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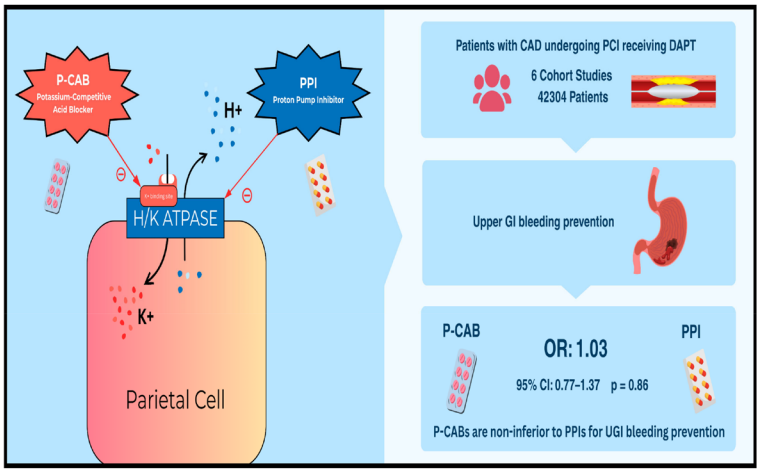
REVIEW

Effect of Potassium-Competitive Acid Blockers Compared with Proton Pump Inhibitors on Upper Gastrointestinal Bleeding in Patients with Coronary Artery Disease on Dual Antiplatelet Therapy: A Systematic Review and Meta-Analysis

Graphical Abstract



Highlights

- P-CABs showed similar efficacy to PPIs in preventing upper gastrointestinal bleeding (UGIB) in patients with coronary artery disease receiving dual antiplatelet therapy (DAPT).
- There were no statistically significant differences between P-CABs and PPIs for major adverse cardiovascular events (MACE) or all-cause mortality.
- P-CABs may offer pharmacologic advantages, including faster onset of action, stronger acid suppression, and minimal CYP2C19 interaction.
- Findings are primarily based on observational studies from East Asian populations, underscoring the need for large randomized controlled trials.

Authors

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In Brief

P-CABs show comparable efficacy to PPIs in preventing upper gastrointestinal bleeding in patients with coronary artery disease receiving dual antiplatelet therapy. No significant differences were observed in cardiovascular outcomes or mortality. Although P-CABs offer pharmacologic advantages, current evidence, largely observational, remains low certainty, highlighting the need for randomized controlled trials.

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REVIEW

Effect of Potassium-Competitive Acid Blockers Compared with Proton Pump Inhibitors on Upper Gastrointestinal Bleeding in Patients with Coronary Artery Disease on Dual Antiplatelet Therapy: A Systematic Review and Meta-Analysis

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Abstract

Dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) increases the risk of upper gastrointestinal bleeding (UGIB). Proton pump inhibitors (PPIs) are widely used for gastroprotection but have limitations including delayed onset of action and potential interactions with clopidogrel. Potassium-competitive acid blockers (P-CABs) might provide an alternative with more rapid and consistent acid suppression. This systematic review and meta-analysis of observational studies compared P-CABs versus PPIs for the prevention of UGIB in patients receiving DAPT after PCI. Major literature databases were searched for articles published until March 2026. Risk of bias was assessed with ROBINS-I, and pooled odds ratios (ORs) were estimated with random-effects models. Six cohort studies in 42,304 patients were analyzed. No significant difference in UGIB was observed between P-CABs and PPIs (OR 1.03, 95% CI 0.77–1.37; $I^2 = 4\%$). Sensitivity analysis excluding studies with high risk of bias yielded consistent results (OR 0.96, 95% CI 0.70–1.30). No significant differences were observed in major adverse cardiovascular events or all-cause mortality. The certainty of evidence was very low because of confounding and imprecision. P-CABs appeared comparable to PPIs in preventing UGIB in this population; however, randomized trials are needed.

Keywords: DAPT; UGIB; CAD; P-CABs; PPIs

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Introduction

Dual antiplatelet therapy (DAPT) is the standard of care in patients with coronary artery disease who

have undergone percutaneous coronary intervention (PCI) [1], because it decreases the risk of thrombosis due to periprocedural myocardial damage from blood vessel wall trauma and stent thrombosis [2, 3]. However, it also increases the risk of upper gastrointestinal bleeding (UGIB) [4].

Proton pump inhibitors (PPIs) are used to decrease UGIB risk in patients receiving antithrombotic therapy [5]. Despite being the first-line acid-suppressive therapy, PPIs have many limitations, including slow onset of action; incomplete acid suppression; possible interaction with clopidogrel due to a shared metabolic pathway (CYP2C19); and potential systemic adverse effects, including hypomagnesemia, osteoporosis, pneumonia, dementia, chronic kidney disease, and elevated risk of spontaneous bacterial peritonitis and enteric infections [6, 7].

