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Laboratory-confirmed Clostridioides difficile infection after potassium-competitive acid blocker versus proton pump inhibitor initiation in a new-user cohort

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Abstract

Background

Comparative gastrointestinal infection safety of potassium-competitive acid blockers (PCABs) and proton pump inhibitors (PPIs) remains uncertain. In this study, we compared laboratory-confirmed *Clostridioides difficile* infection (CDI) after initiation of these drug classes in a hospital cohort.

Methods

In this retrospective active-comparator new-user cohort, prescription and stool-test records from a Korean hospital clinical data warehouse were linked. Adults initiated PCABs or PPIs between January 2020 and June 2025, after a 1-year washout for both drug classes and without CDI during the prior 5 years. PCAB and PPI initiators were matched 1:4 using propensity scores. Cox models estimated hazard ratios for incident laboratory-confirmed CDI.

Results

The matched cohort included 13,714 PCAB initiators and 54,856 PPI initiators, with 30 and 267 CDI events, respectively. Incidence rates were 5.69 and 7.15 per 1,000 person-years; mean observed follow-up was 140.5 and 248.8 days, respectively. PCAB initiation was associated with a lower observed CDI incidence (hazard ratio, 0.57; 95% confidence interval, 0.39–0.84). Nested secondary outcomes showed associations in the same direction.

Conclusions

In this single-center observational cohort, PCAB initiation was associated with a lower observed incidence of laboratory-confirmed CDI than PPI initiation. These findings add comparative gastrointestinal safety evidence for newer acid-suppressive therapies and support confirmation in multicenter cohorts. The observational association does not establish causal protection or individual-agent superiority.

Background

Acid-suppressive drugs are widely used for the treatment of gastroesophageal reflux disease and peptic ulcer disease, eradication of *Helicobacter pylori*, prevention of nonsteroidal anti-inflammatory drug–related ulcers, and prophylaxis of upper gastrointestinal bleeding. As the range of available agents continues to expand, comparative gastrointestinal safety has become increasingly important in clinical practice. One relevant safety concern is *Clostridioides difficile* infection (CDI), a clinically important healthcare-associated gastrointestinal infection linked to increased morbidity, recurrence, prolonged

hospitalization, and antimicrobial use [1–4]. As clinically indicated acid-suppressive therapy cannot always be discontinued, an important safety question is whether the risk of CDI differs among the available classes of acid-suppressive drugs.

Proton pump inhibitor (PPI) use has consistently been associated with incident and recurrent CDI in observational studies and meta-analyses [5–7]. Although residual confounding limits the causal interpretation of these findings, the accumulated evidence supports medication review and deprescribing when acid suppression is no longer clinically indicated. However, comparative evidence involving newer acid-suppressive agents remains limited, particularly among studies in which both treatment groups have clear indications for acid suppression.

Potassium-competitive acid blockers (PCABs) achieve rapid, potent, and sustained acid suppression without requiring acid activation, and they are increasingly used in East Asia. Moreover, tegoprazan and fexuprazan are available in South Korea. Japanese studies have reported that CDI risk with vonoprazan is not higher than that with PPIs [8, 9], and a Korean cohort study compared tegoprazan and PPIs, each with histamine-2 receptor antagonists [10]. More recently, a 15-hospital Korean new-user cohort study directly compared PCABs with PPIs and observed no statistically significant difference in 90-day CDI risk (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.69–1.10) [11]. A systematic review also identified substantial heterogeneity in agents, outcome definitions, and effect measures [12]. Therefore, further evidence from studies requiring laboratory confirmation of CDI through stool testing is valuable for assessing the consistency of comparative safety findings across different settings.

The aim of this study was to compare the incidence of laboratory-confirmed CDI after PCAB versus PPI initiation using integrated prescription and stool-test data from a hospital clinical data warehouse (CDW). The primary analysis used propensity-score matching, with supportive analyses of prescription coverage and nested outcome definitions. Agent-specific comparisons were exploratory. Laboratory confirmation provides evidence relevant to the comparative gastrointestinal safety of newer acid-suppressive therapies.

Methods

Data source

This retrospective active-comparator new-user cohort study compared CDI after PCAB versus PPI initiation using the CDW of CHA Bundang Medical Center, a secondary-care hospital in South Korea. The CDW contains longitudinal electronic medical records for approximately two million patients, including International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes, prescriptions, inpatient and outpatient encounters, surgical procedures, and hematological, biochemical, and qualitative laboratory results [13]. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of CHA Bundang Medical Center (No. CHAMC 2026-01-039). The study protocol was approved before study-specific data extraction and

analysis. The requirement for informed consent was waived owing to the retrospective study design and the use of fully de-identified data.

Study population and design

The source database included prescription records through December 31, 2025. Eligible index prescriptions were restricted to those issued to adults (aged 18 years or older) between January 1, 2020, and June 30, 2025, allowing at least 6 months of potential follow-up before the administrative database end date. No patients were excluded based on the actual duration of follow-up. The index date was defined as the date of the first PCAB or PPI prescription within the eligible index period. To implement a new-user design, patients who had received any PCAB or PPI within 1 year before the index date were excluded. Additionally, patients with a diagnosis of CDI within 5 years before the index date were excluded to restrict the analysis to incident CDI.

