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POTASSIUM-COMPETITIVE ACID BLOCKERS VERSUS PROTON PUMP INHIBITORS FOR HEALING OF ACID-RELATED UPPER GASTROINTESTINAL DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT: Acid-related upper gastrointestinal disorders (ARUGDs), including erosive oesophagitis and peptic ulcer disease, are commonly treated with proton pump inhibitors (PPIs). However, delayed onset of action, variable metabolism, and inconsistent acid suppression may limit their healing efficacy. Potassium-competitive acid blockers (PCABs) offer rapid and reversible inhibition of gastric H^+/K^+-ATPase and may provide improved mucosal healing. This systematic review and meta-analysis evaluated the comparative effectiveness of PCABs versus PPIs for endoscopic healing of ARUGDs. A comprehensive search of major databases identified seven randomised controlled trials (RCTs) involving 3,289 adults. All studies assessed endoscopic healing after 4–8 weeks of treatment. Using a prespecified fixed-effect model, PCABs demonstrated a small statistical advantage over PPIs (RR 1.02; 95% CI 1.00–1.04). However, this benefit was not significant under the random-effects model (RR 1.02; 95% CI 0.98–1.05). Substantial heterogeneity (I^2 = 70.28%) was largely driven by one large erosive-oesophagitis trial; removal of this study reduced I^2 to 29.72%. Subgroup analysis suggested that advantages of PCABs were limited to erosive oesophagitis and longer treatment duration, while healing rates for gastric and duodenal ulcers were comparable. No evidence of publication bias was detected, and the overall certainty of evidence was rated as moderate. Although PCABs, particularly vonoprazan, may provide slightly improved healing in selected settings, the overall incremental benefit over PPIs is modest. Larger, diverse trials are warranted to clarify the clinical significance of PCABs across different acid-related disorders.

INTRODUCTION: Acid-related upper gastrointestinal disorders (ARUGDs), including erosive oesophagitis and peptic ulcer disease, remain common worldwide and are associated with substantial clinical and economic burden.

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Excess gastric acid exposure drives mucosal injury and leads to symptoms and complications that often require long-term therapy. Proton pump inhibitors (PPIs) have served as first-line treatment for decades because of their established ability to suppress gastric acid secretion.

However, their delayed onset, need for acid activation, variable metabolism influenced by CYP2C19 genotype, and inadequate nocturnal acid control result in incomplete healing in a subset of patients, particularly those with severe disease or rapid metaboliser phenotypes [1, 2].

Potassium-competitive acid blockers (PCABs) were developed to overcome these limitations. By directly and reversibly inhibiting the gastric H^+/K^+-ATPase, PCABs provide rapid, predictable, and acid-independent suppression of intragastric acidity [3-5]. Agents such as vonoprazan, tegoprazan, and keverprazan have demonstrated favourable efficacy in gastro-oesophageal reflux disease, peptic ulcer disease, and *Helicobacter pylori* eradication regimens, suggesting potential therapeutic advantages over PPIs [6-9].

Despite expanding clinical use, the comparative effectiveness of PCABs versus PPIs across the full range of ARUGDs remains unclear. Prior systematic reviews have typically focused on single disease subtypes, specific PCAB agents, or restricted populations, limiting the generalizability of their conclusions [10]. Moreover, previous analyses have not uniformly assessed heterogeneity across disease types, treatment durations, or drug classes, leaving uncertainty regarding the specific clinical contexts in which PCABs may offer meaningful advantages over PPIs. The absence of an integrated, up-to-date synthesis that evaluates different ARUGDs together, incorporates newer PCAB agents, and compares outcomes using consistent methodological standards represents a key evidence gap. Therefore, a comprehensive meta-analysis of randomised controlled trials is warranted to provide a unified assessment of mucosal healing outcomes, clarify the magnitude and clinical relevance of any therapeutic advantage, and inform evidence-based decision-making regarding the role of PCABs in routine clinical practice.

Accordingly, this evidence-based synthesis of published randomised controlled trials (RCTs) aimed to critically evaluate and compare the mucosal healing efficacy of PCABs versus PPIs across ARUGDs, integrating data from diverse clinical settings and patient populations.

MATERIALS AND METHODS:

Study Design and Reporting Framework: The present work systematically synthesized evidence from randomised clinical studies evaluating PCABs against PPIs for the healing of ARUGDs. To uphold transparency and reproducibility, the review was performed in alignment with the methodological standards proposed by the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [11]. The entire process from literature search and data selection to synthesis and reporting was performed in accordance with PRISMA standards for evidence synthesis.

Eligibility Criteria: Eligible studies were required to be prospective, parallel-group randomised controlled trials that enrolled adults aged 18 years or older with endoscopically confirmed acid-related upper gastrointestinal diseases, including erosive oesophagitis, gastric ulcer, or duodenal ulcer. Trials were considered for inclusion if they evaluated a potassium-competitive acid blocker such as vonoprazan, tegoprazan, or keverprazan and compared it with a proton pump inhibitor, most commonly lansoprazole, administered either as monotherapy or within an eradication regimen. Only studies that reported extractable, endoscopically assessed mucosal-healing outcomes and were published in English were included. Studies were excluded if they were non-randomised, quasi-experimental, observational, cohort-based, or retrospective in nature; if they involved paediatric populations, pregnant or lactating women, or patients with prior gastric surgery; or if they were pharmacokinetic, pharmacodynamic, or *in-vitro* mechanistic investigations. In addition, studies published only as abstracts, conference proceedings, editorials, letters to the editor, or non-peer-reviewed theses were excluded owing to insufficient methodological detail. When duplicate publications from the same dataset were identified, the most comprehensive and recent version was retained.

