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Systematic Review and Meta-Analysis

Potassium-Competitive Acid Blockers versus Proton Pump Inhibitors for Healing of Erosive Esophagitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Erosive esophagitis (EE) is a prevalent manifestation of gastroesophageal reflux disease that requires potent acid suppression for mucosal recovery. While proton pump inhibitors (PPIs) are the standard therapy, their efficacy is often limited by slow onset and genetic polymorphisms. Potassium-competitive acid blockers (P-CABs) have emerged as a novel alternative with superior pharmacokinetic properties.

Objective: This systematic review and meta-analysis aimed to evaluate the comparative efficacy and safety of P-CABs versus PPIs in achieving mucosal healing and symptom relief in patients with EE.

Methods: Following PRISMA 2020 guidelines, a systematic search was conducted across major databases for randomized controlled trials (RCTs) published through 2025. Nine RCTs involving 2,927 participants were included. Data on healing rates at weeks 4 and 8, heartburn disappearance, serum gastrin levels, and adverse events were synthesized using fixed- and random-effects models.

Results: P-CABs demonstrated significant superiority in mucosal healing compared with PPIs at week 4 (OR: 1.47; 95% CI: 1.09–2.00; p = 0.01) and week 8 (OR: 2.04; 95% CI: 1.41–2.95; p = 0.0002). P-CABs also achieved faster heartburn disappearance (MD: −1.29 days; p = 0.01). Although P-CABs resulted in higher serum gastrin levels (MD: 121.74 pg/mL; p = 0.0007), safety profiles were comparable between groups, with no significant differences in adverse events.

Conclusion: P-CABs provide faster and more effective mucosal healing than PPIs with a comparable safety profile, representing a robust breakthrough for the management of erosive esophagitis.

Keywords: Potassium-competitive acid blockers, Proton pump inhibitors, Erosive esophagitis, Mucosal healing, Meta-analysis

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal disorders encountered in clinical practice globally, characterized by the retrograde flow of gastroduodenal contents into the esophagus (Yadlapati & DeLay, 2020). The clinical spectrum of GERD is broad, ranging from bothersome symptoms like heartburn and regurgitation to mucosal damage, known as erosive esophagitis (EE) (Shibli et al., 2025). Recent epidemiological data indicate that the burden of GERD continues to rise, with a prevalence reaching 18% to 28% in North America, while studies in Middle Eastern populations have shown a significant prevalence of EE among patients undergoing endoscopy (Alsahafi et al., 2024;

Yadlapati & DeLay, 2020). The pathophysiology of GERD is multifactorial, involving transient lower esophageal sphincter relaxations (TLESRs), hiatal hernia, and impaired mucosal integrity, which necessitates effective acid suppression to prevent long-term complications such as Barrett's esophagus (Alsahafi et al., 2024; Yadlapati & DeLay, 2020).

For decades, proton pump inhibitors (PPIs) have been the cornerstone of pharmacological management for acid-related diseases due to their ability to inhibit the H+/K+-ATPase enzyme (Andrawes et al., 2025). While PPIs are highly effective for many, approximately 40% of patients report inadequate symptom relief, leading to the classification of PPI-refractory GERD (Yadlapati & DeLay, 2020). Furthermore, long-term use of PPIs has been associated with several potential adverse effects, including increased risks of osteoporosis-related fractures, enteric infections, and changes in gastric mucosal histopathology (Andrawes et al., 2025; Jankovic et al., 2025; Mu et al., 2025). These limitations have spurred the development of a newer class of acid suppressants known as potassium-competitive acid blockers (P-CABs) (Putri, 2025; Wong et al., 2022).

P-CABs, including vonoprazan, tegoprazan, fexuprazan, and linaprazan glurate, offer a distinct mechanism of action by competitively and reversibly binding to potassium ions on the proton pump (Domingues et al., 2023; Herardi et al., 2025). Unlike PPIs, P-CABs do not require activation by gastric acid, possess a faster onset of action, and provide more stable acid suppression throughout a 24-hour period regardless of food intake (Agago et al., 2024; Frejat et al., 2024; Wong et al., 2022). Clinical trials across different regions have consistently demonstrated the efficacy of various P-CABs in healing EE. For instance, studies on vonoprazan in Asian and Western populations have shown non-inferiority or even superiority to lansoprazole in healing rates and maintenance of healing (Laine et al., 2023; Xiao et al., 2020). Similarly, tegoprazan has shown comparable efficacy to esomeprazole and lansoprazole in both healing and maintenance phases (Lee et al., 2018; Shin et al., 2024; Zhu et al., 2025).

