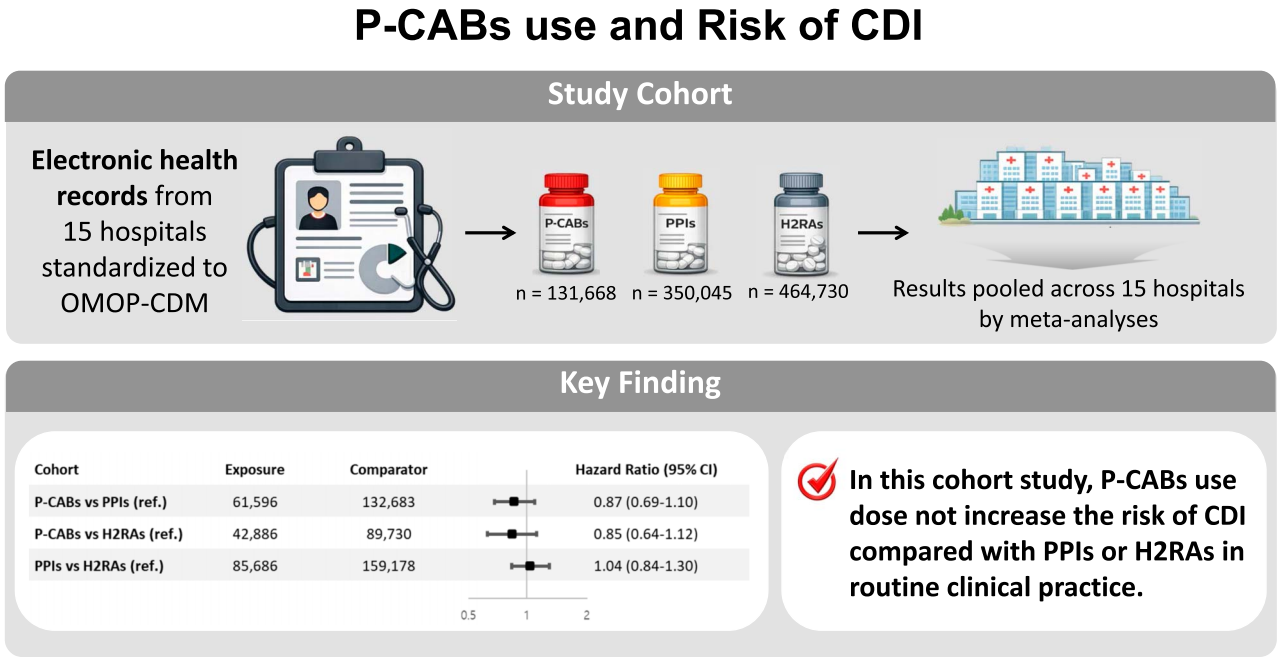
Comparative Safety of Potassium-Competitive Acid Blockers on the Risk of *Clostridioides difficile* Infection: A Multicenter Cohort Study

Gyeongmin Lim, BS[1,*], Ju-Young Shin, PhD[1,2,3,*], Da Eun Hyeon, BS[4], Jie-Hyun Kim, PhD[5], Yuna Kim, PhD[5], Hyun-Soo Kim, PhD[6], Woo Hyeon Yoo, BS[1], Byeong Jun Song, PhD[7], Chang Won Jeong, PhD[8], Hang A. Park, PhD[9], Jae Myung Cha, PhD[10], Ji Hyun Kim, PhD[11], Jongtak Jung, PhD[12], Kyoung Min Moon, PhD[13], Sang Youl Rhee, PhD[14,15], Seung-Jin Kwag, PhD[16], Shi Nae Yu, PhD[17], Soyoung Lee, BS[18], Sunghee Park, PhD[19], Rae Woong Park, PhD[3,20] and Ju Hwan Kim, PhD[1,2]



Gyeongmin Lim et al. *Am J Gastroenterol.* 2026. doi: 10.14309/ajg.0000000000004011

[1]Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon, Republic of Korea; [2]School of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea; [3]Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Seoul, South Korea; [4]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, Republic of Korea; [5]Department of Internal Medicine, Division of Gastroenterology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [6]Division of Gastroenterology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [7]Department of Internal Medicine, Myongji Hospital, Goyang, Republic of Korea; [8]Smart Business Team in Information Management Office, Wonkwang University Hospital, Iksan, Republic of Korea; [9]Department of Emergency Medicine, Hallym University Dongtan Sacred Heart Hospital, Hwaseong-si, Republic of Korea; [10]Department of Gastroenterology, Kyung Hee University Hospital at Gang Dong, Kyung Hee University, School of Medicine, Gangdong-gu, Republic of Korea; [11]Department of Internal Medicine, Kangwon National University College of Medicine, Chuncheon, Republic of Korea; [12]Division of Infectious Diseases, Department of Internal Medicine, Soonchunhyang, University Seoul Hospital, Seoul, Republic of Korea; [13]Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea; [14]Department of Endocrinology and Metabolism, Kyung Hee University College of Medicine, Seoul, Republic of Korea; [15]Center for Digital Health, Kyung Hee University, Seoul, Republic of Korea; [16]Department of Surgery, Gyeongsang National University College of Medicine and Gyeongsang National University Hospital, Jinju-si, Republic of Korea; [17]Division of Infectious Diseases, Department of Internal Medicine, Soonchunhyang University Hospital Cheonan, Soonchunhyang University College of Medicine, Cheonan, Republic of Korea; [18]Ewha Medical Data Organization, Ewha Womans University Medical Center, Seoul, Republic of Korea; [19]Division of Infectious Diseases, Department of Internal Medicine, Soonchunhyang University of Bucheon Hospital, Bucheon, Republic of Korea; [20]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Republic of Korea.
Correspondence: Rae Woong Park, PhD. E-mail: veritas@ajou.ac.kr. Ju Hwan Kim, PharmD, PhD. E-mail: jukim928@skku.edu.
*Gyeongmin Lim and Ju-Young Shin contributed equally to this work.
Received November 11, 2025; accepted March 18, 2026; published online March 31, 2026

COLON

INTRODUCTION: **Proton pump inhibitors (PPIs) have been associated with an increased risk of *Clostridioides difficile* infection (CDI) in previous observational studies. However, real-world evidence on the CDI risk of potassium-competitive acid blockers (P-CABs), a newer class of acid suppressive agents, remains limited.**

