square test for categorical variables, as appropriate. A cumulative incidence curve for UGI bleeding was plotted according to the use of acid-suppressive drugs, and a log-rank test was conducted. We used a multivariate Cox regression model and calculated the adjusted hazard ratio (aHR) and 95% confidence interval (CI) to evaluate the effect of acid-suppressive drugs in reducing the risk of UGI bleeding. Adjustments were made for age, sex, hypertension, diabetes, heart failure, prior myocardial infarction, chronic kidney disease, chronic obstructive

pulmonary disease, liver disease, cancer, functional dyspepsia, recent UGI bleeding, index PCI indication, DAPT during PCI admission, statin, NSAIDs, steroids, and H2 blockers/other agents. We also evaluated the risk of the primary outcome according to the type of P-CAB used. For the secondary outcome analysis, we constructed individual Cox regression models for each outcome.

To reduce the potential confounding effects of different baseline characteristics in the groups treated with acid-suppressive drugs (none, PPI, and P-CAB), we conducted a sensitivity analysis employing 1:1:1 propensity score matching (PSM)–based samples. Common-referent matching was performed to create sets of patients from each of the three treatment groups using P-CAB users as the reference group. Propensity scores were estimated using a logistic regression model based on the use of acid-suppressive drugs, including age, sex, hypertension, diabetes, heart failure, prior myocardial infarction, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, cancer, functional dyspepsia, recent UGI bleeding, index PCI indication, DAPT during PCI admission, statin, NSAIDs, steroids, and H2 blockers/other agents. A nearest-neighbor-matching algorithm was employed using a caliper width of 0.1 times the standard deviation of the logit-transformed propensity scores. Covariate balance was evaluated by calculating standardized mean differences, with a standardized mean difference < 0.1 considered as adequate balance. Following PSM, stratified Cox regression analyses were performed to evaluate the association between acid-suppressive drug use and outcomes. Additionally, we investigated the differential risks of outcomes between PPI users and P-CAB users. Statistical analyses were performed using SAS (Version 9.4.2, SAS Institute) and R (Version 3.5.1, R Foundation for Statistical Computing). Statistical significance was set at $p < 0.05$.

3 | Results

3.1 | Study Population and Baseline Characteristics

Between January 2019 and January 2023, 259 085 patients who underwent PCI using a DES were identified, of whom 230 194 were treated with DAPT (Figure 1). Among them, 5112 patients with prior PCI, 477 patients with prior coronary artery bypass graft surgery, 10 468 patients treated with concomitant anticoagulants, 1542 patients admitted for ≥ 30 days after the index PCI, 931 patients followed up for < 30 days, and 1217 patients who were prescribed both PPIs and P-CABs were excluded. After applying the exclusion criteria, 210 447 patients were finally included (mean age ± standard deviation, 65.5 ± 11.4 years; 157 198 [74.7%] males). Of these, 9633 (4.6%) and 100 046 (47.5%) were treated with P-CABs and PPIs, respectively (Table 1).