Potassium-competitive acid blockers (P-CABs) are a new class of acid-suppressive therapies that competitively bind the potassium-binding sites in proton pumps [8]. These drugs, in contrast to PPIs, have a faster onset of action, stronger acid suppression, negligible CYP2C19 interaction, longer half-life, and high tolerability with an excellent safety profile. Therefore, P-CABs provide alternative acid-suppressive drugs for preventing UGIB after PCI [9, 10]. One Japanese cohort study has reported that P-CABs are not inferior to PPIs in decreasing UGIB incidence in patients with ischemic heart disease [11]. Another cohort study has indicated lower UGIB risk in patients receiving P-CABs than PPIs, without an elevated risk of myocardial infarction or all-cause mortality [12].

In this systematic review and meta-analysis, we aimed to evaluate the efficacy of P-CABs versus PPIs in preventing UGIB in patients receiving DAPT after PCI. To our knowledge, this is the first systematic review and meta-analysis addressing this topic.

Methods

Study Design and Data Sources

This systematic review and meta-analysis was conducted in accordance with PRISMA 2020 guidelines [13]. A comprehensive literature search was performed to identify studies comparing P-CABs versus PPIs in patients receiving DAPT after PCI.

Searching Strategy

We systematically searched the PubMed, Scopus, Embase, Cochrane Library, and Web of Science databases from inception to March 2026. Details of the search strategy are provided in Supplementary Table 1.

Eligibility Criteria

We included studies that met the following criteria: (1) any study design (randomized controlled trial [RCT], non-RCT, case-control, or cohort studies) comparing any P-CABs versus any PPIs in patients with coronary artery disease receiving DAPT; (2) studies reporting UGIB as an outcome; and (3) studies published in peer-reviewed journals indexed in major databases. No study design restrictions or language restrictions were applied. Reviews, meta-analyses, case reports, case series, editorials, letters, and conference abstracts were excluded.

Study Selection

Two reviewers (O.S. and H.A.) independently examined the titles and abstracts of the search records according to predefined criteria. Records retrieved from all databases were imported into EndNote 21, and duplicate entries were removed. The remaining records were imported into Rayyan for title and abstract screening. The full texts of the potential target articles were downloaded. In cases of uncertainty or disagreement between reviewers, issues were resolved through discussion with a third reviewer (T.E.).

Data Extraction and Outcomes

Data extraction was performed by two reviewers (A.D. and A.A.) using standardized, pre-designed Excel sheets (2024). The two reviewers independently extracted the data and cross-checked their results. Any disagreements were resolved through consultation with a third reviewer (T.E.). The extracted data included study design; publication year; participant characteristics, e.g., age, sex, and

Table 1 Summary Characteristics of Studies Comparing P-CABs vs PPIs.

Study ID	Year	Study design	Adjustment method	Country	Types of P-CABs vs PPIs	Sample size (N)			Follow-up period	Main study findings	Conclusion
						P-CABs	PPIs	Total			
Tsujita	2020	Retrospective cohort study	Multivariable regression (adjusted HR)	Japan	P-CAB: vonoprazan PPI: esomeprazole, omeprazole, rabeprazole, lansoprazole	779	5276	6055	6 months	The UGIB occurrence with vonoprazan and other PPI treatment in patients receiving DAPT was 2.82% (22/779) and 3.96% (209/5276), respectively; this non-significant difference (aHR 0.74; 95 CI 0.48–1.16; P = 0.189) demonstrated non-inferiority (P < 0.0001).	P-CABs are non-inferior to PPIs in terms of UGIB occurrence over 6 months in patients with IHD receiving DAPT.
Sasaki	2024	Retrospective cohort study	No clear adjustment/ limited adjustment reported	Japan	P-CAB: vonoprazan PPI: lansoprazole, esomeprazole, rabeprazole	153	341	494	24 months	The high bleeding risk rate significantly differed between groups (90.5% and 47.6% in groups A and B, respectively; P = 0.0001). A total of 95.9% of patients were taking PPIs or P-CABs, and no significant differences were found between groups.	PPIs or P-CABs prevent gastric acid-associated UGIB after PCI.
Baik	2025	Retrospective cohort study Propensity score matching	Propensity score matching plus adjusted analysis	South Korea	P-CAB: revaprazan, tegoprazan, fexuprazan PPI: esomeprazole, pantoprazole, lansoprazole, rabeprazole, omeprazole, ilaprazole, dexlansoprazole	9632	9632	19,264	6 months	P-CABs and PPIs, respectively. Overall, 0.3% of patients experienced UGIB within 6 months of PCI. P-CAB users had a lower risk of UGIB (adjusted hazard ratio 0.59; 95% CI 0.38–0.92; P = 0.019) than patients not receiving P-CABs or PPIs. No significant difference was observed between P-CAB and PPI users (P > 0.05).	Among Korean patients undergoing PCI with DAPT, P-CABs decrease UGIB comparably to PPIs. Therefore, P-CABs are potential alternatives to PPIs for preventing UGIB.
Y. J. Lee	2025	Retrospective cohort study Propensity score matching	Propensity score matching	South Korea	P-CAB: fexuprazan, revaprazan, tegoprazan PPI: dexlansoprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, spantoprazole	3434	3434	6868	12 months	No statistically significant difference was found in gastrointestinal bleeding incidence between PPI and P-CAB users among patients receiving DAPT after coronary stent implantation.	Both PPIs and P-CABs are viable acid suppressants in patients receiving DAPT; no significant differences in gastrointestinal outcomes were observed.