METHODS: **We conducted a retrospective cohort study using electronic health record data from 15 hospitals standardized to the Observational Medical Outcomes Partnership Common Data Model and integrated through Federated E-Health Big Data for Evidence Renovation Network. Patients newly prescribed P-CABs, proton pump inhibitors (PPIs), or histamine 2 receptor antagonists (H2RAs) were included and the primary outcome was the occurrence of CDI. After 1:4 propensity score matching, pairwise comparisons were conducted using Cox proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were then pooled across databases by meta-analysis.**

RESULTS: **In the 1:4 matched cohorts, we identified 61,596 P-CAB users (mean follow-up, 72.6 ± 29.9 days) and 132,683 PPI users (74.9 ± 28.6 days), 42,794 P-CAB users (69.5 ± 32.4 days) and 89,415 H2RA users (69.9 ± 33.1 days), and 85,686 PPI users (71.1 ± 31.2 days) and 159,178 H2RA users (68.0 ± 33.8 days) across the 3 pairwise comparisons. The pooled HRs were 0.87 (95% CI, 0.69–1.10) for P-CABs vs PPIs, 0.85 (0.64–1.12) for P-CABs vs H2RAs, and 1.13 (0.98–1.29) for PPIs vs H2RAs. Results were generally consistent across subgroup and sensitivity analyses.**

DISCUSSION: **In this cohort study, P-CAB use was not associated with a higher risk of CDI compared with PPIs or H2RAs.**

KEYWORDS: P-CAB; PPI; H2RA; CDI; multicenter study

ABBREVIATIONS: CDM, common data model; CDI, *Clostridioides difficile* infection; EMR, electronic medical record; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; OMOP, observational medical outcomes partnership; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; PS, propensity score; PSM, propensity score matching; SMD, standardized mean difference

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D919

Am J Gastroenterol 2026;00:1–9. https://doi.org/10.14309/ajg.0000000000004011

INTRODUCTION

Clostridioides difficile infection (CDI) is a major healthcare-associated infection, leading to serious complications such as pseudomembranous colitis, sepsis, and death (1). The global incidence of CDI has increased in recent decades, attributable to factors such as widespread antibiotic utilization, an aging demographic, and extended hospital stays (2–5). Among various risk factors, acid-suppressive drugs, particularly the use of proton pump inhibitors (PPIs), has been suggested as a potential contributor to increased susceptibility to CDI (6,7).

PPIs, widely used as acid-suppressive drugs, inhibit the gastric H^+/K^+-ATPase enzyme, resulting in profound acid suppression (8). Although generally well tolerated, several observational studies have associated PPIs use with an increased risk of CDI, potentially because of elevated gastric pH reducing the stomach's barrier against ingested pathogens and altering gut microbiota composition (7,9,10). Potassium-competitive acid blockers (P-CABs) represent a newer class of acid-suppressive drugs. Unlike PPIs, P-CABs exert their effect by reversible, K^+-competitive inhibition of the H^+/K^+-ATPase enzyme, offering a more rapid and sustained suppression of gastric acid secretion (11). In addition, P-CABs can be administered regardless of meal timing and are not influenced by cytochrome P450 2C19 metabolic pathways, providing more predictable pharmacokinetics across patients (12,13). Building on these benefits, several P-CAB agents have been developed and introduced into clinical practice, leading to the replacement of PPIs in acid-related disorders such as gastroesophageal reflux disease, nonerosive reflux disease, and peptic ulcer (14). However, given their pharmacological similarities to PPIs, concerns have arisen regarding a potential association between P-CABs use and an increased risk of CDI, with some observational studies reporting elevated CDI risk with vonoprazan (15,16).

Since the development of vonoprazan in Japan in 2015, 4 P-CABs— fexuprazan, keverprazan, tegoprazan, vonoprazan and zastaprazan—have been introduced into clinical practice, with their use primarily concentrated in Japan and South Korea (14,17). In 2023, vonoprazan became the first P-CABs to be approved by the US Food and Drug Administration, signaling a potential shift toward global adoption of P-CABs as alternatives to PPIs for the management of acid-related disorders (18). Despite the extensive body of evidence regarding the safety concerns of PPIs, real-world data-based evaluations of the safety profile of P-CABs remain limited. Given the availability of multiple P-CABs, including those developed in South Korea—tegoprazan, fexuprazan, and zastaprazan—in addition to vonoprazan, it provides an optimal environment for conducting comprehensive real-world data (RWD)-based safety assessments of P-CABs. Accordingly, we conducted a nationwide study using electronic health records (EMRs) from South Korean general hospitals,

standardized to the observational medical outcomes partnership (OMOP) common data model (CDM), to evaluate the risk of CDI associated with P-CABs use.

METHODS

Study design and data source

We conducted a multicenter, retrospective cohort study using EMR data from 15 secondary or tertiary hospitals in South Korea. The data were standardized to the OMOP CDM version 5.3 and integrated for analysis through the Federated E-Health Big Data for Evidence Renovation Network (FeederNet) platform (19–21). Each hospital's EMR, comprising deidentified patient-level data, was mapped to standardized vocabularies following the observational health data sciences and informatics protocols (22). A detailed list of participating institutions is provided in Supplementary Table 1 (see Supplementary Digital Content, http://links.lww.com/AJG/D919). Ethical approval for this study was obtained from the Institutional Review Board of Ajou University. The requirement for informed consent was waived because the study used anonymized administrative data. In all other participating institutions, Institutional Review Board review was exempted, and their respective boards likewise confirmed that informed consent was not required. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE, https://www.equator-network.org/reporting-guidelines/strobe/) reporting guideline.