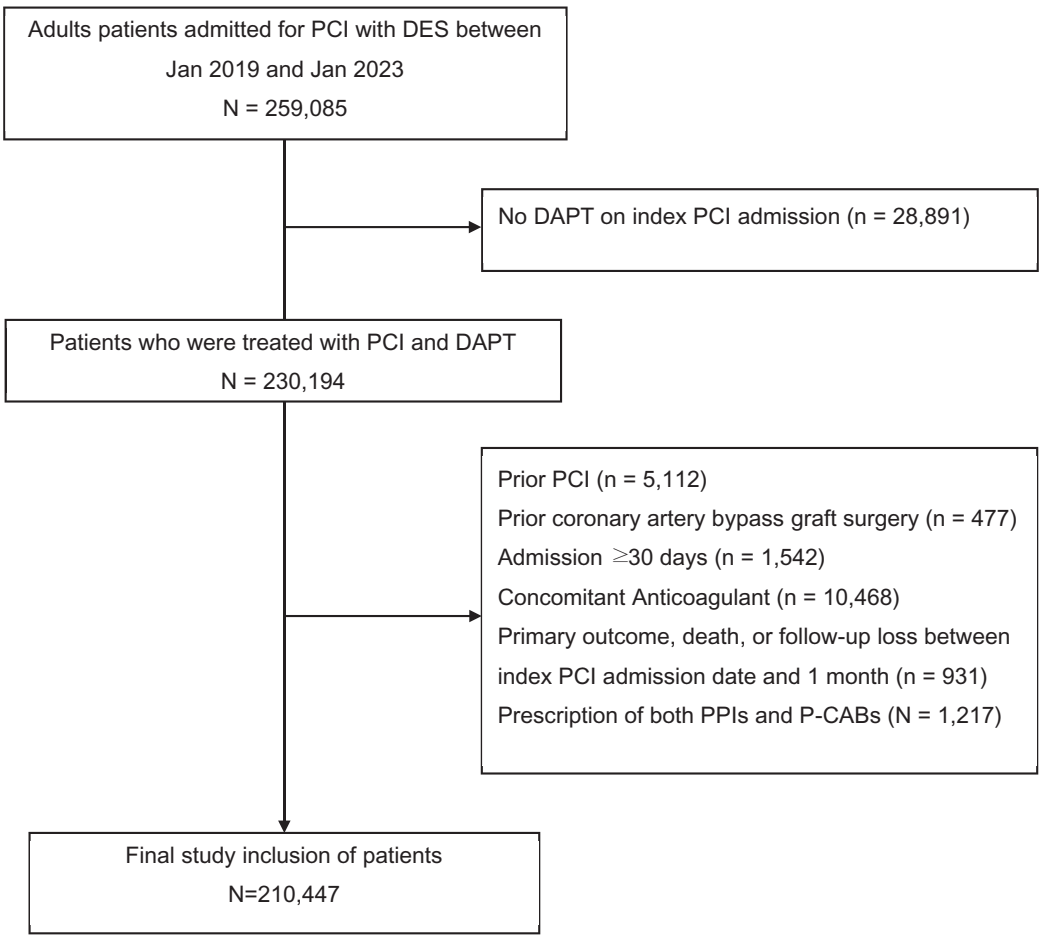

FIGURE 1 | Flow diagram of patient inclusion. DAPT, dual antiplatelet therapy; HIRA, Health Insurance Review and Assessment Service; MI, myocardial infarction; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

TABLE 1 | Baseline characteristics of patients according to acid-suppressive drugs before and after propensity score matching.

	Before PSM				After PSM			
	None ($n=100\,768$)	PPI ($n=100\,046$)	P-CAB ($n=9633$)	SMD	None ($n=9632$)	PPI ($n=9632$)	P-CAB ($n=9632$)	SMD*
Sex, male	77 482 (76.9)	72 615 (72.6)	7101 (73.7)	0.097	7164 (74.4)	7107 (73.8)	7101 (73.7)	0.015
Age, years	64.9 ± 11.2	66.0 ± 11.5	65.7 ± 11.4	0.093	65.5 ± 11.3	65.8 ± 11.3	65.7 ± 11.4	0.021
Comorbidities								
Hypertension	87 387 (86.7)	86 247 (86.2)	8295 (86.1)	0.018	8252 (85.7)	8299 (86.2)	8294 (86.1)	0.014
Diabetes mellitus	39 016 (38.7)	38 008 (38.0)	3677 (38.2)	0.015	3739 (38.8)	3621 (37.6)	3676 (38.2)	0.025
Heart failure	40 130 (39.8)	45 883 (45.9)	4241 (44.0)	0.121	4225 (43.7)	4231 (43.9)	4240 (44.0)	0.003
Prior MI	10 348 (10.3)	9724 (9.7)	837 (8.7)	0.056	802 (8.3)	785 (8.1)	837 (8.7)	0.019
CKD	10 666 (10.6)	11 361 (11.4)	1062 (11.0)	0.024	1050 (10.9)	1057 (11.0)	1062 (11.0)	0.004
COPD	10 304 (10.2)	12 830 (12.8)	1314 (13.6)	0.099	1262 (13.1)	1342 (13.9)	1314 (13.6)	0.024
Liver disease	3585 (3.6)	3963 (4.0)	425 (4.4)	0.042	424 (4.4)	408 (4.2)	425 (4.4)	0.009
Cancer	5549 (5.5)	5586 (5.6)	603 (6.3)	0.031	627 (6.5)	603 (6.3)	603 (6.3)	0.010
Functional dyspepsia	4208 (4.2)	4960 (5.0)	570 (5.9)	0.074	570 (5.9)	522 (5.4)	569 (5.9)	0.022
Recent UGI bleeding	1693 (1.7)	2116 (2.1)	159 (1.6)	0.036	165 (1.7)	162 (1.7)	159 (1.6)	0.005
Index PCI indication				0.195				0.005
Acute MI	69 747 (69.2)	59 671 (59.6)	6158 (63.9)		6135 (63.7)	6158 (63.9)	6158 (63.9)	
Others	31 021 (30.8)	40 375 (40.4)	3475 (36.1)		3497 (36.3)	3474 (36.1)	3474 (36.1)	
DAPT during PCI admission				0.144				0.002
ASA + classic P2Y12i	77 600 (77.0)	71 863 (71.8)	6784 (70.4)		6776 (70.4)	6774 (70.0)	6784 (70.4)	
ASA + potent P2Y12i	23 168 (23.0)	28 183 (28.2)	2849 (29.6)		2856 (29.6)	2858 (30.0)	2848 (29.6)	
Concomitant medications								
Statin	97 577 (96.8)	96 999 (97.0)	9416 (97.7)	0.062	9427 (97.9)	9416 (97.8)	94 156 (97.7)	0.008
NSAIDs	3573 (3.5)	6737 (6.7)	492 (5.1)	0.127	446 (4.6)	500 (5.2)	491 (5.1)	0.025
Steroids	1231 (1.2)	2059 (2.1)	158 (1.6)	0.059	157 (1.6)	166 (1.7)	158 (1.6)	0.007
H2 blockers/other agents	19 483 (19.3)	10 893 (10.9)	1005 (10.4)	0.291	972 (10.1)	1047 (10.9)	1005 (10.4)	0.025