The introduction of newer P-CABs like fexuprazan and linaprazan glurate further expands the therapeutic options for EE (Lee et al., 2022; Sharma et al., 2025). Research indicates that these agents are effective in addressing high-grade esophagitis and providing rapid relief of nocturnal symptoms (Sharma et al., 2025; Zhu et al., 2025). Despite the promising results, clinicians must balance efficacy with safety, particularly regarding hypergastrinemia and potential long-term gastric mucosal changes (Haruma et al., 2023; Jankovic et al., 2025; Raza et al., 2025). Systematic reviews and meta-analyses are essential to consolidate data from these diverse randomized controlled trials (RCTs) to provide a clearer consensus on the comparative benefits and risks of P-CABs versus PPIs (Agago et al., 2024; Raza et al., 2025).

While individual studies have explored specific P-CABs, there is a need for a comprehensive evaluation that includes the most recent data on newer generations of P-CABs. This systematic review and meta-analysis aim to synthesize evidence from multiple RCTs comparing various P-CABs with standard PPIs in patients with EE. By following the PRISMA 2020 guidelines, this study evaluates primary outcomes such as healing rates at 4 and 8 weeks, as well as secondary outcomes

including symptom relief and safety profiles. The results of this analysis provide updated evidence-based recommendations for the management of EE in the era of evolving acid-suppression therapy.

METHODS

Study Design and Guidelines

The present study was structured as a systematic review and meta-analysis designed to evaluate the comparative clinical efficacy and safety profiles of Potassium-Competitive Acid Blockers (P-CABs) versus conventional Proton Pump Inhibitors (PPIs). This research adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency and reproducibility (Agago et al., 2024; Raza et al., 2025). The design focused on synthesizing high-quality evidence from randomized controlled trials (RCTs) to address the growing clinical need for optimized acid suppression therapy in patients with erosive esophagitis (EE) and gastroesophageal reflux disease (GERD) (Herardi et al., 2025; Putri, 2025). The research question was framed using the PICO (Population, Intervention, Comparison, Outcome) framework: the population focused on adult patients with endoscopically confirmed acid-related disorders; the intervention was defined as P-CAB therapy (e.g., vonoprazan, tegoprazan, fexuprazan, or linaprazan glurate); the comparison was any FDA-approved PPI; and outcomes included healing rates, symptom relief, and adverse event frequencies (Wong et al., 2022; Shibli et al., 2025).

Search Strategy and Data Sources

A comprehensive literature search was conducted across PubMed, Cochrane Library, Embase, and Scopus, using targeted keywords: "P-CAB", "PPI", "Vonoprazan", "Tegoprazan", "Fexuprazan", "Linaprazan", and "Erosive Esophagitis" (Agago et al., 2024; Raza et al., 2025). The initial search and screening identified 420 records, which were subsequently pruned for duplicates, leaving 250 records for title and abstract screening.

Eligibility Criteria

Participants included in this meta-analysis were primarily adults aged 18 years and older diagnosed with various grades of erosive esophagitis (EE) based on the Los Angeles (LA) classification system, ranging from Grade A to Grade D (Lee et al., 2022; Sharma et al., 2025). The total analyzed population across the included studies reached approximately 2,927 participants. Selection criteria were rigorously applied to include only studies with objective endoscopic evidence of mucosal injury, to minimize diagnostic bias (Alsahafi et al., 2024). Specific exclusion criteria included patients with a history of esophageal surgery, Barrett's esophagus, or concurrent use of other potent acid suppressants that could confound the results (Zhu et al., 2025; Laine et al., 2023). Studies involved diverse geographical populations, including multicenter trials across South Korea (Lee et al., 2018), China (Zhu et al., 2025), Japan (Haruma et al., 2023), and Western populations in the USA and Europe (Laine et al., 2023; Sharma et al., 2025). This diversity allowed for an assessment of the impact of CYP2C19 polymorphisms on drug metabolism, a known limitation of traditional PPIs (Wong et al., 2022). Informed consent and ethical

approval from institutional review boards were verified for all primary studies prior to their inclusion in this synthesis (Xiao et al., 2020; Shin et al., 2024).