Table 1 (continued)

Study ID	Year	Study design	Adjustment method	Country	Types of P-CABs vs PPIs	Sample size (N)			Follow-up period	Main study findings	Conclusion
						P-CABs	PPIs	Total			
Y. Lee	2024	Pharmacoepidemiology cohort study	Descriptive/ no outcome adjustment	South Korea	P-CABs vs PPIs (various)	P-CABs: 166; PPIs: 8853; total: 9019 PPI use increased; P-CABs accounted for 7.8% by 2020			11 years (2009–2020)	Trend analysis indicated growing PPI preference and limited P-CAB uptake	The use of PPIs steadily increased over the study period in patients administered clopidogrel-based DAPT.
J. Lee	2026	Retrospective cohort study	Multivariable regression (inadequate confounding control)	South Korea	Tegoprazan vs PPIs (various)	265	339	604	17 months,	Overt GI bleeding occurred in one patient in the PPI group and none in the tegoprazan group (no significant difference; P = 0.376). The Cox model indicated that tegoprazan had an HR of 0.34 for GI events compared with PPIs (95% CI 0.04–2.97; P = 0.33, indicating no significant difference).	No significant differences were observed in GI- or CV-related complications between patients treated with tegoprazan versus PPIs.

P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; DAPT, dual antiplatelet therapy; UGIB, upper gastrointestinal bleeding; GIB, gastrointestinal bleeding; PCI, percutaneous coronary intervention; IHD, ischemic heart disease; aHR, adjusted hazard ratio; CI, confidence interval; N/A, not applicable.

number of patients; details regarding the intervention and/or control conditions; study methods; outcomes; and follow-up periods. The primary outcome was UGIB. Secondary outcomes included major adverse cardiovascular events (MACE) and all-cause mortality.

Handling of Confounding and Adjustment Methods

Given the observational nature of the included studies, we paid particular attention to the methods used to control for confounding. During data extraction, we recorded whether studies applied adjustment techniques such as propensity score matching, multivariable regression analysis, or stratification.

When available, we preferentially extracted adjusted effect estimates (e.g., adjusted hazard ratios or odds ratios [ORs]) rather than crude estimates. We also documented the covariates included in adjustment models, including demographic characteristics, comorbidities, and concomitant medications.

Quality Assessment

Two reviewers (S.G. and M.B.A.) independently assessed the quality of the included studies with the Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool [14] for observational studies. The specific evaluated domains included bias due to confounding factors, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurements, and selective reporting. Each domain was rated as "low risk," "moderate risk," "serious risk," "critical risk," or "no information," according to methodological rigor. The overall risk of bias for each study was categorized as (1) low concern if most domains were rated low/moderate risk or (2) high concern if one or more domains was rated as having serious/critical risk. Discrepancies in the ratings were resolved through discussion or consultation with a third reviewer (T.E.).

Data Analysis

Review Manager software (RevMan, version 5.4.1) was used to conduct quantitative analysis of dichotomous data. ORs and 95% confidence

intervals (95% CIs) were used to compare the outcomes of P-CABs versus PPIs. Outcomes were pooled with inverse variance. Heterogeneity among studies was considered present if the I^2 statistic was ≥50% or the P-value was ≤0.10. A random-effects model was used. Sensitivity analyses were performed to explore potential sources of heterogeneity.

Sensitivity analyses were conducted by exclusion of studies at serious risk of bias (ROBINS-I) for the primary outcome in R.

Certainty of Evidence

The quality of evidence was independently assessed by two reviewers (T.E. and H.R.M.) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria in five aspects: risk of bias, inconsistency, indirectness, imprecision, and publication bias. In the GRADE approach to quality of evidence, randomized trials without important limitations constitute high-quality evidence, whereas observational studies without special strengths or important limitations constitute low-quality evidence. However, limitations or special strengths can modify the quality of the evidence. The quality of evidence of the included outcomes was graded as high (high confidence that the true effect lies close to the estimate of the effect), moderate (moderate confidence regarding the true effect, which is likely to be close to the estimate of the effect, but could substantially differ), low (limited confidence that the true effect might be close to the estimate of the effect), or very low (very little confidence regarding the true effect, which is likely to substantially differ from the estimate of the effect) [15].

Results

Study Selection

This systematic review was registered with PROSPERO. A PRISMA flowchart illustrating the literature search and selection process is shown in Figure 1. A literature search identified 240 potentially relevant articles, 40 of which were duplicates that were removed in EndNote 21 software. On the basis of a review of the titles and abstracts of the remaining 200 studies in Rayyan, the number was further decreased to 14. After further full-text screening of these 14 studies, only six were deemed eligible and included in the meta-analysis [11, 12, 16–19] (Figure 1 and Supplementary Table 2).