Note: Data are presented as numbers (%) or means ± standard deviations.

Abbreviations: ASA, aspirin; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; P-CAB, potassium-competitive acid blocker; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PSM, propensity score matching; P2Y12i, P2Y12 inhibitor; SMD, standardized mean difference; UGI, upper gastrointestinal.

*All absolute standardized mean difference values were less than 0.1 in the propensity score–matched cohort.

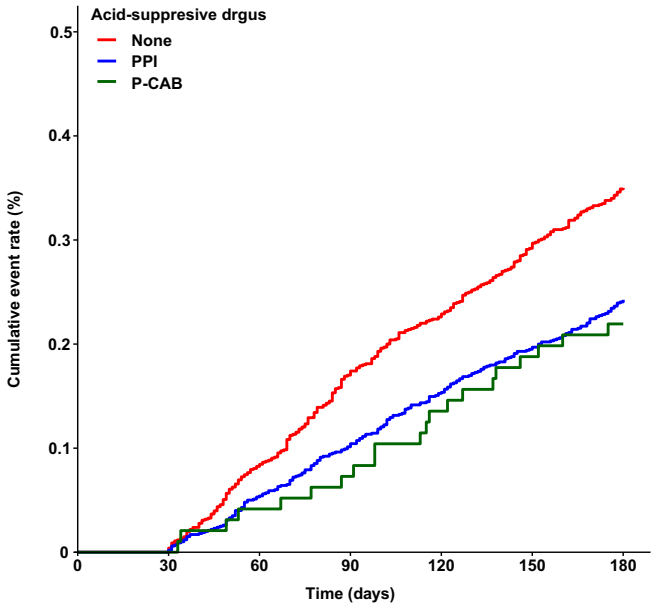

FIGURE 2 | Cumulative incidence of primary outcome, UGI bleeding. P-CABs and PPIs reduced the risk of UGI bleeding after PCI with DAPT for over a 6-month period (log-rank test, $p < 0.001$). UGI, upper gastrointestinal; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; DAPT, dual antiplatelet therapy.

3.2 | Primary and Secondary Outcomes

During the 6-month follow-up period after PCI, 613 (0.3%) patients were positive for the primary outcome, UGI bleeding. The cumulative incidence curve showed that patients treated with PPIs or P-CABs had a decreased risk of UGI bleeding compared to those without the medications ($p < 0.001$, Figure 2). Regarding secondary outcomes, there were 428 (0.2%) patients with severe UGI bleeding, 1064 (0.5%) with all types of GI bleeding, 1759 (0.8%) with myocardial infarction, and 2181 (1.0%) with all-cause mortality within 6 months of PCI.

In the multivariable Cox regression analysis, P-CAB use was associated with a 41% reduced risk of UGI bleeding (aHR, 0.59; 95% CI, 0.38–0.92; $p = 0.019$ (Table 2)) compared with patients not receiving P-CAB or PPI. PPI users had a 35% reduced risk of UGI bleeding (aHR, 0.65; 95% CI, 0.55–0.77; $p < 0.001$ (Table 2)). There was no significant difference in the risk of UGI bleeding between the P-CAB and PPI groups (Table S3, $p > 0.05$). The risk factors associated with the primary outcome included advanced age, male sex, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, cancer, recent UGI bleeding, potent P2Y12 inhibitor as DAPT during PCI admission, and the nonuse of statin (Table S2). Additionally, we did not find a significant difference between the P-CAB agents in reducing the risk of UGI bleeding ($p > 0.05$, Table S4).