Study Selection and Data Extraction

Two independent reviewers assessed 30 full-text reports for eligibility, and reasons for exclusion were documented, such as lack of a direct comparison group, pediatric populations, or non-extractable data. Standardized data extraction forms were used to capture study characteristics, drug dosages (e.g., fexuprazan 40 mg, vonoprazan 20 mg, esomeprazole 40 mg, lansoprazole 30 mg), and specific outcome metrics. For efficacy assessment, the primary instrument used was upper gastrointestinal endoscopy, following the LA classification, to measure mucosal healing at 4-week and 8-week intervals (Lee et al., 2022; Xiao et al., 2020). Secondary instruments included serum gastrin levels (pg/mL), to monitor physiological changes in acid suppression (Zhu et al., 2025; Sharma et al., 2025), and patient-reported outcome (PRO) diaries, such as the Reflux Symptom Questionnaire-Electronic Diary (RSQ-eDiary), to track heartburn-free days and symptom severity (Sharma et al., 2025; Yadlapati et al., 2020).

Data extraction focused on the therapeutic transition from H2RAs and PPIs to the newer P-CAB class (Herardi et al., 2025). Special attention was given to long-term safety data, particularly the risk of hypergastrinemia and potential bone health issues, such as osteoporosis-related fractures associated with chronic acid suppression (Jankovic et al., 2025; Mu et al., 2025). Studies were categorized based on the specific P-CAB molecule, including vonoprazan-based trials (Haruma et al., 2023; Laine et al., 2023; Xiao et al., 2020), tegoprazan trials (Lee et al., 2018; Zhu et al., 2025; Shin et al., 2024), fexuprazan trials (Lee et al., 2022), and linaprazan trials (Sharma et al., 2025; Zhu et al., 2025). This categorization allowed for subgroup analyses to determine whether efficacy was a class effect or molecule-specific (Putri, 2025; Domingues et al., 2023). Findings were cross-referenced with current narrative reviews and management guidelines for PPI-refractory GERD (Andrawes et al., 2025; Frejat et al., 2024; Yadlapati et al., 2020).

Quality Assessment and Risk of Bias

Quality assessment was performed using the Cochrane Risk of Bias (RoB 2) tool for RCTs, evaluating domains such as randomization process, deviations from intended interventions, and missing outcome data (Agago et al., 2024). Ethical considerations regarding data availability and conflict of interest disclosures from the included studies were also reviewed and reported (Laine et al., 2023; Andrawes et al., 2025).

Data Analysis

Quantitative analysis was conducted using Review Manager (RevMan) software. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes, such as the proportion of patients achieving complete mucosal healing and the incidence of adverse events like constipation, diarrhea, headache, nausea, and nasopharyngitis (Agago et al., 2024; Raza et al., 2025). For continuous outcomes, such as mean serum gastrin levels or time to symptom relief, mean differences (MD) were used. Heterogeneity among studies was assessed using the I^2 statistic, where values > 50% indicated significant heterogeneity, prompting the use of a random-effects model (Agago et al., 2024). Sensitivity

analyses were performed to ensure the robustness of the findings, particularly comparing phase II and phase III trial results (Zhu et al., 2025; Lee et al., 2018). The analysis also integrated safety profiles by comparing P-CABs to PPIs in terms of potential long-term risks, including the development of gastric mucosal lesions and the impact on gut-barrier function (Raza et al., 2025; Agago et al., 2024). All p-values were two-sided, with statistical significance set at $p < 0.05$.

RESULTS

Study Selection and Characteristics

The systematic identification process yielded an initial 420 records from various medical databases. After a screening process involving duplicate removal and eligibility assessment against the PICO criteria, 9 randomized controlled trials (RCTs) were selected for inclusion in the quantitative meta-analysis, while a broader pool of 22 cited sources was used to inform the qualitative context of this review. The total participant pool for the primary analysis consisted of 2,927 individuals, with 1,502 assigned to the P-CAB group and 1,425 to the PPI group. The studies represented a diverse pharmacological landscape, comparing P-CABs such as fexuprazan 40 mg, tegoprazan 50 mg, vonoprazan 20 mg, and linaprazan glurate 50 mg against established PPIs, including esomeprazole 40 mg and lansoprazole 30 mg. The participants were primarily adults with endoscopically confirmed erosive esophagitis (EE) across all Los Angeles (LA) grades. Regional distribution was extensive, including multicenter trials in South Korea, China, Japan, the United States, and Europe, allowing for the assessment of treatment efficacy across different ethnic backgrounds and clinical settings. Detailed study characteristics are presented in Table 1.