Study Characteristics

The analysis included six observational cohort studies in 42,304 patients receiving DAPT after PCI. Study characteristics and adjustment methods are summarized in Table 1, whereas Table 2 presents the baseline characteristics of the study population.

Two studies used propensity score matching [12, 17], whereas other studies used multivariable regression or provided limited adjustment. Covariates included in the adjustment models are detailed in Supplementary Table 3.

Meta-analysis

Primary Outcome: Upper Gastrointestinal Bleeding

Six studies in 42,304 patients were included in the evaluation of UGIB risk between treatments: 14,429 receiving P-CABs and 27,875 receiving PPIs. Across all studies, UGIB was present in 81 patients in the P-CAB group and 357 patients in the PPI group. The pooled OR was 1.03 (95% CI 0.77–1.37), and no statistically significant difference was observed in the risk of UGIB between P-CABs and PPIs (P = 0.86). The low heterogeneity among studies (I^2 = 4%, P = 0.39) indicated acceptable consistency across trials. Notably, Tsujita et al. [11] reported an OR of 0.70 (95% CI 0.45–1.10) suggesting a possible trend toward lower bleeding risk with P-CABs, although this finding was not statistically significant. Other studies reported variable estimates with CIs crossing unity, thus underscoring the lack of clear superiority of either drug class in preventing UGIB. Overall, our findings indicated that the associated UGIB risk did not significantly differ between P-CABs and PPIs in a broad patient population (Figure 2).

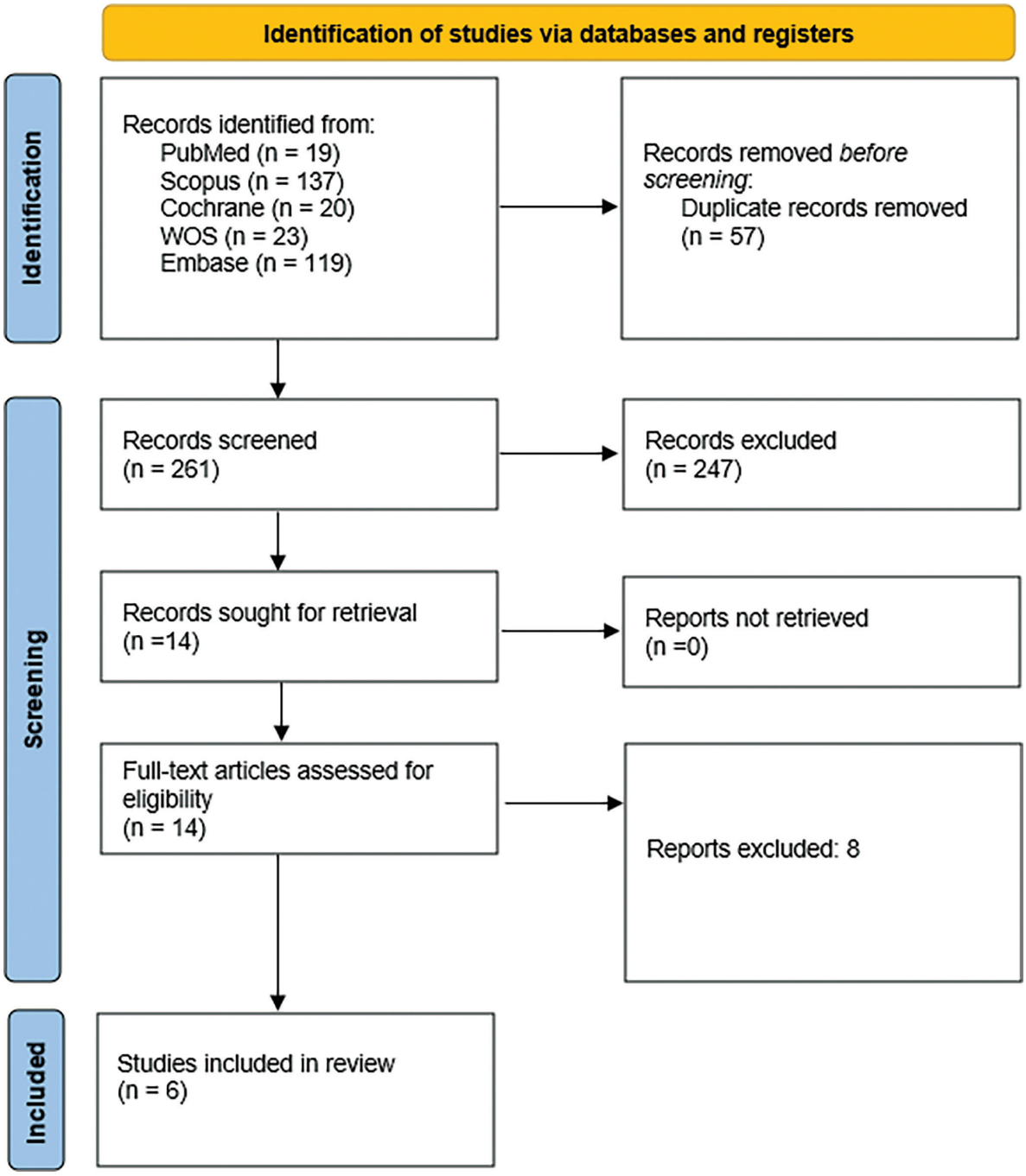

Figure 1 PRISMA Flowchart of the Literature Search and Selection Process.