Study population

This study included individuals aged 18 years or older who were newly initiated on acid-suppressive drugs, specifically P-CABs, PPIs, or histamine 2 receptor antagonists (H2RAs) between 2019 and 2024. A new-user design was adopted to minimize bias from previous exposure, where patients were required to have no prescription records for any P-CABs, PPIs, or H2RAs in the 180 days before the index date. The index date was defined as the date of the first prescription for any class of the acid suppressive drugs. Follow-up began on the index date and continued for 90 days. To ensure sufficient baseline data for assessing previous medical history and confirming new-user status, patients were required to have at least 180 days of continuous medical records before the index date. Patients were excluded if they had received a prescription for oral vancomycin, had a positive stool test for *C. difficile* toxin A or had a recorded diagnosis of CDI within 90 days before the index date. These criteria aimed to minimize confounding by previous CDI occurrence (see Supplementary Figure 1, Supplementary Digital Content, http://links.lww.com/AJG/D919).

Exposure and outcome

The exposure of interest was the initiation of acid suppressive drugs, categorized into 3 groups: P-CABs (tegoprazan, fexuprazan), PPIs (omeprazole, esomeprazole, lansoprazole, ilaprazole, dexlansoprazole, pantoprazole, rabeprazole), and H2RAs (cimetidine, famotidine, lafutidine, nizatidine, ranitidine, roxatidine). The listed agents represent all acid suppressive drugs within each class that were authorized in South Korea during the study period. The primary outcome of this study was the occurrence of CDI within 90 days after the initiation of acid-suppressive drugs. CDI was identified using a composite definition, in alignment with previous observational studies and clinical practice guidelines. Specifically, CDI was defined as the presence of at least 1 of the following criteria during the 90-day period, which was chosen to capture acute-onset CDI events occurring shortly after initiation of acid-suppressive therapy: (i) a prescription for oral vancomycin, (ii) a diagnostic code indicating CDI (systematized nomenclature of medicine—clinical terms: 186431008, KCD-7: A04.7), or (iii) a positive result from a *C. difficile* toxin A test. Secondary outcomes included healthcare facility-onset CDI (HO-CDI) and community-onset CDI (CO-CDI). HO-CDI was defined as CDI diagnosed on or after hospital day 4 (>72 hours after admission). CO-CDI was defined as CDI diagnosed in individuals without a history of hospitalization within the preceding 4 weeks and diagnosed either in outpatient settings or within the first 3 days (<72 hours) of hospitalization (23). In routine practice, CDI is frequently diagnosed through a combination of clinical judgment, laboratory testing, and treatment decision (24,25). Oral vancomycin is rarely prescribed for indications other than CDI, and thus its use was considered a highly specific marker of CDI events (26). In addition, CDI treatment is common and may precede confirmatory toxin testing, potentially resulting in false-results because of early antibiotic initiation (27). Given these considerations, a broad, composite case definition was adopted to ensure comprehensive capture of clinically relevant CDI events.

Statistical analysis

Baseline characteristics of the study population, including demographics (age, sex), Charlson Comorbidity Index and previous use of high-risk antibiotics for CDI and systemic corticosteroids, were summarized using descriptive statistics (28) (see Supplementary Table 2, Supplementary Digital Content, http://links.lww.com/AJG/D919). Potential confounding was addressed using a large-scale propensity score (PS) model, constructed by logistic regression incorporating a comprehensive set of covariates, including age, sex, Charlson Comorbidity Index, and previous medication use and conditions identified within 90 days preceding the index date (29). After 1:n propensity score matching with up to 4 matches per exposed individual using a caliper of 0.2, pairwise comparison among the acid suppressive drugs were conducted to estimate the hazard ratio (HR) and 95% confidence interval (CI) of using Cox proportional hazards model. The balance of covariates after matching was assessed using standardized mean differences (SMD), with an SMD less than 0.1 indicating adequate balance. To obtain overall effect estimates across the 15 databases, meta-analyses were performed using a fixed-effect model when $I^2 < 50\%$ and a random-effects model when $I^2 \geq 50\%$. In this study, variables were binary or indices derived from them (e.g., Charlson Comorbidity Index), with missing values interpreted as the absence of the corresponding condition or exposure.

Subgroup analyses were performed according to age (<65 vs ≥65 years), sex, and previous antibiotic use within 30 days before the index date. To evaluate the robustness of the main findings, several sensitivity analyses were conducted. First, an on-treatment analysis was performed, in which patients were censored at treatment discontinuation or switching. Discontinuation was defined as the absence of index prescription for more than 30 days. Switching was defined as a prescription for an alternative acid-suppressive drug class during follow-up. Second, propensity score (PS) stratification was conducted using 5 strata. Third, analyses were repeated by restricting the cohort to individuals with a minimum exposure duration of 7 days and 14 days, respectively. Fourth, an extended follow-up analysis was conducted by lengthening the observation period from 90 days to 180 days. Fifth, we conducted an analysis in a patient-restricted cohort,

including only those with an indication for acid-suppressive drugs identified within 30 days before the index date (see Supplementary Table 2, Supplementary Digital Content, http://links.lww.com/AJG/D919). Finally, comparisons were conducted with individuals who were not exposed to acid-suppressive drugs during the study period. This nonacid-suppressive drug group included individuals without any prescriptions for acid-suppressive drugs during the 180 days before the index date and with no evidence of CDI within 90 days before cohort entry. The index date was defined as the date of the first prescription for any medication other than acid-suppressive drugs.

RESULTS

Baseline characteristics

Among 17 million individuals from 15 institutions, 131,668 P-CABs users, 350,045 PPIs users, and 464,730 H2RAs users were identified. After PS matching, 61,596 P-CABs and 132,683 PPIs users, 42,794 P-CABs and 89,415 H2RAs users, and 85,686 PPIs and 159,178 H2RAs users were included in the respective cohorts (Figure 1). Across all matched cohorts, baseline characteristics were well balanced, with SMDs below 0.1 (Table 1 and Supplementary Table 3 [see Supplementary Digital Content, http://links.lww.com/AJG/D919]).

Risk of CDI: P-CABs vs PPIs

In the pairwise comparison between P-CABs (mean follow-up, 72.6 ± 29.9 days) and PPIs (74.9 ± 28.6 days), 112 (0.18%) and 355 (0.27%) CDI events were identified as the primary outcome, corresponding to pooled HR of 0.87 (95% CI, 0.69–1.10) (Figure 2 and Supplementary Figure 2 [see Supplementary Digital Content, http://links.lww.com/AJG/D919]). For secondary outcomes, the risk of HO-CDI (0.89 [0.64–1.24]) and CO-CDI (1.22 [0.50–2.98]) did not show significant differences between the 2 groups (Figure 2). Results from subgroup analyses were largely consistent except for male patients with P-CABs, which showed a higher point estimate for CDI risk compared with PPIs (1.31 [0.92–1.88]) but did not reach conventional statistical significance. In sensitivity analyses, P-CABs were associated with a lower CDI risk in the as-treated approach (HR 0.59 [0.31–0.91]) and among those with exposure durations >7 days (0.75 [0.57–0.97]) and >14 days (0.73 [0.55–0.97]) (Figure 2).