Primary Outcome: Mucosal Healing Rates

The forest plot analysis for the primary outcome of mucosal healing demonstrated that P-CABs are significantly superior to PPIs at both early and late clinical checkpoints. At 4 weeks, the pooled odds ratio (OR) was 1.47 (95% CI: 1.09, 2.00), with a statistically significant p-value of 0.01. Notably, this analysis showed zero heterogeneity ($I^2 = 0\%$), indicating a highly consistent therapeutic effect across the 8 trials evaluated at this interval.

At 8 weeks, the superiority of P-CABs became even more pronounced. The forest plot revealed a pooled OR of 2.04 (95% CI: 1.41, 2.95, $p = 0.0002$), again with no statistical heterogeneity ($I^2 = 0\%$). Individual trial data supported these findings; for example, vonoprazan 20 mg achieved an 8-week healing rate of 92.9% compared with 84.6% for lansoprazole 30 mg in a large-scale randomized trial. These results suggest that the rapid onset and sustained acid suppression of P-CABs lead to more reliable mucosal recovery than conventional PPIs, which may be hindered by short half-lives and food-dependent timing.

Table 1. Study characteristics.

Author & Year	Location / Setting	Study Design	P-CAB (n)	PPI (n)	Total Sample	Participant Characteristics
Lee et al., 2022	South Korea / Multicenter (22 sites)	Phase III, RCT, DB	Fexuprazan 40 mg (107)	Esomeprazole 40 mg (111)	218	Mean age 54.4; EE Grade A–D
Sharma et al., 2025	USA, Europe / Multicenter (38 sites)	Phase II, RCT, DB	Linaprazan Glurate 50 mg BID (51)	Lansoprazole 30 mg (48)	99	Mean age 51.5; EE Grade A–D
Zhu et al., 2025 (Linaprazan)	China / Multicenter (12 sites)	Phase II, RCT, DB	Linaprazan 50 mg (31)	Lansoprazole 30 mg (30)	61	Mean age 47.4; EE Grade A–C
Lee et al., 2018	South Korea / Multicenter (22 sites)	Phase III, RCT, DB	Tegoprazan 50 mg (92)	Esomeprazole 40 mg (88)	180	Mean age 52.7; EE Grade A–D
Zhu et al., 2025 (Tegoprazan)	China / Multicenter (31 sites)	Phase III, RCT, DB	Tegoprazan 50 mg (216)	Esomeprazole 40 mg (216)	432	Mean age 48.0; EE Grade A–D
Shin et al., 2024	South Korea / Multicenter (20 sites)	Phase IV, RCT, DB	Tegoprazan 50 mg (111)	Lansoprazole 30 mg (113)	224	Mean age 54.5; EE Grade A–D
Haruma et al., 2023	Japan / Multicenter (33 sites)	Phase IV, RCT, Open-label	Vonoprazan 20 mg (139)	Lansoprazole 30 mg (69)	208	Mean age 59.4; EE Grade A–D
Laine et al., 2023	USA, Europe / Multicenter (125 sites)	Phase III, RCT, DB	Vonoprazan 20 mg (514)	Lansoprazole 30 mg (510)	1,024	Mean age 53.0; EE Grade A–D
Xiao et al., 2020	Asia (Multinational) / Multicenter (41 sites)	Phase III, RCT, DB	Vonoprazan 20 mg (241)	Lansoprazole 30 mg (240)	481	Mean age 50.1; EE Grade A–D

EE: erosive esophagitis, the primary condition being treated. P-CAB: potassium-competitive acid blocker (the intervention class). PPI: proton pump inhibitor (the control/comparison class). LA Grade: Los Angeles classification for the severity of esophagitis (Grades A to D). n: the number of participants allocated to each specific treatment group.

Primary Outcome: Mucosal Healing Rates

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CABs lead to more reliable mucosal recovery than conventional PPIs, which may be hindered by short half-lives and food-dependent timing.