Secondary Outcomes: Major Adverse Cardiovascular Events and Mortality

Three studies reported MACE [12, 17, 19]. The pooled OR of 0.86 (95% CI 0.66–1.10; P = 0.23) suggested a non-significant trend toward lower risk with P-CABs than PPIs. The negligible heterogeneity (I^2 = 0%) supported consistency across studies.

Three studies reported all-cause mortality [12, 17, 19]. The pooled OR of 1.04 (95% CI 0.73–1.48; P = 0.84) indicated no significant difference between P-CABs and PPIs. The heterogeneity was low (I^2 = 17%). Individual study estimates were

Table 2 Baseline Clinical Characteristics of Patients in the Included Studies.

Study ID	Age, mean (SD)		Sex, no. males (%)		History of GI event, n (%)		Diabetes mellitus, n (%)		HTN, n (%)		NSAIDs, n (%)		Corticosteroids, n (%)	
	P-CAB	PPI	P-CAB	PPI	P-CAB	PPI	P-CAB	PPI	P-CAB	PPI	P-CAB	PPI	P-CAB	PPI
Tsujita 2020	70.0 (11.5)	70.0 (11.6)	1673.1 (75.2%)	10,647.3 (75.0%)	334 (15%)	2128.4 (15%)	N/A				91.3 (4.1%)	595.9 (4.2%)	75.7 (3.4%)	482.4 (3.4%)
Sasaki 2024	72.2 (1.34)		359 (69.7%)		N/A						36 (7%)		18 (3.5%)	
Lee 2025	67.33 (12.6)	67.33 (12.6)	2394 (69.7%)	2388 (69.5%)	130 (3.8%)	120 (3.5%)	1601 (46.6%)	1626 (47.4%)	2366 (68.9%)	2339 (68.1%)	N/A			
Baik 2025	65.7 (11.4)	65.8 (11.3)	7101 (73.7%)	7107 (73.8%)	159 (1.6%)	162 (1.7%)	3676 (38.2%)	3621 (37.6%)	8294 (86.1%)	8299 (86.2%)	491 (5.1%)	500 (5.2%)	158 (1.6%)	166 (1.7%)
Lee 2024	Variable		95 (57%)	5709 (64.4%)	N/A		59 (35.5%)	4088 (46%)	106 (64%)	5994 (67.7%)	N/A			
Lee 2026	63.0 ± 9.2	64.0 ± 8.8	217 (81.9)	267 (78.8)	12 (4.5)	6 (1.8)	83 (31.3)	104 (30.8)	126 (47.5)	163 (48.1)	26 (9.8)	18 (5.3)	N/A	

P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; GI, gastrointestinal; DAPT, dual antiplatelet therapy; GIB, gastrointestinal bleeding; HTN, hypertension; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; N/A, not applicable.

imprecise, particularly that by Lee [19], in a study reporting very few events.

Therefore, P-CABs and PPIs were associated with comparable risks of both MACE and death (Figures 3 and 4).

Risk of Bias Assessment

The risk of bias of the included studies was assessed with the ROBINS-I tool (results summarized in Supplementary Figure 1). Overall, the risk of bias varied across studies, and confounding was identified as the primary source of bias.

Specifically, two studies [12, 17] were judged to have low risk of bias across all domains, a finding reflecting the use of robust adjustment methods, including propensity score matching. One study [11] was assessed as having moderate risk of bias, primarily because of residual concerns regarding confounding.

In contrast, three studies [16, 18, 19] were judged to have serious risk of bias, which was largely driven by inadequate control of confounding, particularly confounding by indication, as well as moderate concerns associated with participant selection and, in one study, missing data.

Across domains, the most frequently identified limitation was bias due to confounding (D1). Several studies lacked sufficient adjustment for key clinical variables. Other domains, including classification of interventions (D3), deviations from intended interventions (D4), measurement of outcomes (D6), and selection of reported results (D7), were generally judged to be at low risk of bias.

Overall, the evidence base was characterized by low to serious risk of bias, and confounding was the predominant methodological concern.

Sensitivity Analysis

To assess the robustness of the primary findings, we conducted sensitivity analyses.

First, we performed a leave-one-out analysis sequentially omitting each study. The pooled estimates remained stable, with effect sizes ranging from an OR of 0.83 (95% CI 0.58–1.20) to 1.26 (95% CI 0.82–1.94), and all CIs crossing unity (Supplementary Figure 2). No single study disproportionately influenced the overall effect estimate.

Second, to further address potential confounding, we performed sensitivity analyses excluding studies at serious risk of bias due to inadequate adjustment for confounders. This analysis yielded a pooled OR of 0.96 (95% CI 0.70–1.30), which was consistent with the primary analysis findings (Supplementary Figure 3).