Risk of CDI: P-CABs vs H2RAs

In the P-CABs (mean follow-up, 69.5 ± 32.4 days) and H2RAs (69.9 ± 33.1 days) groups, the primary outcome occurred in 86 (0.20%) and 225 (0.25%) patients, respectively, resulting in a pooled HR of 0.85 (95% CI, 0.64–1.12) (Figure 3 and Supplementary Figure 2 [see Supplementary Digital Content, http://links.lww.com/AJG/D919]). Regarding secondary outcomes, the HRs were 0.78 (0.52–1.14) for HO-CDI, and 1.89 (0.17–21.30) for CO-CDI (Figure 3). Subgroup analyses did not reveal any major deviations from the overall effect estimate. However, in sensitivity analyses, CDI risk was significantly reduced in P-CAB users in the PS-stratified analysis (HR 0.75 [0.59–0.96]) and among those treated for >7 days (0.65 [0.46–0.93]) (Figure 3).

Risk of CDI: PPIs vs H2RAs

A total of 422 CDI events (0.49%) occurred in the PPIs group (mean follow-up, 71.1 ± 31.2 days) and 600 events (0.38%) in the

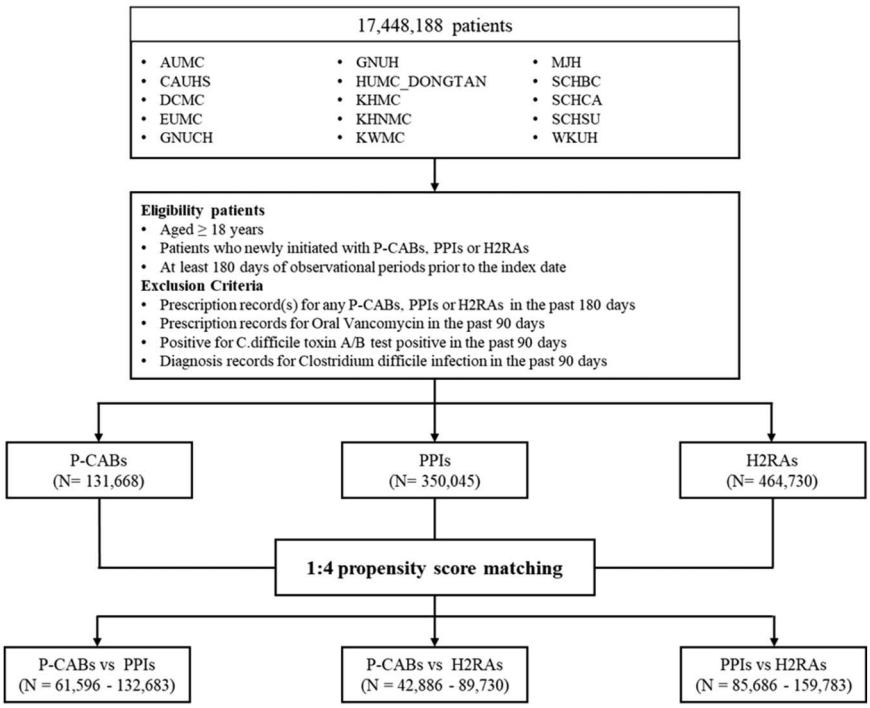


Figure 1. Attrition diagram of study population. AUMC, Ajou University Medical Center; CAUHS, Chung-Ang University Hospital; DCMC, Daegu Catholic University Medical Center; EUMC, Ewha Womans University Medical Center; GNUCH, Gyeongsang National University Changwon Hospital; GNUH, Gyeongsang National University Hospital; H2RA, histamine 2 receptor antagonist; HUMC_DONGTAN, Hallym University Dongtan Sacred heart hospital; KHMC, Kyung Hee University Medical Center; KHNMC, Kyung Hee University Hospital at Gangdong; KWMC, Kangwon National University Hospital; MJH, Myongji Hospital; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitors; SCHBC, Soon Chun Hyang University hospital bucheon; SCHCA, Soon Chun hyang University Hospital Cheonan; SCHSU, Soon Chun Hyang University Hospital Seoul; WKUH, Wonkwang University Hospital.

Table 1. Baseline characteristics of study population after 1:4 propensity score matching

Baseline characteristics	P-CABs vs PPIs			P-CABs vs H2RAs			PPIs vs H2RAs		
	P-CABs	PPIs	aSMD	P-CABs	H2RAs	aSMD	PPIs	H2RAs	aSMD
No. of patients	61,596	132,683		42,794	89,415		85,686	159,178	
Age group, n (%), yr			<0.01			0.02			0.06
18–65	38,489 (62.5)	83,310 (62.8)		27,987 (65.4)	59,217 (66.2)		56,043 (65.4)	108,806 (68.3)	
≥65	23,107 (37.5)	49,373 (37.2)		14,807 (34.6)	30,198 (33.8)		29,643 (34.6)	50,372 (31.7)	
Sex, n (%)			<0.01			0.01			<0.01
Female	32,882 (53.3)	70,865 (53.4)		23,020 (53.8)	48,615 (54.4)		45,764 (53.4)	85,718 (53.8)	
Male	28,774 (46.7)	61,818 (46.6)		19,774 (46.2)	40,800 (45.6)		39,922 (46.6)	73,460 (46.2)	
CCI, mean	1.015	1.031	<0.01	0.898	0.925	0.02	0.802	0.811	0.04
CDI high-risk ABX (%)	8,477 (13.8)	19,412 (14.6)	0.02	7,085 (16.5)	16,643 (18.6)	0.06	25,533 (29.8)	49,001 (30.8)	0.02
Corticosteroid for systemic use (%)	7,853 (13.8)	17,145 (12.9)	0.03	5,912 (13.8)	13,096 (14.6)	0.02	14,554 (17.0)	27,209 (17.1)	<0.01

ABX, antibiotics; aSMD, absolute standardized mean difference; CCI, Charlson Comorbidity Index; CDI, *Clostridioides difficile* infection; H2RAs, histamine 2 receptor antagonists; P-CABs, potassium-competitive acid blockers; PPIs, Proton pump inhibitors; PSM, propensity score matching.