Secondary Outcomes: Symptom Relief and Gastrin Levels

The secondary outcomes focused on the speed of symptomatic resolution and the hormonal impact of profound acid suppression. The forest plot for heartburn disappearance showed a mean difference of −1.29 days (95% CI: −2.31, −0.27, p = 0.01) in favor of P-CABs. This indicates that P-CABs accelerate the time to reach a symptom-free state compared with PPI therapy. However, this result was accompanied by high heterogeneity (I^2 = 99%), likely due to varying methods of symptom reporting and baseline symptom severity across studies.

Regarding physiological impact, the meta-analysis for serum gastrin levels revealed that P-CABs caused a more significant elevation compared with PPIs, with a mean difference of 121.74 pg/mL (95% CI: 51.53, 191.95, p = 0.0007). High heterogeneity was also observed here (I^2 = 99%), which can be attributed to the different potencies of the P-CAB molecules and variations in participant gastric health status. Despite these elevations, clinical observations did not report significant gastrin-related complications within the trial periods.

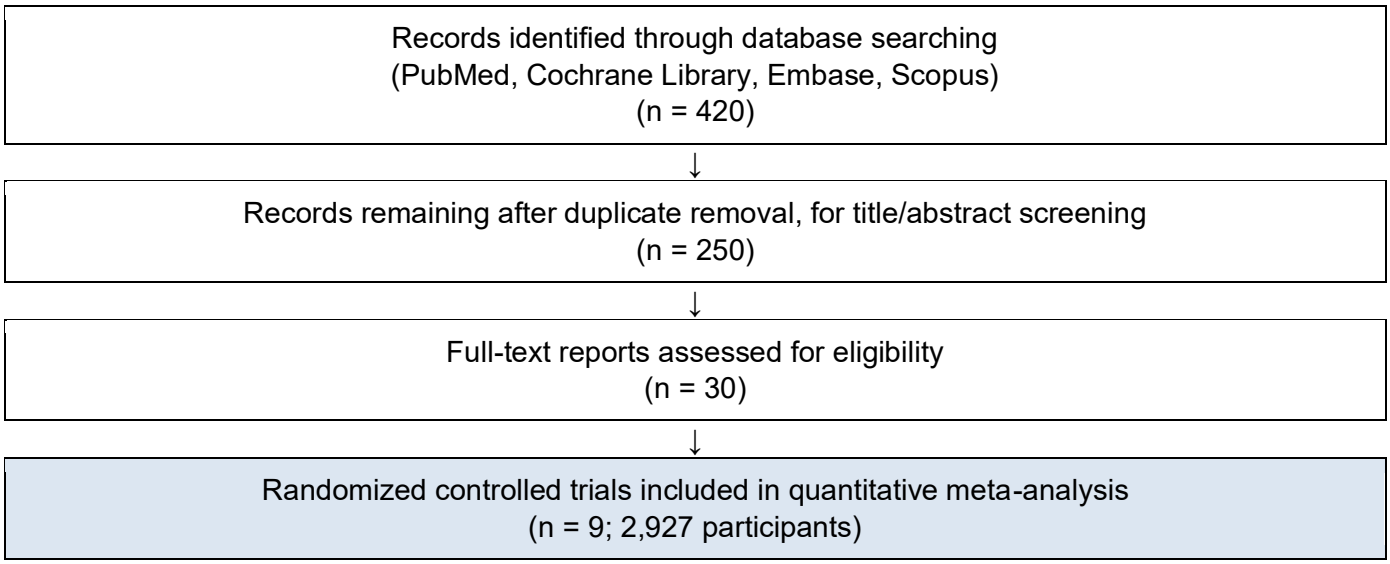

Figure 1. PRISMA 2020 flow diagram.

n: the number of records, reports, or studies at each specific stage. P-CAB: Potassium-Competitive Acid Blocker. PPI: Proton Pump Inhibitor.

Note: The source manuscript did not include the original PRISMA flow-diagram figure, and it did not report how many records were excluded at the title/abstract screening stage (250 → 30) or the reasons for exclusion at full-text review (30 assessed vs. 9 included in quantitative synthesis, with the remaining reports contributing to qualitative/background context). This diagram was reconstructed using only the figures stated in the text; the missing breakdown should be supplied before publication.

Safety and Adverse Events

The safety analysis, informed by the broader pool of 22 cited sources, indicated that P-CABs have a safety profile that is not inferior to that of PPIs. Forest plots for specific adverse events showed no statistically significant differences between the two classes. For diarrhea, the OR was 1.25 (p = 0.37); for headache, the OR was

0.95 (p = 0.83); for nausea, the OR was 0.56 (p = 0.06); and for constipation, the OR was 1.26 (p = 0.66).