A retrospective active-comparator new-user design was employed [14]. PCAB initiators were compared with PPI initiators rather than with nonusers to reduce confounding by indication for acid-suppressive therapy. To further improve baseline comparability, PCAB initiators were matched to PPI initiators at a 1:4 ratio using propensity scores [15]. Follow-up began on the index date and continued until the first laboratory-confirmed CDI, initiation of the comparator drug class, death, or December 31, 2025, whichever occurred first. Accordingly, treatment switching was handled by censoring follow-up at the date of the first prescription for a drug in the comparator class. Discontinuation of the index drug class alone did not trigger censoring; therefore, this analysis was not an on-treatment analysis.

Exposure and outcomes

Exposure was assigned according to the drug class initiated on the index date. The PCAB group included tegoprazan and fexuprazan, while the PPI group included omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, ilaprazole, dexlansoprazole, and PPI-containing fixed-dose combinations. Fixed-dose combinations, including analgesic–PPI combinations, were classified as PPI exposure if they contained an active PPI component (Additional file 1: Supplementary Methods: Exposure classification). The primary comparison was conducted at the drug-class level. Exploratory agent-specific estimates were examined within the original class-level matched cohort.

The primary outcome was the first laboratory-confirmed CDI during follow-up, identified from stool-test results rather than from diagnosis codes alone. Laboratory confirmation required a positive stool nucleic acid amplification test or toxin enzyme immunoassay; glutamate dehydrogenase antigen testing was supportive when combined with toxin testing [16]. Symptoms were not separately adjudicated for this analysis. The secondary outcomes, severe CDI and CDI with recorded treatment, were nested subsets of the primary events. Severe CDI was defined by a white blood cell count of > 15,000 cells/μL (15×10^9/L) or serum creatinine level of ≥ 1.5 mg/dL (133 μmol/L) within 14 days before or after laboratory diagnosis

[16]. CDI with recorded treatment was defined by a prescription for a drug used in CDI management, such as vancomycin and metronidazole, that started between 7 days before and 90 days after laboratory diagnosis. This prescription-based definition did not require independent confirmation of the treatment indication. A 7-day gap between consecutive prescriptions was permitted in the construction of treatment episodes. CDI meeting the white blood cell criterion, CDI meeting the creatinine criterion, and CDI with at least 14 days of recorded treatment were also examined as exploratory outcomes.

Covariates

Baseline covariates included demographic characteristics, comorbidities, and previous medication use (Additional file 1: Supplementary Methods: Baseline and outcome definitions). Age and sex were assessed at the index date. Comorbidities, including components of the Charlson Comorbidity Index and chronic kidney disease, were identified using ICD-10 diagnosis codes recorded during inpatient and outpatient encounters in the 1-year baseline period preceding the index date [17]. Medication covariates included antibiotics, glucocorticoids, azathioprine, and other immunosuppressive agents. Baseline exposure to high-risk antibiotics for CDI, including fluoroquinolones, cephalosporins, and clindamycin, was assessed during the 3 months preceding the index date, whereas all other medication covariates were examined during the 1-year baseline period. Antibiotic exposure during follow-up was not modeled as a time-varying covariate.

Statistical analysis

Study size was determined by the number of eligible initiators available in the CDW during the index period; the final comparative cohort was determined by propensity-score matching. During initial CDW cohort construction, records missing information required to establish eligibility or define prespecified baseline analytic variables were excluded rather than imputed. This handling of unavailable source data is distinct from clinician-directed CDI stool testing during follow-up.

Baseline characteristics of the participants are summarized using descriptive statistics before and after propensity-score matching. Propensity scores were estimated using multivariable logistic regression incorporating all baseline patient characteristics. PCAB and PPI initiators were matched at a 1:4 ratio using greedy nearest-neighbor matching with a caliper width of 0.2 times the standard deviation of the logit of the propensity score, implemented using the MatchIt package in R [15, 18]. Covariate balance was assessed using standardized mean differences (SMDs), with an absolute SMD of < 0.1 indicating negligible imbalance [19]. The propensity-score–matched analysis was prespecified as the primary comparative analysis, with the percentage of days covered (PDC)-adjusted model serving as a supportive analysis.

Incidence rates (IRs) per 1,000 person-years were calculated from event counts and person-time, with log-scale Wald 95% CIs based on Poisson standard errors. Cox proportional hazards models estimated HRs and 95% CIs. IRs and HRs were also estimated in the cohort before matching. The supportive model

included the PDC by the index acid-suppressive drug class as an additional covariate. PDC was the number of unique prescription-covered calendar days divided by observed follow-up days, multiplied by 100; overlapping prescription periods were counted once (Additional file 1: Supplementary Methods: Prescription-based percentage of days covered). PDC reflected prescribed exposure rather than confirmed medication use. Given that PDC incorporated postbaseline information throughout the full observed follow-up, adjustment for PDC could introduce bias; therefore, PDC-adjusted estimates were interpreted only as supportive data. Kaplan–Meier curves described the cumulative probability of CDI and were compared using the log-rank test. Treatment duration was summarized among patients with recorded treatment, without formal between-group hypothesis testing. No multiplicity adjustment was applied.