Overall, the pooled estimates remained consistent, thereby suggesting that the overall findings were robust despite variability in confounding control.

Subgroup Analyses

Because of the limited number of studies and the heterogeneity in adjustment methods, we were unable to perform formal subgroup analyses by adjustment strategy (e.g., propensity score–matched versus non-matched studies).

Publication Bias

Publication bias was not assessed, because of the limited number of studies ($n < 10$), in accordance with the Cochrane Handbook for Systematic Reviews of Interventions guidelines [20].

GRADE Assessment

Six observational studies were included in the GRADE evaluation of UGIB risk associated with P-CABs versus PPIs. The pooled OR of 1.03 (95% CI 0.77–1.37) indicated no statistically significant

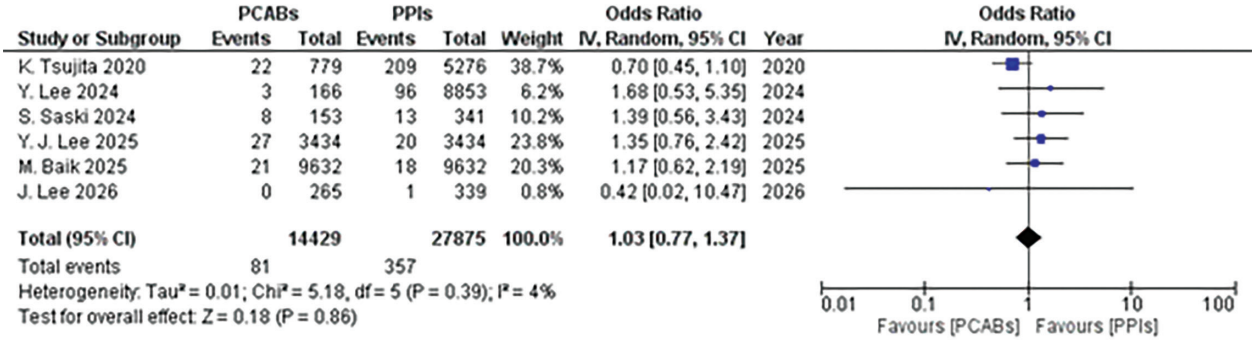

Figure 2 Odds Ratio Forest Plot Comparing UGIB Incidence between P-CABs and PPIs.

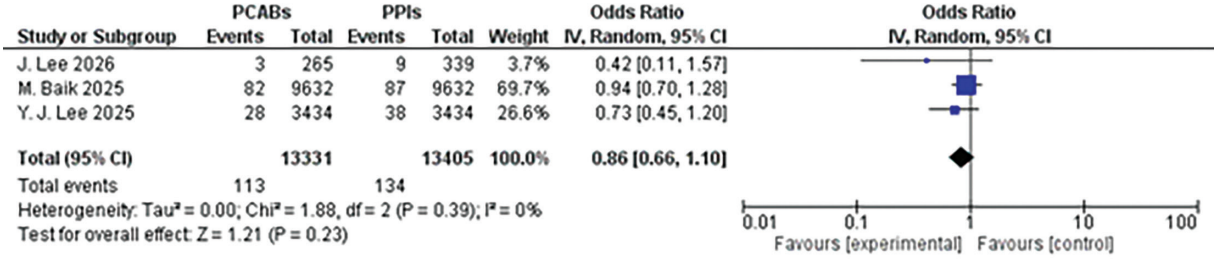

Figure 3 Odds Ratio Forest Plot Comparing MACE Incidence between P-CABs and PPIs.

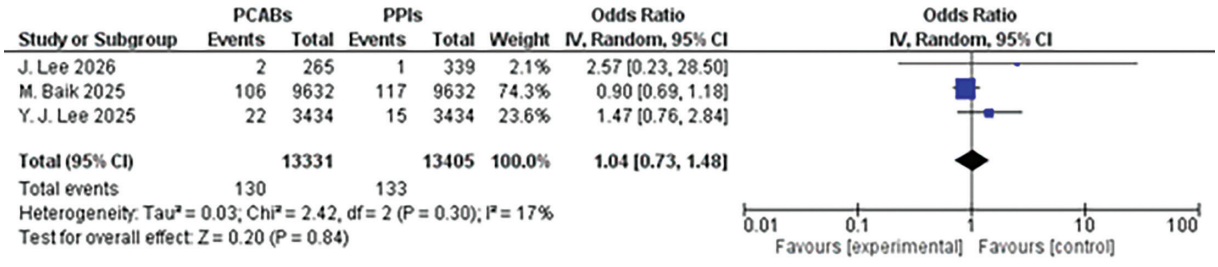

Figure 4 Odds Ratio Forest Plot Comparing Death Incidence between P-CABs and PPIs.

difference between drug classes. The certainty of evidence was rated as very low, thus reflecting downgrading for risk of bias and imprecision. The risk of bias was deemed serious, because of observational study design and residual confounding, and the imprecision was considered serious, because of the relatively small number of UGIB events and the wide CIs. Inconsistency, indirectness, and publication bias were not identified as major concerns.