TABLE 2 | Effect of acid-suppressive drugs on bleeding efficacy outcomes.

	Primary outcome			Secondary outcomes					
	UGI bleeding			Severe UGI bleeding			All GI bleeding		
	Event/ total	HR (95% CI)	*p*	Event/ total	HR (95% CI)	*p*	Event/ total	HR (95% CI)	*p*
Before PSM[a]									
No	351/100 787	Reference		261/100 787	Reference		535/100 787	Reference	
PPI	241/100 027	0.65 [0.55–0.77]	< 0.001	155/100 027	0.55 [0.45–0.67]	< 0.001	490/100 027	0.87 [0.77–0.99]	0.028
P-CAB	21/9633	0.59 [0.38–0.92]	0.019	12/9633	0.44 [0.25–0.79]	0.006	39/9633	0.73 [0.52–1.01]	0.055
After PSM[b]									
No	48/9632	Reference		39/9632	Reference		72/9632	Reference	
PPI	18/9632	0.37 [0.22–0.64]	< 0.001	13/9632	0.33 [0.18–0.62]	< 0.001	41/9632	0.56 [0.38–0.83]	0.003
P-CAB	21/9632	0.44 [0.26–0.73]	0.002	12/9632	0.31 [0.16–0.59]	< 0.001	39/9632	0.53 [0.36–0.79]	0.002

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; GI, gastrointestinal; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; P-CAB, potassium-competitive acid blocker; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PSM, propensity score matching; UGI, upper GI.
[a]Data were obtained using a multivariate Cox proportional hazards regression model for outcome development. Adjustments were made for age, sex, hypertension, diabetes mellitus, heart failure, prior myocardial infarction, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, cancer, functional dyspepsia, recent UGI bleeding, index PCI indication, DAPT during PCI admission, statin, NSAIDs, steroids, and H2 blockers/other agents.
[b]A 1:1:1 PSM was performed, and stratified Cox regression analysis was performed in the matched cohort.

Considering the secondary efficacy outcomes, the use of P-CABs was associated with a decreased risk of severe UGI bleeding (aHR, 0.44; 95% CI, 0.25–0.79; $p = 0.006$) and demonstrated a tendency of association with all types of GI bleeding (aHR, 0.73; 95% CI, 0.52–1.01; $p = 0.055$ (Table 2)). PPIs showed similar results (Table 2). Regarding the secondary safety outcomes, neither P-CAB use nor PPI use was associated with the risk of myocardial infarction or all-cause death (all $p > 0.05$, Table 3). When we compared the safety outcomes between P-CAB group and PPI group, there was no significant difference between the two groups (Table S5, all $p > 0.05$).

3.3 | Sensitivity Analysis Using PSM

After 1:1:1 PSM, 28896 patients (9632 patients in each matched group) were included in the analysis (Table 1). The matched cohorts were well balanced in terms of the absolute standardized mean difference < 0.1 (Table 1). A stratified Cox proportional hazard regression analysis with the matched cohorts showed that P-CAB use was consistently associated with a decreased risk of UGI bleeding (HR, 0.44; 95% CI, 0.26–0.73; $p = 0.002$). PPI use was also associated with a decreased risk of UGI bleeding (HR, 0.37; 95% CI, 0.22–0.64; $p < 0.001$). In the secondary efficacy outcome analyses of the matched cohorts, P-CAB and PPI use is associated with a decreased risk of severe UGI bleeding and all types of GI bleeding (all $p < 0.05$, Table 2). Regarding the secondary safety outcomes in the matched cohorts, neither P-CAB nor PPIs were associated with an increased risk of all-cause death (all $p > 0.05$, Table 2). PPI use was associated with an increased risk of myocardial infarction (HR 1.46; 95% CI, 1.05–2.02; $p = 0.025$ (Table 3)).

We also conducted an analysis with 1:1 PSM cohorts of P-CAB users ($n = 9632$) and PPI users ($n = 9632$). No significant difference was observed in the efficacy and safety outcomes between the two groups (Tables S3 and S5, all $p > 0.05$).