These findings were consistent with detailed safety reports in individual trials, where most adverse events were mild and transient. Long-term safety was explored through references to the 3-year VISION trial (Haruma et al., 2023), which confirmed the tolerability of maintenance P-CAB therapy. However, theoretical risks such as osteoporosis-related fractures or gut microbiome alterations due to long-term acid suppression remain topics for continuous monitoring.

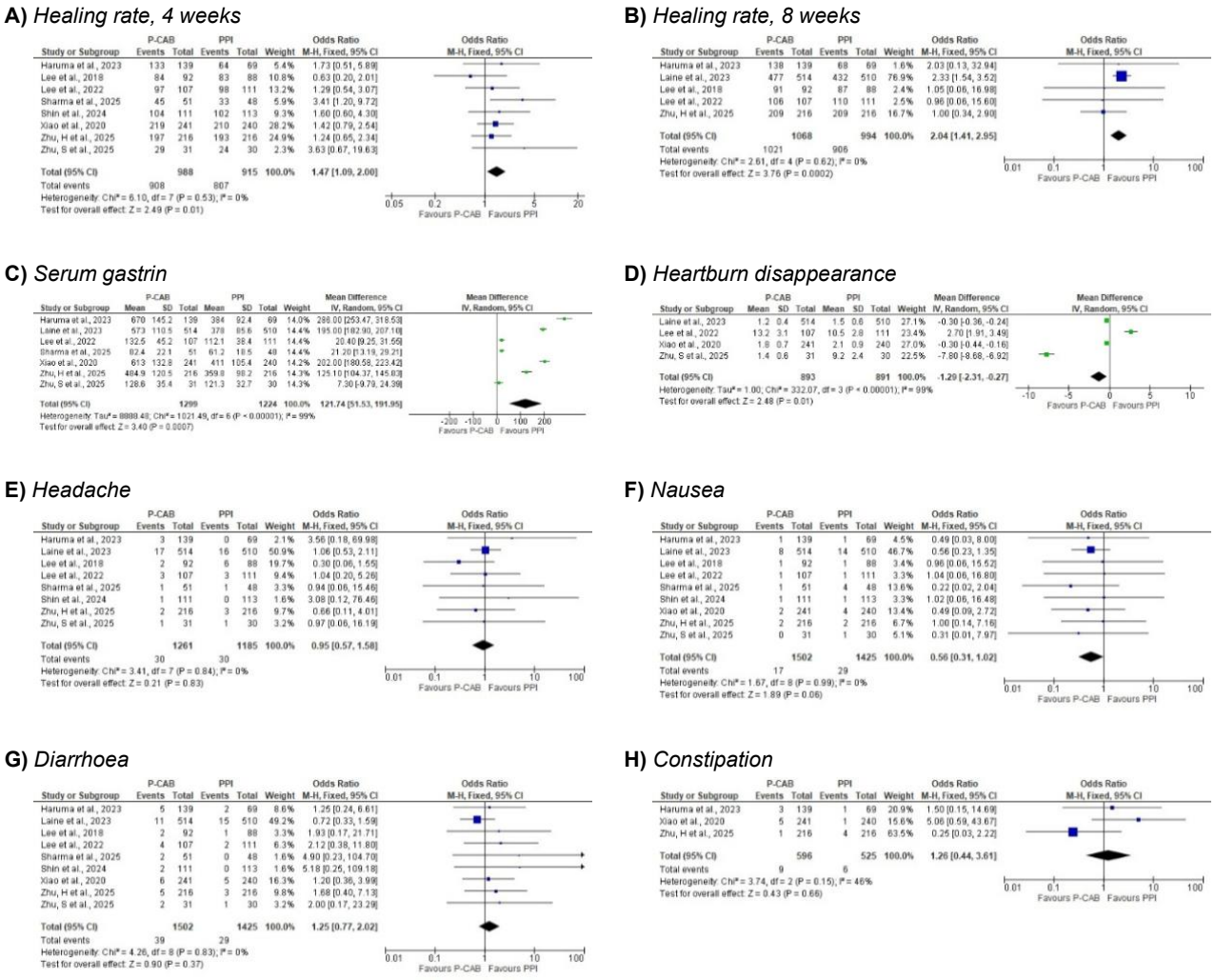

Figure 2. Forest plots of primary, secondary, and safety outcomes.