Overall, the evidence suggested that P-CABs do not confer a clear advantage or disadvantage with respect to PPIs in terms of UGIB risk. However, because of the low certainty rating, further high-quality randomized trials are needed to provide more definitive conclusions (Supplementary Table 4).

Discussion

Our meta-analysis was aimed at evaluating the efficacy of P-CABs versus PPIs in preventing UGIB in patients receiving DAPT after PCI. P-CABs did not show a statistically significant difference in decreasing UGIB incidence below that observed with PPIs (OR 1.03, 95% CI 0.77–1.37; P = 0.86). Therefore, the existing evidence indicated similar UGIB risk between treatments.

Several studies have documented elevated UGIB risk in patients with coronary artery disease undergoing PCI and receiving DAPT [21–23]. The 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guidelines for the Management of Patients with Acute Coronary Syndromes recommend the use of PPIs in patients undergoing PCI who have high risk of gastrointestinal bleeding. Specifically, PPIs are advised in combination with DAPT, oral anticoagulants, or both to mitigate bleeding risk [23].

Despite their widespread use, PPIs have several limitations and adverse effects, including a relatively slow onset of action; incomplete acid suppression; instability under acidic conditions, thus requiring pre-meal dosing; and variable efficacy influenced by CYP2C19 polymorphisms. Because clopidogrel, a key component of DAPT, is activated by CYP2C19, concerns have been raised that PPIs might lower clopidogrel's antiplatelet activity because of shared metabolic pathways. Furthermore, long-term PPI use has been associated with a range of adverse outcomes including hypomagnesemia, osteoporosis, pneumonia, dementia, chronic kidney disease, certain malignancies, and elevated risk of spontaneous bacterial peritonitis and enteric infections [6, 7, 24, 25].

Most studies linking PPIs to adverse events have been observational in design, and high-level evidence from RCTs is lacking. Therefore, potential residual confounding cannot be excluded, and causality remains uncertain [24].

P-CABs are promising alternatives to PPIs that offer a new acid-suppressive therapy by binding the potassium-binding sites of proton pumps. P-CABs have several advantages over PPIs, including more rapid onset, more potent acid suppression, longer half-life, sustained acid suppression, and negligible CYP2C19 interaction [9, 26].

Moreover, unlike PPIs, P-CABs are not affected by intragastric pH or food intake and are not metabolized predominantly by CYP2C19, thus avoiding drug–gene interactions that can compromise efficacy [8, 9, 24, 27, 28]. Vonoprazan, a representative P-CAB, reaches peak plasma levels within 2 hours after administration and inhibits its acid secretion by directly blocking potassium binding to the H^+/K^+ATPase in gastric parietal cells [9, 24].

Tsujita et al. have confirmed the non-inferiority of vonoprazan to PPI in preventing UGIB in patients with ischemic heart disease taking two or more antithrombotic agents, including DAPT [11]. In a Korean cohort study by Baik et al., P-CABs, compared with PPIs, significantly decreased UGIB risk in patients undergoing PCI while receiving DAPT [12]. Another Korean study reported no significant difference in UGIB risk between P-CABs and PPIs [17]. However, data on P-CAB use in PCI patients receiving DAPT are limited, and only several cohort studies were included in our meta-analysis. High-quality RCTs are therefore needed to improve confidence in the current estimates and verify or potentially change the conclusions. One such study is the ongoing PROTECT-HBR trial (NCT04416581), a multicenter, randomized, double-blind clinical trial comparing the P-CAB tegoprazan (50 mg) and the PPI rabeprazole (20 mg) for gastroprotection in high-risk patients receiving antithrombotic therapy. This trial is expected to

provide evidence of the role of P-CABs in preventing UGIB in this vulnerable population [29].

P-CABs have demonstrated efficacy in the treatment of various acid-related disorders. P-CABs have been found to be non-inferior to PPIs in healing gastric ulcers and in preventing UGIB among patients with a history of peptic ulcers who were taking low-dose aspirin for cardiovascular prophylaxis [30, 31]. P-CABs have also been associated with a higher healing rate of severe grades of erosive esophagitis, a lower rate of recurrence in the maintenance phase, and a higher *Helicobacter pylori* eradication rate than PPIs [32, 33].

However, like PPIs, P-CABs are associated with certain risks. Common treatment-emergent adverse events associated with P-CABs include nasopharyngitis, diarrhea, constipation, upper respiratory tract inflammation, falls, gastroenteritis, and eczema, among which nasopharyngitis is the most common, followed by falls [31, 34]. Hypomagnesemia has also been reported with short-term vonoprazan use, because of impaired intestinal magnesium absorption [35, 36]. The comparable safety profile between vonoprazan and lansoprazole in a 5-year RCT by Uemura et al. has suggested that vonoprazan is as safe as PPIs for long-term use [37]. Although data have suggested potentially comparable long-term safety profiles between P-CABs and PPIs, current evidence remains limited. Additional data from long-term clinical trials are required to confirm the safety profile of P-CABs [24].