4 | Discussion

Using a nationwide claims database in Korea, we investigated the relationship between the use of P-CABs and the risk of UGI bleeding in patients undergoing PCI who were treated with DAPT. P-CAB use showed a significant reduction in the risk of UGI bleeding in patients undergoing PCI on DAPT, comparable to traditional medication, PPIs. These findings indicate that P-CABs may be a reasonable alternative to PPIs for preventing UGI bleeding, a potentially fatal complication in patients undergoing PCI with DAPT.

In patients with coronary artery disease who are at an increased risk of UGI bleeding when DAPT is required, PPIs were recommended to protect against UGI bleeding [6–9]. However, many epidemiological reports suggested potential adverse effects associated with long-term PPI use, including reduced efficacy of DAPT (particularly with clopidogrel) and heightened risks of kidney disease, bone fractures, infections, cardiovascular events, dementia, and cancer [12]. The concerns regarding PPI use, mainly reported from retrospective observational studies, are likely due to residual confounding factors related to conditions treated with PPIs, rather than a true causal relationship [28–30]. The expert review by American Gastroenterology Association recommended against using PPI-associated adverse events as an independent indication for PPI withdrawal but still recommend the regular review of the need for PPIs and deprescribing of PPIs in patients without a definite indication, considering the theoretical risks [31]. Controversy still exists regarding the potential risks of PPIs, leading to underprescription in clinical practice even in high-risk patients on DAPT, with 50%–75% of them not being treated with PPIs [13–15]. In fact, in our study, PPI use was associated with an increased risk of myocardial infarction in PSM model; however, this association was not observed in multivariate Cox regression model before PSM. Furthermore, PPIs have several theoretical limitations despite

TABLE 3 | Effect of acid-suppressive drugs on safety outcomes.

	Myocardial infarction			All-cause death		
	Event/total	HR (95% CI)	*p*	Event/total	HR (95% CI)	*p*
Before PSM[a]						
No	738/100787	Reference		921/100787	Reference	
PPI	939/100027	1.08 [0.98–1.19]	0.113	1154/100027	1.07 [0.98–1.17]	0.126
P-CAB	82/9633	1.05 [0.84–1.33]	0.648	106/9633	1.04 [0.85–1.27]	0.720
After PSM[b]						
No	61/9632	Reference		100/9632	Reference	
PPI	87/9632	1.46 [1.05–2.02]	0.025	117/9632	1.19 [0.91–1.55]	0.208
P-CAB	82/9632	1.34 [0.97–1.87]	0.080	106/9632	1.06 [0.81–1.39]	0.676

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; GI, gastrointestinal; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; P-CAB, potassium-competitive acid blocker; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PSM, propensity score matching; UGI, upper GI.
[a]Data were obtained using a multivariate Cox proportional hazards regression model for outcome development. Adjustments were made for age, sex, hypertension, diabetes mellitus, heart failure, prior myocardial infarction, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, cancer, functional dyspepsia, recent UGI bleeding, index PCI indication, DAPT during PCI admission, statin, NSAIDs, steroids, and H2 blockers/other agents.
[b]A 1:1:1 PSM was performed, and stratified Cox regression analysis was performed in the matched cohort.

their widespread use, including slow onset of action, incomplete acid suppression leading to night-time acid breakthrough, instability in acidic conditions requiring premeal administration, and efficacy influenced by cytochrome P450 CYP2C19 genetic polymorphisms [12]. These limitations result in unmet needs during UGI disease treatment, including the prevention of UGI bleeding in patients on DAPT.

P-CABs are a novel class of acid-suppressive drugs with several advantages over PPIs. P-CABs inhibit H+/K+ ATPase in a reversible and K+-competitive manner, resulting in near complete suppression of gastric acid production [17–20]. P-CABs exhibit a rapid onset of action, acid stability, and prolonged inhibition of gastric acid secretion, providing a more potent and sustained acid-suppressive effect compared with that of PPIs [17–20]. Indeed, P-CABs achieved longer periods with intragastric pH > 4 and the higher healing rates of erosive esophagitis after 4 and 8 weeks, compared to PPIs [32]. Based on these pharmacologic advantages, P-CABs have demonstrated excellent clinical efficacy as an alternative to PPIs for various UGI diseases [19,20], including gastroesophageal reflux disease [21,22], gastric ulcer [23], and in combination therapy for *Helicobacter pylori* (*H. pylori*) eradication [19, 24]. The development of prototype P-CABs, such as SCH28080, YH4808, and AZD0865, was discontinued due to hepatotoxicity; however, recent P-CABs are free from these issues [33]. Although further studies with longer follow-up periods are still needed, available P-CABs have not shown long-term adverse effects thus far. P-CABs were well tolerated for longer than 1 year, with a safety profile comparable with that of PPIs and without significant safety concerns when used to prevent ulcer recurrence during long-term NSAID therapy [25]. Our study also demonstrated that P-CAB use was not associated with an increased risk of myocardial infarction or all-cause death. Owing to their merits and tolerability, P-CABs are increasingly used to treat various UGI diseases. Currently, vonoprazan (Takeda Pharma, Tokyo, Japan, 2015), a type of P-CAB, has been approved in Japan for treating various conditions, including gastric and duodenal ulcers, reflux esophagitis, and *H. pylori* infections [34]. Recent Korean guidelines for gastroesophageal reflux disease recommend both P-CABs and PPIs as first-line treatments, highlighting the potential of P-CABs to address the limitations of current PPI therapy [35].