H2RAs group (68.0 ± 33.8 days), yielding a pooled HR of 1.04 (95% CI, 0.84–1.30) for the primary outcome (Figure 4 and Supplementary Figure 2 [see Supplementary Digital Content, http://links.lww.com/AJG/D919]). In secondary outcome analyses, the risk of HO-CDI was increased in the PPI group compared with H2RAs (HR 1.20 [95% CI, 1.00–1.43]), whereas no significant difference was observed for CO-CDI (1.16 [0.76–1.77]) (Figure 4). Subgroup analyses revealed significantly increased risks among male patients (1.24 [1.01–1.52]) and those exposed to high-risk antibiotics (1.24 [1.05–1.47]). Sensitivity analyses also demonstrated increased CDI risk, particularly in the 180-day follow-up cohort (1.19 [1.05–1.36]) and among patients with longer exposure durations, including those treated for ≥7 days (1.22 [1.03–1.45]) and ≥14 days (1.29 [1.06–1.57]) (Figure 4).

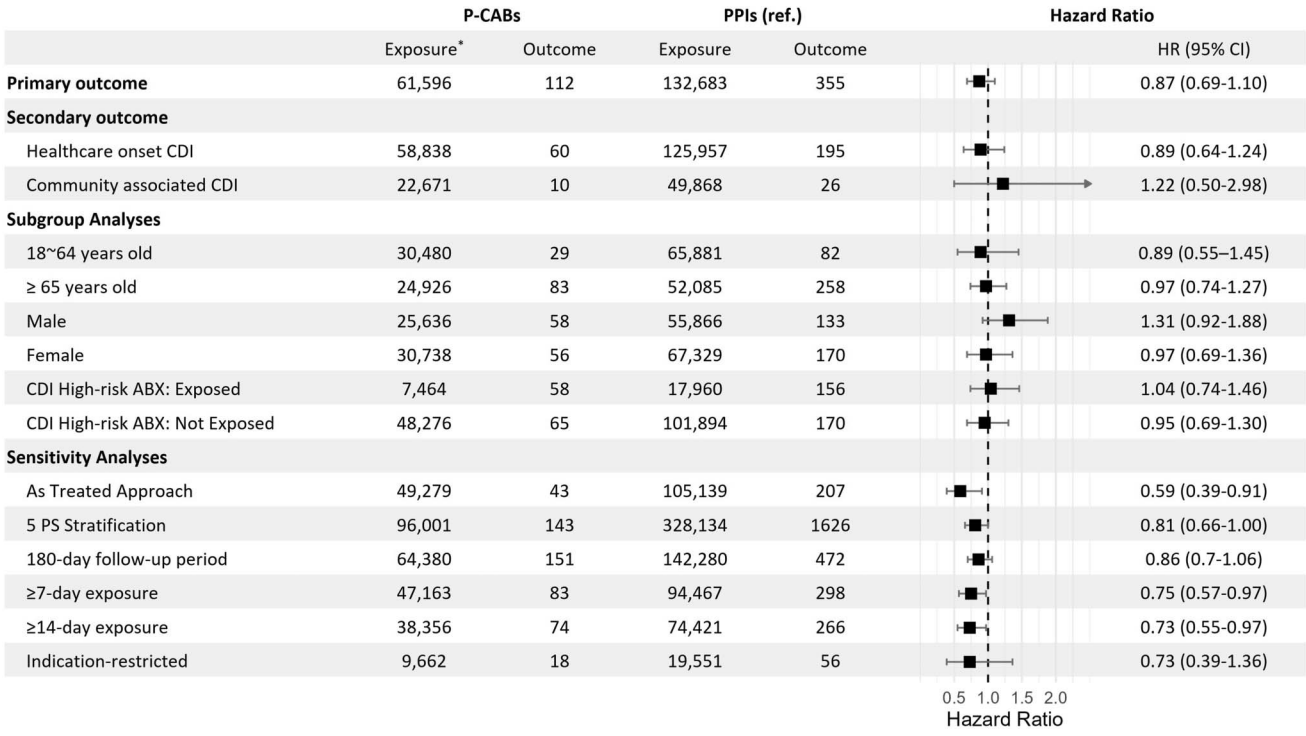


Figure 2. Risk of *Clostridioides difficile* infection associated with P-CABs vs PPIs use. *The numbers of exposed individuals may differ across analyses. This reflects the use of a meta-analytic approach based on federated analyses of multicenter electronic medical record databases. For a given analysis, databases with zero outcome events in either comparison group were excluded from that specific meta-analysis, which may result in varying exposure counts across analytic strata. ABX, antibiotics; CDI, *Clostridioides difficile* infection; HR, hazard ratio; P-CABs, potassium-comparative acid blockers; PPIs, proton pump inhibitors; PS, propensity score.

	P-CABs		H2RAs (ref.)		Hazard Ratio
	Exposure*	Outcome	Exposure	Outcome	HR (95% CI)
Primary outcome	42,886	86	89,730	225	0.85 (0.64-1.12)
Secondary outcome					
Healthcare onset CDI	39,681	43	80,471	134	0.78 (0.52-1.14)
Community associated CDI	3,509	5	7,120	5	1.89 (0.17-21.30)
Subgroup Analyses					
18~64 years old	20,840	14	42,709	37	0.78 (0.35-1.76)
≥ 65 years old	15,158	68	30,179	173	0.92 (0.67-1.26)
Male	17,240	41	35,777	99	1.03 (0.67-1.57)
Female	18,908	45	39,321	113	0.95 (0.63-1.44)
CDI High-risk ABX: Exposed	5,886	34	14,774	109	0.79 (0.50-1.25)
CDI High-risk ABX: Not Exposed	29,225	49	59,869	108	0.93 (0.63-1.37)
Sensitivity Analyses					
As Treated Approach	21,219	23	44,968	61	0.79 (0.43-1.47)
5 PS Stratification	89,341	141	425,618	1,169	0.75 (0.59-0.96)
180-day follow-up period	43,809	109	91,824	291	0.81 (0.62-1.04)
≥7-day exposure	23,954	51	42,451	158	0.65 (0.46-0.93)
≥14-day exposure	18,692	48	32,209	118	0.82 (0.56-1.21)
Indication-restricted	3,589	14	6,090	30	1.15 (0.53-2.47)