Exploratory agent-specific comparisons (fexuprazan vs. PPIs, tegoprazan vs. PPIs, and fexuprazan vs. tegoprazan) were based on the PCAB agent initiated on the index date within the original class-level matched cohort. The original matched PPI group was retained for both comparisons; no separate agent-specific propensity-score matching was performed. Estimates from models incorporating PDC and the baseline variables used in the main propensity-score analysis were reported as exploratory.

All statistical analyses were performed using R software (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria).

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement [20].

Manuscript preparation

ChatGPT (OpenAI) was used to assist with language revision and preparation of the submission materials. The authors retain responsibility for the accuracy and integrity of the manuscript.

Results

Cohort selection and baseline characteristics

Of the 163,228 patients screened from the source database, 10,752 were excluded because of a candidate index prescription issued between July 1 and December 31, 2025, outside the eligible index period; 18,942 because of prior PCAB or PPI use within the year preceding the index date; and 180 because of a history of CDI within the past 5 years. The resulting eligible cohort comprised 133,354 initiators (Fig. 1). Before matching, PCAB initiators were older and had a greater comorbidity burden than PPI initiators, as reflected by a greater proportion of patients aged 65 years or older (35.8% vs. 28.9%) and a higher mean Charlson Comorbidity Index score (mean ± standard deviation, 0.54 ± 1.15 vs. 0.38 ± 1.03; SMD = 0.141; Table 1). After 1:4 propensity-score matching, 13,714 PCAB initiators and 54,856 PPI initiators were retained, and all measured baseline characteristics were well balanced, with SMDs of < 0.1.

Table 1

Baseline characteristics of PCAB and PPI initiators before and after 1:4 propensity-score matching

Characteristic	Before propensity-score matching			After propensity-score matching		
	PCAB (n = 14153)	PPI (n = 119201)	SMD	PCAB (n = 13714)	PPI (n = 54856)	SMD
Age, years						
Mean ± SD	57.28 ± 16.46	53.43 ± 17.69	0.225	56.90 ± 16.46	57.33 ± 16.72	0.026
18–39	2322 (16.4)	29494 (24.7)	0.223	2319 (16.9)	9126 (16.6)	0.027
40–64	6761 (47.8)	55245 (46.3)		6622 (48.3)	25935 (47.3)	
≥ 65	5070 (35.8)	34462 (28.9)		4773 (34.8)	19795 (36.1)	
Sex						
Male	6496 (45.9)	56896 (47.7)	0.037	6277 (45.8)	25011 (45.6)	0.004
Female	7657 (54.1)	62305 (52.3)		7437 (54.2)	29845 (54.4)	
Comorbidities						
CCI, score						
Mean ± SD	0.54 ± 1.15	0.38 ± 1.03	0.141	0.46 ± 1.05	0.44 ± 1.04	0.021
0–1	12212 (86.3)	106093 (89.0)	0.087	12176 (88.8)	48831 (89.0)	0.009
2–3	1550 (11.0)	10846 (9.1)		1257 (9.2)	4954 (9.0)	
≥ 4	391 (2.8)	2262 (1.9)		281 (2.0)	1071 (2.0)	
Myocardial infarction	155 (1.1)	653 (0.5)	0.061	118 (0.9)	467 (0.9)	0.001

PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker; CCI, Charlson Comorbidity Index; SMD, standardized mean difference; CHF, congestive heart failure; CVD, cerebrovascular disease; PUD, peptic ulcer disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation; DM, diabetes mellitus; Hemi/Para, hemiplegia or paraplegia; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Values are n (%) unless otherwise indicated. Percentages are within treatment groups. Chronic kidney disease (N18) is a subset of the broader CCI renal-disease category.