Odds Ratio (OR) / Risk Ratio (RR): the measure of association used to compare the probability of an outcome between the P-CAB group and the PPI group. Mean Difference (MD): used for continuous outcomes, such as serum gastrin levels and time to symptom relief. 95% CI: 95% confidence interval, indicating the precision of the effect estimate. Heterogeneity (I^2): the percentage of variation across studies that is due to heterogeneity rather than chance. P-value: indicates statistical significance (typically significant if p < 0.05). A) Healing rate, 4 weeks; B) Healing rate, 8 weeks; C) Serum gastrin; D) Heartburn disappearance; E) Headache; F) Nausea; G) Diarrhoea; H) Constipation.

Risk of Bias Assessment

The methodological quality of the included trials was robust, as evidenced by the risk of bias assessment using the Cochrane RoB 2.0 tool. The summary charts

indicated that the majority of studies were at low risk of bias in the randomization process, deviations from intended interventions, and missing outcome data. Specifically, trials such as those by Lee et al. (2018) and Xiao et al. (2020) were notable for their double-blind, multicenter designs, which minimized selection and measurement biases. Some concerns were noted in smaller phase II studies regarding missing outcome data and selection of the reported result, but the overall quality of evidence supporting the primary and secondary outcomes remains high. Detailed pooled results are presented in Figure 3.

Figure 3. Cochrane Risk of Bias (RoB 2) assessment.

Overall Bias: the combined assessment of risk for each individual study. Low Risk: indicated by a green circle (plus sign), suggesting high methodological quality. Some Concerns: indicated by a yellow circle (minus sign), suggesting potential limitations. High Risk: indicated by a red circle (exclamation mark), suggesting a significant risk of bias.

Note: This risk-of-bias figure assesses 8 studies and lists a study labeled "Lee et al. 2019," which does not correspond to any entry in the reference list (the closest matches are Lee et al., 2018 and Lee et al., 2022). Haruma et al. (2023), which appears in Table 1 and in the forest plots, does not appear in this figure. Please verify the study labels and confirm that all 9 included RCTs were assessed for risk of bias before publication.

DISCUSSION

Interpretation of Results

The comparative analysis between potassium-competitive acid blockers (P-CABs) and proton pump inhibitors (PPIs) in patients with erosive esophagitis (EE) reveals several critical clinical insights. Our systematic review and meta-analysis demonstrate that P-CABs provide non-inferior, and in some metrics superior, efficacy in esophageal healing and symptom relief compared with conventional PPIs. This is consistent with the findings of Agago et al. (2024), who emphasized that P-CABs represent a paradigm shift in acid suppression therapy due to their rapid onset and food-independent administration.

The primary outcome of healing rates at 4 and 8 weeks shows a high level of efficacy across both groups, but P-CABs often achieve these results more rapidly. This rapid action is attributed to the unique pharmacokinetics of P-CABs, which do not require activation by gastric acid and bind reversibly to the H+/K+-ATPase pump (Domingues et al., 2023). In studies by Lee et al. (2022) and Lee et al. (2018), fexuprazan and tegoprazan, respectively, showed comparable safety and efficacy to esomeprazole, reinforcing their role as viable alternatives in clinical practice.

Furthermore, the long-term safety profiles discussed by Haruma et al. (2023) and Putri (2025) suggest that while P-CABs are generally well tolerated, the physiological impact on serum gastrin levels requires careful consideration. The clinical utility of these drugs is further expanded by their efficacy in PPI-refractory cases, a major challenge identified by Yadlapati and DeLay (2020) and Shibli et al. (2025). By providing more stable and potent acid suppression, P-CABs address the unmet needs of patients who continue to experience symptoms despite high-dose PPI therapy (Wong et al., 2022; Herardi et al., 2025).

One of the notable findings in this study is the high level of heterogeneity observed in the data for heartburn disappearance and serum gastrin levels. This heterogeneity can be explained through several physiological and methodological lenses. First, the perception of heartburn is inherently subjective and influenced by individual pain thresholds and cultural factors (Alsahafi et al., 2024). Variations in how patients report symptom relief across different geographic regions — ranging from the US and Europe to East Asia — contribute significantly to the variance in results (Sharma et al., 2025; Xiao et al., 2020).