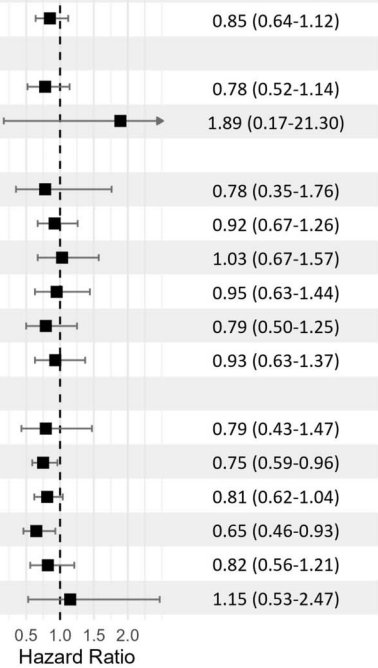


Figure 3. Risk of *Clostridioides difficile* infection associated with P-CABs vs H2RAs use. *The numbers of exposed individuals may differ across analyses. This reflects the use of a meta-analytic approach based on federated analyses of multicenter electronic medical record databases. For a given analysis, databases with zero outcome events in either comparison group were excluded from that specific meta-analysis, which may result in varying exposure counts across analytic strata. ABX, antibiotics; CDI, *Clostridioides difficile* infection; H2RAs, histamine 2 receptor antagonists; HR, hazard ratio; P-CABs, potassium-comparative acid blockers; PS, propensity score,

Risk of CDI: acid suppressive drugs vs nonuser

In comparisons with nonusers, P-CABs (HR 0.67, 95% CI 0.45–1.01) and H2RAs (1.06 [0.85–1.33]) were not significantly associated with an increased risk of CDI in the primary outcome. Similarly, no significant associations were observed for any of the secondary outcomes in these 2 groups. (see Supplementary Figure 3, Supplementary Digital Content, http://links.lww.com/AJG/D919) By contrast, PPI use was associated with a significantly higher risk of CDI for the primary outcome (1.43 [1.08–1.89]). However, this risk did not reach statistical significance in the secondary outcome analyses, including both HO and CO CDI. (see Supplementary Figure 3, Supplementary Digital Content, http://links.lww.com/AJG/D919).

DISCUSSION

To our knowledge, this is the first retrospective cohort study to comprehensively evaluate the risk of CDI associated with P-CABs including tegoprazan and fexuprazan. We found no evidence that P-CABs use was associated with an increased risk of CDI compared with PPIs or H2RAs, and this finding was consistent across subgroup and sensitivity analyses. By contrast, PPIs showed a higher point estimate for CDI risk relative to H2RAs, but this difference was not statistically significant. Most CDI events identified in our study were HO-CDI, reflecting the hospital-based nature of the participating institutions. CO-CDI events were relatively rare, resulting in limited statistical power and wide confidence intervals, and no statistically significant associations were observed for this outcome. The findings across various sensitivity analyses were generally consistent with the main finding, further reinforcing the robustness of the operational definitions used in the main analysis. Taken together, these findings indicate that P-CABs do not seem to increase the risk of CDI compared with PPIs or H2RAs and may, under specific conditions, be associated with a reduced risk.

This observation is generally consistent with previous studies from Japan that focused on vonoprazan. Previous studies have reported that the risk of CDI associated with vonoprazan is comparable to that of PPIs. In a hospital-based case-control study, Watanabe et al (16) found that both PPIs (adjusted odds ratio 1.3 [95% CI, 1.2–1.4]) and vonoprazan (1.4 [1.2–1.7]) were significantly associated with CDI compared with nonusers, with no significant difference between the 2 drugs. Similarly, Saruta et al reported increased CDI risk with both PPIs (3.15 [1.67–5.96]) and vonoprazan (2.63 [1.01–6.88]) in a hospital-based cohort, and matched analyses showed no additional risk associated with vonoprazan beyond that of PPIs (30). By incorporating data from multiple hospitals, a larger study population, and diverse sensitivity analyses, our study extends this evidence and enhances the robustness and generalizability of the findings.

Gastric acid serves as a critical defense barrier against ingested pathogens, and its suppression can increase the survival of *Clostridioides difficile* spores that reach the intestine. Pharmacologically, P-CABs provide a potent and rapid acid suppression, theoretically surpassing that of PPIs, which in turn is greater than that of H2RAs (31). This might suggest that P-CABs would be at least as likely—if not more so—to precipitate CDI through acid suppression. However, as demonstrated by the findings of this

	PPIs		H2RAs (ref.)		Hazard Ratio
	Exposure*	Outcome	Exposure	Outcome	HR (95% CI)
Primary outcome	85,686	422	159,178	600	1.04 (0.84-1.30)
Secondary outcome					
Healthcare onset CDI	75,789	266	138,458	353	1.20 (1.00-1.43)
Community associated CDI	53,907	49	119,132	82	1.16 (0.76-1.77)
Subgroup Analyses					
18~64 years old	54,196	116	105,386	164	1.27 (0.96-1.69)
≥ 65 years old	32,896	300	55,411	435	1.02 (0.86-1.20)
Male	39,763	213	72,987	290	1.24 (1.01-1.52)
Female	45,503	219	84,696	301	1.12 (0.92-1.37)
CDI High-risk ABX: Exposed	26,716	303	53,804	398	1.24 (1.05-1.47)
CDI High-risk ABX: Not Exposed	59,051	171	102,710	232	1.18 (0.95-1.48)
Sensitivity Analyses					
As Treated Approach	56,439	168	100,831	193	1.00 (0.75-1.35)
5 PS Stratification	247,471	1,249	371,635	979	1.11 (0.99-1.25)
180-day follow-up period	91,348	532	165,964	720	1.19 (1.05-1.36)
≥7-day exposure	43,008	274	69,205	335	1.22 (1.03-1.46)
≥14-day exposure	31,616	210	49,405	258	1.29 (1.06-1.57)
Indication-restricted	4,774	43	6,917	60	1.04 (0.66-1.62)