Characteristic	Before propensity-score matching			After propensity-score matching		
	PCAB (n = 14153)	PPI (n = 119201)	SMD	PCAB (n = 13714)	PPI (n = 54856)	SMD
Age, years						
CHF	190 (1.3)	786 (0.7)	0.069	141 (1.0)	518 (0.9)	0.008
Peripheral vascular disease	162 (1.1)	792 (0.7)	0.051	129 (0.9)	493 (0.9)	0.004
CVD	1059 (7.5)	4359 (3.7)	0.167	838 (6.1)	3202 (5.8)	0.012
Dementia	210 (1.5)	1177 (1.0)	0.045	178 (1.3)	645 (1.2)	0.011
COPD	282 (2.0)	1880 (1.6)	0.031	257 (1.9)	953 (1.7)	0.010
Rheumatic disease	107 (0.8)	590 (0.5)	0.033	90 (0.7)	344 (0.6)	0.004
PUD	174 (1.2)	786 (0.7)	0.059	137 (1.0)	544 (1.0)	0.001
Liver disease (mild)	597 (4.2)	2687 (2.3)	0.111	458 (3.3)	1869 (3.4)	0.004
Liver disease (moderate to severe)	12 (0.1)	183 (0.2)	0.020	12 (0.1)	41 (0.1)	0.004
Uncomplicated DM	1058 (7.5)	4333 (3.6)	0.168	803 (5.9)	2908 (5.3)	0.024
Complicated DM	212 (1.5)	1237 (1.0)	0.041	184 (1.3)	686 (1.3)	0.008
Hemi/Para	157 (1.1)	346 (0.3)	0.098	60 (0.4)	120 (0.2)	0.038
Malignancy	865 (6.1)	8319 (7.0)	0.035	835 (6.1)	3398 (6.2)	0.004
Metastatic cancer	85 (0.6)	604 (0.5)	0.013	76 (0.6)	269 (0.5)	0.009
Renal disease	298 (2.1)	1820 (1.5)	0.043	257 (1.9)	975 (1.8)	0.007
Chronic kidney disease	273 (1.9)	1710 (1.4)	0.038	237 (1.7)	921 (1.7)	0.004
AIDS/HIV	1 (< 0.1)	16 (< 0.1)	0.006	1 (< 0.1)	4 (< 0.1)	< 0.001

PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker; CCI, Charlson Comorbidity Index; SMD, standardized mean difference; CHF, congestive heart failure; CVD, cerebrovascular disease; PUD, peptic ulcer disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation; DM, diabetes mellitus; Hemi/Para, hemiplegia or paraplegia; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Values are n (%) unless otherwise indicated. Percentages are within treatment groups. Chronic kidney disease (N18) is a subset of the broader CCI renal-disease category.

Characteristic	Before propensity-score matching			After propensity-score matching		
	PCAB (n = 14153)	PPI (n = 119201)	SMD	PCAB (n = 13714)	PPI (n = 54856)	SMD
Age, years						
Previous medications						
High-risk antibiotics (within 3 months)						
Fluoroquinolones	334 (2.4)	4381 (3.7)	0.077	330 (2.4)	1116 (2.0)	0.025
Cephalosporins	1800 (12.7)	19147 (16.1)	0.095	1732 (12.6)	7045 (12.8)	0.006
Clindamycin	45 (0.3)	621 (0.5)	0.031	45 (0.3)	162 (0.3)	0.006
Other medications (within 1 year)						
Other antibiotics	744 (5.3)	8889 (7.5)	0.090	727 (5.3)	2783 (5.1)	0.010
Glucocorticoids	1095 (7.7)	7655 (6.4)	0.051	976 (7.1)	3950 (7.2)	0.003
Azathioprine	22 (0.2)	104 (0.1)	0.020	19 (0.1)	65 (0.1)	0.006
Other immunosuppressants	128 (0.9)	600 (0.5)	0.048	104 (0.8)	414 (0.8)	< 0.001

PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker; CCI, Charlson Comorbidity Index; SMD, standardized mean difference; CHF, congestive heart failure; CVD, cerebrovascular disease; PUD, peptic ulcer disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation; DM, diabetes mellitus; Hemi/Para, hemiplegia or paraplegia; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Values are n (%) unless otherwise indicated. Percentages are within treatment groups. Chronic kidney disease (N18) is a subset of the broader CCI renal-disease category.

Primary outcome: incident CDI

The matched cohort contributed 5,276 person-years in the PCAB group and 37,365 person-years in the PPI group. The mean observed follow-up duration was 140.5 and 248.8 days, respectively. Incident CDI occurred in 30 of 13,714 PCAB initiators and 267 of 54,856 PPI initiators. IRs were 5.69 per 1,000 person-years (95% CI, 3.98–8.13) and 7.15 per 1,000 person-years (95% CI, 6.34–8.06), respectively, corresponding to an observed incidence-rate difference of 1.46 per 1,000 person-years (Table 2). Before matching, the HR was 0.67 (95% CI, 0.48–0.94; Table 2).

Table 2
Incidence rates and hazard ratios for laboratory-confirmed CDI

Group	No. of patients	No. of CDI events	Person-years	IR per 1000 PY (95% CI)	HR (95% CI)	PDC-adjusted HR (95% CI)
Before propensity-score matching						
PCAB	14153	36	5597	6.43 (4.64–8.92)	0.67 (0.48–0.94)	0.61 (0.43–0.85)
PPI	119201	532	72986	7.29 (6.70–7.94)	Reference	Reference
After propensity-score matching						
PCAB	13714	30	5276	5.69 (3.98–8.13)	0.57 (0.39–0.84)	0.52 (0.36–0.77)
PPI	54856	267	37365	7.15 (6.34–8.06)	Reference	Reference

Results before and after propensity-score matching are shown for PCAB and PPI initiators. The HR column reports Cox estimates within each analysis cohort. The PDC-adjusted model is a supportive analysis incorporating the prescription-based percentage of days covered by the index acid-suppressive drug class. PDC was the number of unique prescription-covered calendar days divided by observed follow-up days, multiplied by 100, with overlapping days counted once. PDC was measured after treatment initiation and therefore was not a baseline confounder.