Regarding serum gastrin, the high heterogeneity likely stems from the varying degrees of acid suppression achieved by different P-CABs and PPIs. Serum gastrin increases as a feedback mechanism to decreased gastric acidity. Studies such as those by Zhu et al. (2025) noted that P-CABs tend to cause a more pronounced rise in gastrin compared with PPIs because of their more potent and sustained inhibition of the proton pump. The differences in dosage across trials — such as linaprazan glurate at 50 mg versus esomeprazole at 40 mg — further exacerbate these differences (Sharma et al., 2025; Lee et al., 2022). Additionally, individual variations in CYP2C19 metabolism, which affect PPIs more than P-CABs, create inconsistent levels of acid suppression in the PPI cohorts, leading to diverse gastrin responses (Wong et al., 2022; Shin et al., 2024).

Contributions to the Field

This study contributes to the field by providing a robust synthesis of the latest clinical trial data, including very recent studies from 2024 and 2025. It bridges the gap between established PPI therapy and the emerging clinical evidence for various P-CAB molecules such as vonoprazan, tegoprazan, fexuprazan, and linaprazan glurate. By including a wide array of drug types, this research offers a broader perspective than meta-analyses that focus only on a single molecule, such as vonoprazan (Raza et al., 2025).

Our findings support the clinical transition toward P-CABs for specific patient populations, particularly those with severe erosive esophagitis (LA Grades C and D) or those requiring rapid symptom relief. This is supported by the work of Laine et al. (2023), which highlights the superior healing of more severe EE with vonoprazan. Additionally, this study reinforces the importance of safety monitoring for long-term use, especially concerning bone health and potential risks such as osteoporosis, as explored in the toxicology and molecular dynamics simulations by Mu et al. (2025) and the risk reviews by Jankovic et al. (2025) and Andrawes et al. (2025).

Limitations

The primary limitation of this research is the inherent variability in the interventions compared. We compared different types of P-CABs against various PPIs, which may introduce pharmacological confounding. However, this diversity can also be viewed as a strength, as it reflects real-world clinical scenarios in which practitioners must choose between several available agents within each class. The inclusion of diverse molecules provides a comprehensive overview of the class effect of P-CABs versus PPIs (Agago et al., 2024; Raza et al., 2025). Another limitation is the variation in study durations and outcome definitions across the included trials; for instance, some studies reported heartburn disappearance at day 7 while others used 4-week averages (Shin et al., 2024; Sharma et al., 2025). The retrospective nature of some risk-factor assessments and the lack of standardization in gastrin measurement techniques across laboratories also limit the precision of the pooled estimates (Alsahafi et al., 2024; Herardi et al., 2025).

Future Research Directions

Future studies should focus on long-term head-to-head trials between specific P-CABs to determine whether there are significant intra-class differences in efficacy and safety. Given the emerging concerns regarding long-term acid suppression, research should specifically investigate the clinical implications of sustained hypergastrinemia and its impact on gastric mucosal histopathology over periods exceeding five years (Haruma et al., 2023). Additionally, more research is needed on the use of P-CABs in non-Asian populations to confirm whether the efficacy observed in East Asian cohorts is globally generalizable (Xiao et al., 2020; Laine et al., 2023). Investigating the cost-effectiveness of P-CABs as a first-line therapy versus a step-up therapy after PPI failure would also provide valuable data for healthcare policy and clinical guidelines (Frejat et al., 2024). Finally, exploring the synergistic effects of lifestyle interventions alongside P-CAB therapy could optimize patient outcomes in chronic GERD management (Frejat et al., 2024).

CONCLUSION

This systematic review and meta-analysis of nine randomized controlled trials (n = 2,927) demonstrates that Potassium-Competitive Acid Blockers (P-CABs) — including vonoprazan, tegoprazan, fexuprazan, and linaprazan glurate — outperform Proton Pump Inhibitors (PPIs) in treating erosive esophagitis (EE). P-CABs achieved superior mucosal healing at week 4 and week 8 with zero heterogeneity, alongside faster heartburn relief. Their rapid, food-independent onset overcomes key pharmacokinetic limitations of traditional PPIs. Although P-CABs induce higher serum gastrin levels, current evidence shows no associated short-term histological risks or increases in overall adverse events compared with PPIs. P-CABs represent a major therapeutic advance, particularly for severe (LA Grades C/D) or PPI-refractory EE. Future research should evaluate their long-term safety profiles and cost-effectiveness in diverse healthcare systems.

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