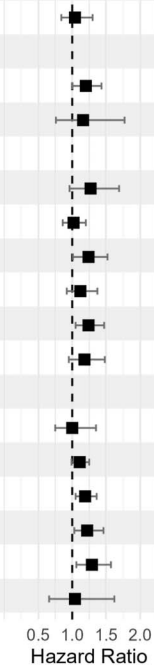


Figure 4. Risk of *Clostridioides difficile* infection associated with PPIs vs H2RAs use. *The numbers of exposed individuals may differ across analyses. This reflects the use of a meta-analytic approach based on federated analyses of multicenter electronic medical record databases. For a given analysis, databases with zero outcome events in either comparison group were excluded from that specific meta-analysis, which may result in varying exposure counts across analytic strata. ABX, antibiotics; CDI, *Clostridioides difficile* infection; H2RAs, histamine 2 receptor antagonists; HR, hazard ratio; P-CABs, potassium-comparative acid blockers; PS, propensity score.

study, the difference in acid suppression potency between P-CABs and PPIs may not seem to be substantial enough to increase the clinical risk of CDI.

Interestingly, sensitivity analyses showed a lower risk of CDI among patients with longer durations of P-CAB exposure. This observation may be partially explained by the pharmacological characteristics of P-CABs, which maintain a more consistent intragastric pH profile compared with PPIs. Unlike PPIs, which require acid-dependent activation and exhibit interindividual variability driven by CYP2C19 polymorphisms, P-CABs act independently of gastric pH and are less influenced by metabolic differences (32,33). Indeed, in a randomized cross-over study, 7-day administration of vonoprazan 20 mg resulted in a 24-hour intragastric pH $\geq$ 4 holding time ratio of 85.8%, compared with 61.2% with esomeprazole 20 mg and 65.1% with rabeprazole 10 mg (34). This sustained acid suppression may reduce fluctuations in the gut environment, potentially limiting dysbiosis and thereby mitigating CDI risk. However, direct evidence supporting this mechanism remains limited and warrants further investigation.

Our findings on the risk of CDI with PPIs vs H2RAs were generally consistent with previous meta-analyses and observational studies. For example, a meta-analysis reported that PPIs use was associated with a significantly higher risk of HO-CDI compared with H2RAs use, with a pooled odds ratio of 1.39 (95% CI, 1.15–1.67) (35). Overall, these findings contribute to the growing body of evidence supporting an elevated risk of HO-CDI with PPIs use compared with H2RAs.

This study has several strengths. By leveraging the OMOP-CDM framework, we were able to integrate data from multiple secondary and tertiary care hospitals, allowing us to evaluate the CDI risk associated with P-CABs use in a large, real-world population. Moreover, we conducted comprehensive sensitivity analyses to assess the robustness of our findings across various scenarios.

However, several limitations should also be acknowledged. First, in routine clinical practice, H2RAs are generally prescribed for conditions such as functional dyspepsia or mild reflux symptoms. PPIs are more often used for indications like peptic ulcer disease and gastrointestinal bleeding. By contrast, although some off-label use may occur, P-CABs currently have more limited approved indications. As a result, differences in approved indications across these drug classes could potentially influence their usage patterns and the underlying risk profiles in clinical practice. These differences in indications and prescribing patterns across acid-suppressive therapies can introduce selection bias in observational studies. To mitigate this potential confounding, we performed large-scale PS matching in this study; however, residual confounding from unmeasured factors may still remain. Second, although we analyzed a large cohort using data from multiple hospitals, these were mainly secondary and tertiary care institutions. Therefore, our findings may not be fully generalizable to primary care. Third, although we used routinely collected data, there may be misclassification of exposures or outcomes despite our use of validated definitions.

In conclusion, our findings suggest that P-CABs use does not increase the risk of CDI compared with PPIs or H2RAs in routine clinical practice. As the use of P-CABs continues to expand, further long-term evaluations are needed to assess their safety

profile, along with mechanistic studies to elucidate how P-CABs might influence the gut environment and microbiota.

CONFLICTS OF INTEREST

Guarantor of the article: Ju Hwan Kim, PharmD, PhD.

Specific author contributions: G.L. and J.-Y.S.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing—original draft, and writing—review & editing. D.E.H.: conceptualization, data curation, investigation, methodology, software, validation, and writing—review & editing. J.-H.K., Y.K. and H.-S.K., conceptualization, data curation, funding acquisition, investigation, methodology, validation, and writing—review & editing. W.H.Y.: Conceptualization, Investigation, Methodology, Validation, Writing—original draft, Writing—review & editing. B.J.S., C.W.J., H.A.P., J.M.C., J.H.K., J.J., K.M.M., S.Y.R., S.-J.K., S.N.Y., S.L., and S.P.: data curation, investigation, resources, validation, and writing—review & editing. R.W.P.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing—original draft, and writing—review & editing. J.H.K.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, writing—original draft, and writing—review & editing.

Financial support: This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Rlic of Korea (grant number: RS-2025-02217133). The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Potential competing interests: None to report.

Ethical approval: Ethical approval for this study was obtained from the Institutional Review Board of Ajou University (IRB number: AJOUIRB-EX-2025-424). The requirement for informed consent was waived, as the study used anonymized administrative data. In all other participating institutions, Institutional Review Board (IRB) review was exempted, and their respective boards likewise confirmed that informed consent was not required.

Study Highlights

WHAT IS KNOWN

- ✓ Acid-suppressive agents have been associated with increased *Clostridioides difficile* infection (CDI) risk.
- ✓ Potassium-competitive acid blockers (P-CABs) are a newer class of acid-suppressive agents.
- ✓ Comparative evidence on CDI risk between P-CABs and other acid-suppressive agents remains limited.

WHAT IS NEW HERE

- ✓ P-CABs use was not associated with an increased CDI risk compared with other acid-suppressive agents.
- ✓ This is the first multicenter real-world evaluation of P-CABs.