CDI, *Clostridioides difficile* infection; PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker; PY, person-years; IR, incidence rate; HR, hazard ratio; CI, confidence interval; PDC, percentage of days covered

In the matched cohort, PCAB initiation was associated with a lower observed incidence of laboratory-confirmed CDI than PPI initiation (HR, 0.57; 95% CI, 0.39–0.84). The supportive prescription-based PDC-adjusted HR was 0.52 (95% CI, 0.36–0.77). Kaplan–Meier curves demonstrated a lower cumulative probability of CDI in the PCAB group than in the PPI group (log-rank P = 0.004; Fig. 2).

Secondary outcomes and recorded treatment

Severe CDI occurred in 24 PCAB initiators and 200 PPI initiators. IRs were 4.55 per 1,000 person-years (95% CI, 3.05–6.79) and 5.35 per 1,000 person-years (95% CI, 4.66–6.15), respectively. The matched-cohort HR was 0.62 (95% CI, 0.40–0.95), and the PDC-adjusted HR was 0.56 (95% CI, 0.36–0.86). CDI with recorded treatment occurred in 28 PCAB initiators and 258 PPI initiators, with IRs of 5.31 (95% CI, 3.66–7.69) and 6.90 (95% CI, 6.11–7.80) per 1,000 person-years, respectively. The matched-cohort and PDC-adjusted HRs were 0.56 (95% CI, 0.38–0.83) and 0.51 (95% CI, 0.34–0.76), respectively (Fig. 3). These outcomes were nested within laboratory-confirmed CDI and do not provide independent replications. The creatinine criterion was met by all 24 PCAB severe-CDI initiators and 192 of the 200 PPI

initiators, indicating that this operational definition was predominantly driven by creatinine. Component outcomes and CDI with at least 14 days of recorded treatment are presented in Supplementary Table S1 (Additional file 1).

Recorded treatment was identified in 28 of 30 patients with incident CDI (93.3%) in the PCAB group and 258 of 267 (96.6%) in the PPI group. Among these patients, the median treatment duration was 20 (interquartile range, 10.75–31.5) and 17 (interquartile range, 11–27) days, respectively (Additional file 1: Supplementary Table S2). These descriptive comparisons were conditional on the occurrence of CDI and should not be interpreted as evidence of comparative treatment effectiveness.

Exploratory agent-specific comparisons

The matched PCAB group comprised 7,426 fexuprazan initiators with 23 CDI events and 6,288 tegoprazan initiators with 7 events. The exploratory model incorporating PDC and the main propensity-score covariates yielded HRs of 0.62 (95% CI, 0.40–0.96) for fexuprazan versus PPIs and 0.44 (95% CI, 0.21–0.93) for tegoprazan versus PPIs. The corresponding HR for fexuprazan versus tegoprazan was 1.28 (95% CI, 0.53–3.06; Additional file 1: Supplementary Table S3). The wide interval for the direct agent comparison does not demonstrate equivalence. These analyses reused the original cohort and are not independent replications of the class-level association.

Discussion

In this propensity-score–matched cohort, PCAB initiation was associated with a lower observed incidence of laboratory-confirmed CDI than PPI initiation (HR, 0.57). The supportive PDC-adjusted estimate was directionally consistent with the primary analysis. CDI was rare, and the observed incidence-rate difference was 1.46 per 1,000 person-years. Severe CDI and CDI with recorded treatment demonstrated associations in the same direction as the primary outcome but represented subsets of the primary events. These findings elucidate a comparative association in this hospital setting and do not establish that PCABs prevent CDI.

These results should be considered alongside the multicenter Korean study by Lim et al. [11], which included tegoprazan and fexuprazan and reported an HR of 0.87 (95% CI, 0.69–1.10) for PCABs versus PPIs. That study used a 90-day outcome defined by a CDI diagnosis code, oral vancomycin prescription, or positive stool toxin test. By contrast, the present analysis required laboratory confirmation and used available follow-up through the database end date, with censoring at treatment switching. These differences in outcome ascertainment, follow-up, and clinical setting may contribute to the differences in effect estimates; however, they do not establish that either estimate is more valid than the other. The recent systematic review by Lee et al. [12] emphasized heterogeneity across PCAB agents and study designs and restricted quantitative pooling to direct vonoprazan–PPI comparisons. The present cohort adds data on tegoprazan and fexuprazan using a laboratory-based outcome.

Pharmacological differences between the two drug classes may partially explain the observed association but are insufficient to establish a causal mechanism. PPIs are acid-labile prodrugs that irreversibly inhibit the H^+/K^+-ATPase, whereas PCABs reversibly and competitively block its potassium-binding site and exhibit distinct pharmacodynamic properties [21, 22]. However, because PCABs also induce potent acid suppression, pharmacodynamic differences alone cannot establish a biologically protective effect against CDI. Variations in prescribing patterns and clinical context may also have contributed. Although the clinical indications for PCABs and PPIs largely overlap, PPIs have a longer history of use in inpatient and critical care settings than PCABs, whereas PCAB prescribing may reflect more recent and potentially distinct patterns of clinical practice [23]. Residual confounding by indication, illness severity, healthcare exposure, or antibiotic burden may therefore have influenced the observed association despite the good balance in measured baseline characteristics.