Compared with PPIs, P-CABs have shown potential efficacy in preventing UGI bleeding. In a previous Phase 3 randomized trial comparing vonoprazan and lansoprazole during the 24-week treatment period, vonoprazan was as effective as lansoprazole in preventing aspirin-associated peptic ulcer recurrence, and the proportion of patients with UGI bleeding was significantly higher in the lansoprazole group (2.9%) than in the vonoprazan group (0%) [26]. A previous Japanese healthcare claim database–based study revealed that in patients with coronary artery disease receiving multiple antithrombotics including antiplatelets and anticoagulants, vonoprazan was not inferior to PPIs in preventing UGI bleeding [36]. Our study provided evidence that P-CABs were comparable to PPIs in preventing UGI bleeding in patients with PCI on DAPT. These results were consistent with those of the propensity score–based sensitivity analysis, which was conducted to reduce the potential bias from confounding factors. P-CABs were also effective in preventing severe UGI bleeding requiring red blood cell transfusion, which may have increased the clinical relevance of our study. An ongoing randomized double-blind Phase 4 trial, the Potassium-Competitive Acid Blocker Versus pROton-Pump Inhibitor for GastroproTECTion Strategies in Patients at High Gastrointestinal Bleeding Risk Receiving Antithrombotic Therapy (PROTECT-HBR, NCT04416581), is focused on comparing P-CAB (tegoprazan 50 mg) and PPI (rabeprazole 20 mg). This study will provide high-quality evidence and reveal the potential role of P-CABs against UGI bleeding in high-risk patient groups.

This study had several limitations. First, as outcomes were assessed 30 days after PCI, early outcomes were not considered. Second, certain risk factors for GI bleeding, such as *H. pylori* infection, a history of gastroesophageal reflux disease, and chronic alcohol use, were not available in the health claims database and were not included in the current study, limiting our ability to fully identify high-risk patients. Third, vonoprazan, a commercially available P-CAB in Japan and the United States, is not approved in Korea and was not included in this analysis. Fourth, due to the use of a claims database, medication compliance could not be evaluated. Finally, considering the retrospective design of the study, confirmation is needed based on prospective randomized trials. Despite these limitations, this study had several strengths. First, we included a substantial number of patients who underwent PCI with DAPT, using a nationwide health claims database. Second, we attempted to minimize the risk of selection bias by using a national-scale database and propensity score–based sensitivity analysis.

5 | Conclusions

The finding of this cohort study suggests that among Korean patients undergoing PCI on DAPT, P-CAB use was associated with a decreased 6-month risk of UGI bleeding comparable to PPI use, without an increased risk of myocardial infarction or all-cause death. Therefore, P-CABs may be a potential alternative for protecting against UGI bleeding in patients treated with DAPT.

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Disclosure

The funders had no role in the study design, data collection, analysis, interpretation of the results, or manuscript preparation.

Ethics Statement

This study was approved by the Institutional Review Board of Yongin Severance Hospital, Yonsei University Health System (No. 9-2024-0002).

Consent

The requirement for informed consent was waived due to the retrospective nature of the study, which was based on an anonymous health insurance claims database.

Conflicts of Interest

M.B. received a research grant from Daewoong and HK inno.N Pharmaceuticals. J.Y. received a research grant from the Chong Kun Dang Pharmaceutical. J.K. received research grants from Chong Kun Dang and Myung in Pharmaceutical. J.J. declares no conflicts of interest.

Data Availability Statement

Researchers can access the HIRA database by submitting requests to the Korean Health Insurance Review and Health Big Data Hub (https://opendata.hira.or.kr).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.