REFERENCES

1. Kelly CP, LaMont JT. *Clostridium difficile*—more difficult than ever. N Engl J Med. 2008;359(18):1932–40.
2. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015;372(9):825–34.
3. Angulo FJ, Furtado M, Gonzalez E, et al. Incidence of public health surveillance-reported *Clostridioides difficile* infections in thirteen countries worldwide: A narrative review. Anaerobe. 2024;88:102878.
4. Webb BJ, Subramanian A, Lopansri B, et al. Antibiotic exposure and risk for hospital-associated *Clostridioides difficile* infection. Antimicrob Agents Chemother. 2020;64(4):e02169-19.
5. Cha JM, Yoon JY, Kwak MS, et al. Demographic characteristics and economic burden of *Clostridioides difficile* infection in Korea: A nationwide population-based study after propensity score matching. Antibiotics (Basel). 2024;13(6):542.
6. Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. Arch Intern Med. 2010;170(9):784–90.
7. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;65(5):740–8.
8. Sachs G, Shin JM, Howden CW. Review article: The clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther 2006; 23(Suppl 2):2–8.
9. Kwok CS, Arthur AK, Anibueze CI, et al. Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: Meta-analysis. Am J Gastroenterol. 2012;107(7):1011–9.
10. Inghammar M, Svanstrom H, Voldstedlund M, et al. Proton-pump inhibitor use and the risk of community-associated *Clostridium difficile* infection. Clin Infect Dis. 2021;72(12):e1084-9.
11. Yang X, Li Y, Sun Y, et al. Vonoprazan: A novel and potent alternative in the treatment of acid-related diseases. Dig Dis Sci 2018;63(2):302–11.
12. Shibli F, Kitayama Y, Fass R. Novel therapies for gastroesophageal reflux disease: Beyond proton pump inhibitors. Curr Gastroenterol Rep 2020; 22(4):16.
13. Yang E, Kim S, Kim B, et al. Night-time gastric acid suppression by tegoprazan compared to vonoprazan or esomeprazole. Br J Clin Pharmacol 2022;88(7):3288–96.
14. Scarpignato C, Hunt RH. Potassium-competitive acid blockers: Current clinical use and future developments. Curr Gastroenterol Rep 2024; 26(11):273–93.
15. Ouyang M, Zou S, Cheng Q, et al. Vonoprazan-associated *Clostridioides difficile* infection: An analysis of the Japanese adverse drug event report and the FDA adverse event reporting system. Ther Adv Drug Saf. 2024;15: 20420986241260211.
16. Watanabe K, Shimodaira Y, Takahashi S, et al. Potent acid suppression with vonoprazan vs proton pump inhibitors does not have higher association with *Clostridioides difficile* infection. Am J Gastroenterol. 2021;116(8):1632–7.
17. Blair HA. Zastaprazan: First approval. Drugs 2024;84(7):863–6.
18. Huang KZ, Weber HC. Potassium-competitive acid blockers and acid-related disorders. Curr Opin Endocrinol Diabetes Obes 2024;31(3): 107–14.
19. You SC, Lee S, Choi B, et al. Establishment of an international evidence sharing network through common data model for cardiovascular research. Korean Circ J 2022;52(12):853–64.
20. Rae Woong P. The distributed research network, observational health data sciences and informatics, and the South Korean research network. Korean J Med 2019;94(4):309–14.
21. Overhage JM, Ryan PB, Reich CG, et al. Validation of a common data model for active safety surveillance research. J Am Med Inform Assoc 2012;19(1):54–60.
22. Makadia R, Ryan PB. Transforming the premier perspective hospital database into the observational medical outcomes partnership (OMOP) common data model. EGEMS (Wash DC) 2014;2(1):1110.
23. Multidrug-Resistant Organism. Clostridioides difficile Infection (MDRO/CDI) Module Centers for Disease Control and Prevention Website. Center for Disease Control and Prevention; https://www.cdc.gov/nhsn/PDFs/pscManual/12pscMDRO_CDADcurrent.pdf (2026, Accessed January 30, 2026).
24. Saade E, Deshpande A, Kundrapu S, et al. Appropriateness of empiric therapy in patients with suspected infection. Curr Med Res Opin 2013; 29(8):985–8.

25. El-Gammal A, Scotto V, Malik S, et al. Evaluation of the clinical usefulness of toxin testing in hospitalized patients with diarrhea. Diagn Microbiol Infect Dis 2000;36(3):169–73.
26. Polgreen PM, Yang M, Kuntz JL, et al. Using oral vancomycin prescriptions as a proxy measure for infections: A spatial and time series analysis. Infect Control Hosp Epidemiol 2011;32(7):723–6.
27. Sunkesula VCK, Kundrapu S, Muganda C, et al. Does empirical infection (CDI) therapy result in false-negative CDI diagnostic test results? Clin Infect Dis 2013;57(4):494–500.
28. Slimings C, Riley TV. Antibiotics and hospital-associated *Clostridioides difficile* infection: Systematic review and meta-analysis 2020 update. medRxiv. 2021.
29. Tian YX, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. Int J Epidemiol 2018;47(6):2005–14.
30. Saruta Y, Watanabe K, Tsuji T, et al. Vonoprazan poses no additional risk of developing infection compared to proton pump inhibitors. J Gastroenterol Hepatol 2023;38(6):940–7.
31. Huang CH, Tseng YH, Tsai WS, et al. Association between risk of infection and duration of proton pump inhibitor or H2-receptor antagonist use in hospitalized patients. Infect Dis Ther. 2024;13(2): 373–83.
32. Jenkins H, Sakurai Y, Nishimura A, et al. Randomised clinical trial: Safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther. 2015;41(7):636–48.
33. Wang WL, Yaseen HS, Li XJ, et al. Tegoprazan: A novel, highly selective, and potent potassium-competitive acid blocker (P-CAB). Eur J Clin Pharmacol 2025;81(8):1103–17.
34. Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—A randomised open-label cross-over study. Aliment Pharmacol Ther 2015;42(6):719–30.
35. Azab M, Doo L, Doo DH, et al. Comparison of the hospital-acquired infection risk of using proton pump inhibitors versus histamine-2 receptor antagonists for prophylaxis and treatment of stress ulcers: A systematic review and meta-analysis. Gut Liver. 2017;11(6):781–8.