For gastrointestinal clinical practice, comparing acid-suppressive therapies requires careful interpretation of CDI safety outcomes. This active-comparator study adds laboratory-based evidence for two newer PCABs, but its observational estimates inform further comparative safety research rather than directly supporting the selection of a PCAB to prevent CDI.

This study has several strengths. The hospital CDW linked prescription, encounter, diagnosis, and laboratory data, enabling stool-test–based ascertainment of CDI. Propensity-score matching achieved balance in measured baseline characteristics, and the active-comparator design improved clinical comparability. Explicit outcome and prescription definitions support the interpretation of the class-level association. However, these strengths do not eliminate confounding or differences in outcome detection.

Certain limitations affect the interpretation of these findings. The single-center observational design leaves potential confounding by indication, illness severity, calendar time, and healthcare exposure. Index year, inpatient versus outpatient initiation, and recent healthcare utilization were not included in the reported matching variables. Mean observed follow-up also differed substantially between the groups. Person-time rates and Cox models accommodate differences in observation time, but they do not establish comparable treatment opportunities or noninformative censoring. Baseline antibiotic indicators did not capture route, duration, combinations, or time-varying antibiotic exposure. CDI testing was clinician-directed and testing frequency was not compared between the groups. Symptoms were not independently adjudicated; thus, laboratory positivity may not always indicate symptomatic infection.

Prescription records did not establish ingestion, and discontinuation did not end follow-up. Postbaseline PDC adjustment may be influenced by subsequent clinical events and does not replace an on-treatment analysis. PPI-containing fixed-dose combinations may have indications different from those of PPI monotherapy. The treatment-based outcome employed a broad prescription window and did not independently verify indication or route; therefore, therapy for other infections may have been misclassified as CDI treatment. Severity measurements within a 14-day window on either side of diagnosis may reflect pre-existing illness, especially renal dysfunction. Exploratory agent-specific

comparisons were vulnerable to imbalance, because subsetting the PCAB group did not preserve the original class-level covariate balance, and to imprecision and overfitting, particularly because only seven tegoprazan events occurred. Generalizability is also limited by differences in drug availability, clinical practice, and CDI testing across healthcare systems.

Conclusions

Using integrated prescription and stool-test data in a propensity-score–matched hospital cohort, PCAB initiation was associated with a lower observed incidence of laboratory-confirmed CDI than PPI initiation. These findings inform the comparative gastrointestinal safety of newer acid-suppressive therapies. The association does not establish causal protection or individual-agent superiority. Multicenter confirmation is needed before using this association to guide drug selection.

Abbreviations

CCI, Charlson Comorbidity Index; CDW, clinical data warehouse; CDI, Clostridioides difficile infection; CI, confidence interval; HR, hazard ratio; IR, incidence rate; PDC, percentage of days covered; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; PS, propensity score; SMD, standardized mean difference.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of CHA Bundang Medical Center (No. CHAMC 2026-01-039).

The requirement for informed consent was waived by the institutional review board.

Consent for publication

Not applicable. No identifiable individual participant data are presented.

Availability of data and materials

The individual-level data analyzed during this study are not publicly available because they originate from an institutional clinical data warehouse and are subject to patient-privacy and institutional access restrictions. Requests for deidentified analytic outputs and operational definitions may be directed to the corresponding authors and are subject to institutional approval and applicable privacy requirements.

Competing interests

The authors declare no competing interests.

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Authors' contributions

WS and JYS had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analysis. WS and JYS participated in the conception and design of the study. SHY, WS, and JYS were involved in the acquisition, analysis, or interpretation of data. SHY, AYL, KL, WS, and JYS drafted the manuscript. SHY, AYL, WS, and JYS critically revised the manuscript for important intellectual content. SHY and WS were involved in the statistical analysis. WS and JYS supervised the work. All authors approved the final manuscript and the decision to submit it for publication.