Vonoprazan was also associated with higher gastrin levels than lansoprazole, in a dose-dependent manner. The increased serum gastrin concentration is believed to be due to vonoprazan's potent gastric acid antisecretory effect [31, 34]. Gastrin increases the proliferation of enterochromaffin-like cells [38]. A 5-year RCT has indicated no significant difference in the incidence of enterochromaffin-like cell hyperplasia between vonoprazan and lansoprazole groups [37].

In terms of cost-effectiveness, Wang et al. have reported a gain of 0.02 QALYs and $943 US associated with the use of vonoprazan versus PPIs for the treatment of reflux esophagitis [39]. Yokoya et al. have also found a higher cost-effectiveness and a gain of 0.14 QALYs associated with the use of a vonoprazan-first strategy than either an esomeprazole-first or rabeprazole-first strategy for GERD treatment [40]. In addition, Jeyarajan et al. have concluded that vonoprazan has potential to be cost-effective in the treatment of patients with severe erosive esophagitis in the healing phase; however, this finding does not apply to mild erosive esophagitis [41].

Clinical Implications

P-CABs might be preferable in patients requiring rapid onset of acid suppression, those with potential CYP2C19-related drug interactions, or those with suboptimal PPI response. However, routine substitution cannot be recommended on the basis of current evidence.

Limitations

Several limitations should be considered in interpreting the findings of this meta-analysis. First, all included studies were observational in design, thus inherently limiting causal inference. Despite the use of adjustment methods such as propensity score matching and multivariable regression in some studies, possible residual confounding, particularly confounding by indication, cannot be excluded. Patients prescribed P-CABs versus PPIs might have systematically differed in their baseline bleeding risk, comorbidities, and clinician prescribing preferences, but these differences might not have been fully captured in the adjusted analyses.

Second, heterogeneity was found in the methodological rigor of confounding control across studies, as highlighted by variability in adjustment strategies and incomplete reporting of covariates. Although we addressed this aspect through ROBINS-I assessment and sensitivity analyses, these approaches cannot fully mitigate bias arising from unmeasured confounders.

Third, the varying outcome definitions (e.g., UGIB) and follow-up durations introduced clinical heterogeneity. Although the statistical heterogeneity was low, such differences might still have influenced the comparability of the results.

Fourth, the relatively small number of events and included studies limited statistical power, particularly for secondary outcomes and subgroup analyses, and precluded formal assessment of publication bias.

Finally, because all studies were conducted in East Asian populations, the generalizability of the findings to other geographic and ethnic groups might be limited.

Given these limitations, the present findings should be interpreted as associative rather than causal. Therefore, adequately powered, randomized controlled trials are needed to provide more definitive evidence.

Beyond bleeding outcomes, our analysis examined MACE and all-cause mortality, and indicated comparable risks between P-CABs and PPIs. Although these results reinforce the overall conclusion of similar efficacy, the limited number of events and incomplete reporting of baseline characteristics (e.g., hypertension and diabetes) limit confidence in extrapolation of the findings to broader high-risk populations.

The overall certainty of evidence, assessed with the GRADE framework, was rated as very low, reflecting downgrading for risk of bias and imprecision. Although P-CABs offer pharmacological advantages over PPIs, such as faster onset of action and negligible CYP2C19 interaction, the current evidence base is insufficient to recommend routine substitution for PPIs. Well-designed randomized controlled trials are urgently needed to confirm these findings, clarify subgroup effects (e.g., acute myocardial infarction versus chronic ischemia), and evaluate long-term safety and cost-effectiveness.

The main strength of this pooled study is its comparison of the efficacy of P-CABs versus PPIs in preventing UGIB in patients receiving DAPT after PCI, with low heterogeneity indicating consistency across studies. To our knowledge, this study is the first meta-analysis to address this issue.

Conclusion

In patients receiving DAPT after PCI, P-CABs appear to have similar effectiveness to PPIs in preventing UGIB, and no significant differences were observed in cardiovascular outcomes or all-cause mortality.

However, the certainty of evidence was low, because of the observational nature of the included studies, the risk of confounding by indication, and imprecise effect estimates. Although sensitivity analyses yielded consistent findings, potential residual confounding cannot be excluded.

Further well-designed randomized controlled trials are required to establish the comparative effectiveness and safety of P-CABs versus PPIs in this population.

Ethics Statement

No direct interactions with human or animal subjects were involved. Therefore, ethical approval and informed consent were not required.

Author Contributions

Taher Elmozugi: Conceptualization, Software, Writing—Reviewing and Editing, Formal analysis, Project administration.

Motasam Belah Al Swayah: Data curation, Writing—Original draft preparation.

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Asma Daoud: Visualization, Investigation, Writing—Original draft preparation.

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Shrook Gomaa: Methodology, Writing—Reviewing and Editing.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Supplementary Material

Supplementary Material can be found at the following link: https://cvia-journal.org/wp-content/uploads/2026/07/Supplementary_Tables.pdf.

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