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Figures

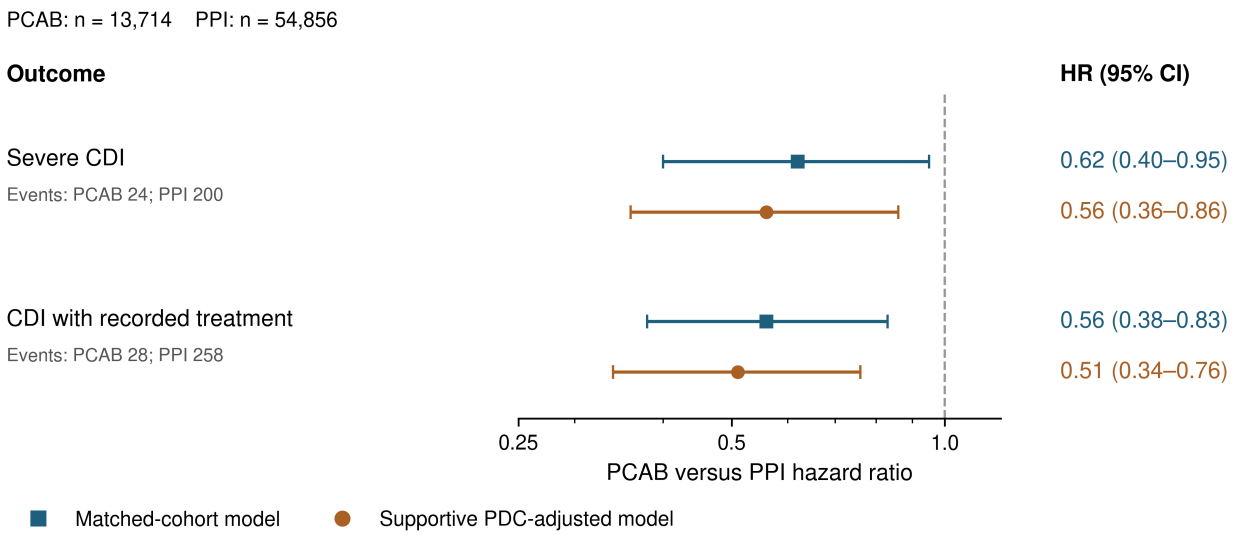
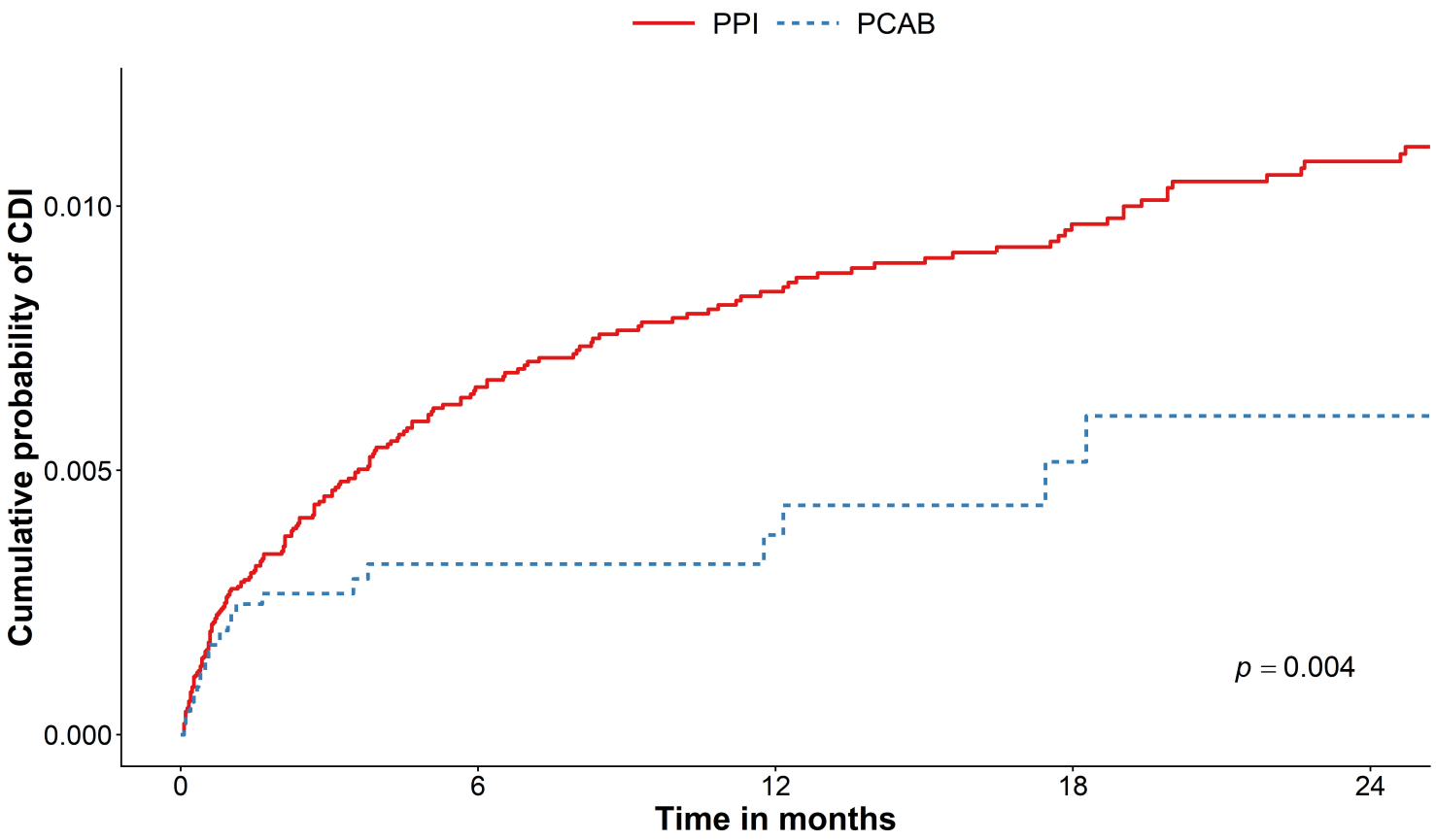


Figure 1

Matched-cohort and supportive PDC-adjusted HRs for severe CDI and CDI with recorded treatment. The secondary outcomes were nested within laboratory-confirmed CDI. PDC incorporated information over observed follow-up and was used only in the supportive model

CDI, *Clostridioides difficile* infection; PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker; HR, hazard ratio; CI, confidence interval; PDC, percentage of days covered



PPI	54856	14812	11441	9033	7314
PCAB	13714	2847	1782	1165	720

Figure 2

Kaplan–Meier estimates of laboratory-confirmed CDI by treatment group. The curves are displayed through 24 months for visual clarity; however, all available follow-up data were included in the time-to-event analyses. The numbers below the plot are the numbers of patients at risk at each time point.

CDI, *Clostridioides difficile* infection; PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker

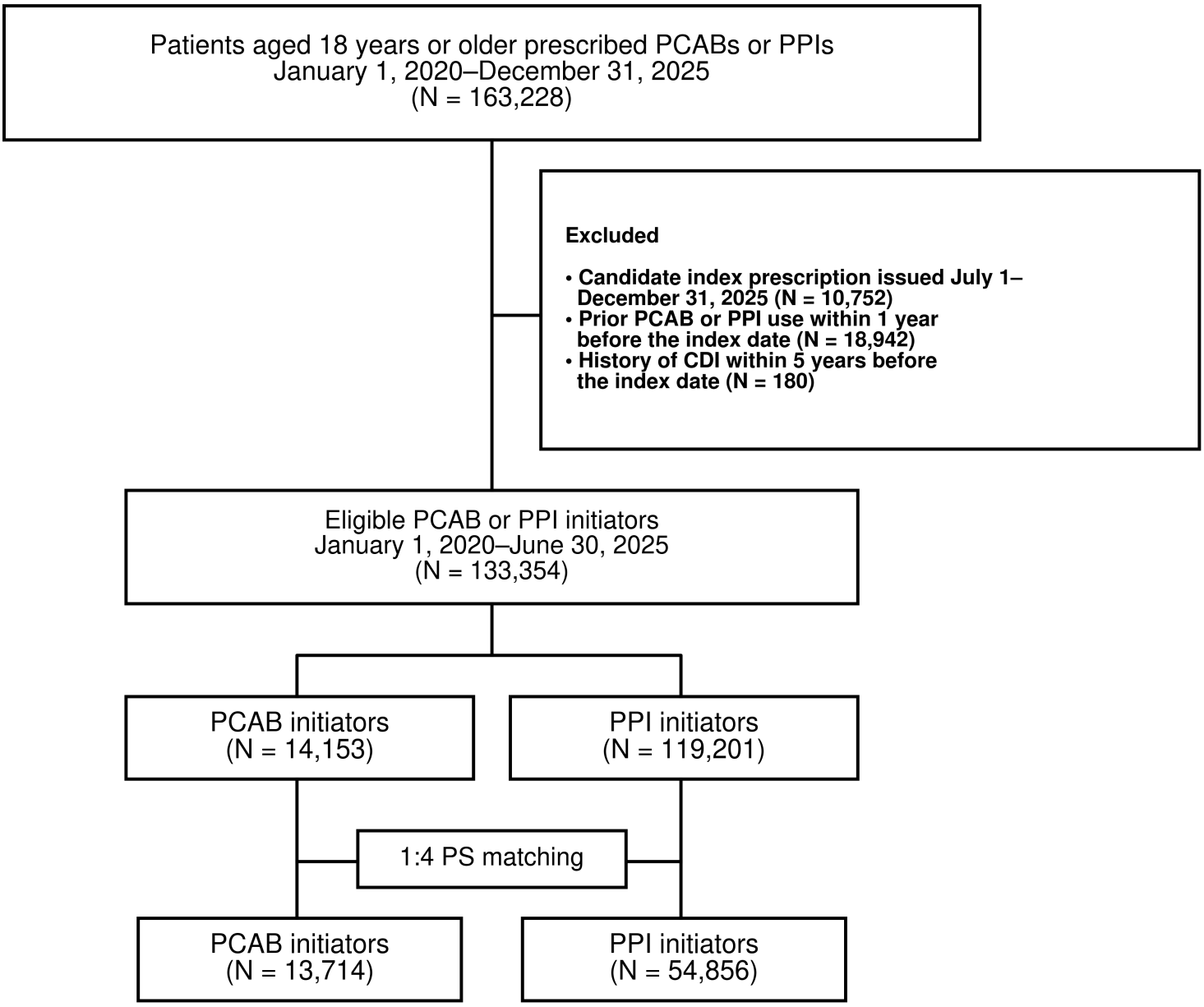


Figure 3

Flowchart of cohort construction

CDI, *Clostridioides difficile* infection; PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker; PS, propensity score

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