Information Sources and Search Strategy: The search strategy formulated as per PRISMA guidelines was conducted in journals and trial registries indexed in PubMed, Embase, MEDLINE, Scopus and in ClinicalTrials.gov, and both controlled vocabulary terms from Medical Subject Headings (MeSH) and free-text search phrases adapted to the syntax and controlled vocabulary of each database were integrated into the search strategy. The primary search terms included:(“potassium-competitive acid blocker” OR “PCAB” OR “vonoprazan” OR “tegoprazan” OR “keverprazan”) AND (“proton pump inhibitor”

OR "PPI" OR "lansoprazole") AND ("acid-related disease" OR "erosive oesophagitis" OR "gastric ulcer" OR "duodenal ulcer" OR "peptic ulcer").Filters were applied to restrict the search to human studies, randomised controlled trials, and articles published in peer-reviewed journals. No restrictions were placed on geographic origin to maximise inclusivity.

Study Selection: All obtained records were separately evaluated for eligibility by two researchers. The initial screening involved an evaluation of titles and abstracts, succeeded by a comprehensive assessment of the entire texts of possibly pertinent papers. All disputes throughout the selecting process were settled by consensus or if any disagreement remains unsettled an opinion of independent third reviewer was taken.

Data Extraction and Management: Data extraction was performed via a tailored Microsoft Excel 365 worksheet. The extracted variables were the initial author, year of publication, study design, disease condition, intervention name and dose, comparator name, period of therapy, and healing results (healed versus non-healed). The principal outcome of interest was the healing of ulcers or mucosal surfaces, validated *via* endoscopy at the conclusion of the therapy period. In trials where several dosages or durations of PCAB were evaluated, only the standard-dose group was chosen to maintain uniformity across investigations.

In cases of incomplete data or ambiguous reporting, efforts were undertaken to reach out to corresponding authors or by referring any supplemental material of the journal article/trial registries. When necessary, effect measures were calculated from raw counts or confidence intervals using standard formulas. No imputation was performed for missing data; instead, studies were included in sensitivity analysis (random-effects model) to assess robustness. To avoid double-counting participants from the same trial, the two disease-specific arms reported in the included study were treated as independent study units because they represented distinct, non-overlapping patient populations (gastric ulcer and duodenal ulcer). Only one comparison (standard-dose PCAB *vs*. standard-dose PPI) from each arm was included, ensuring that each participant contributed data to the meta-analysis once.

Outcome Measures: The principal outcome under evaluation was the frequency of endoscopically verified resolution of acid-related mucosal pathology. Healing was defined by endoscopic verification of mucosal restoration, as indicated by the respective trials. The healing of erosive oesophagitis was characterized by the resolution of observable erosions as per the Los Angeles Classification system, often classified as Grade A to D [12]. In instances of stomach or duodenal ulcers, recovery was verified with endoscopic observation of full re-epithelialization or scar formation, devoid of any remaining mucosal disruption [13]. Despite slight discrepancies in healing criteria among trials, the fundamental outcome was uniform: a binary evaluation of healed versus non-healed mucosa at the conclusion of a treatment period, generally spanning between 4 to 8 weeks. All trials included standardized endoscopic techniques performed by expert professionals.

Assessment of Study Bias: The potential for bias in each selected trial was examined using the updated Cochrane framework for assessing bias in randomised studies (RoB2 tool for bias assessment) [14].

Leave-One-Out Sensitivity Analysis: This analysis aimed to determine the influence of individual studies on the overall effect size and to evaluate the stability of the meta-analytic outcomes. Leave-one-out sensitivity analysis was conducted using the fixed-effect model, which was prespecified as the primary analytical framework. Thus, random-effects pooling was performed only as an overall sensitivity analysis. Leave-one-out diagnostics were not repeated under the random-effects model.

Publication Bias Assessment: Assessment of publication bias was conducted using Funnel plot and Egger's regression test. Evidence of publication bias was inferred when the corresponding probability value (p-value) in Egger's regression test fell below 0.05.

GRADE Assessment: The GRADE (Grading of Recommendations, Assessment, Development and

Evaluations) methodology was utilized to assess the certainty of evidence in the aggregated data [15].

Data Synthesis and Statistical Analysis: Effect-size calculations were performed in Microsoft Excel 365using explicit formulas, and all computational steps were directly visible within the worksheets. In addition to standard statistical references, the analysis followed the procedures described in a dedicated, ISBN-registered textbook on conducting meta-analysis in Excel, from which all core formulas for risk ratio, variance, and inverse-variance pooling were adopted. Using a published methodological guide ensured consistency, transparency, and reproducibility of computations [16]. Although Excel is limited by manual data entry, lack of automated diagnostics, and increased risk of formula-based errors, the small size and simplicity of the dataset made it feasible. For each study, the risk ratio (RR) was calculated from raw event counts by entering the below-mentioned formula in Excel cell:

$$RR = (a / (a + b)) / (c / (c + d))$$

Where, a and b represent healed and non-healed participants in the PCAB group, and c and d represent corresponding values for the PPI group. The standard error (SE) of the log-transformed RR was computed in Excel cell by incorporating this formula:

$$SE (\log RR) = \text{sqrt } (1/a) - (1/(a + b)) + (1/c) - (1/(c + d)$$

A fixed-effect inverse-variance model was prespecified as the primary analytical approach. This was justified by the uniformity of clinical outcomes across studies (endoscopic healing), the use of comparable comparator regimens (standard-dose lansoprazole), and the broadly consistent direction of effect observed during preliminary inspection. Subgroup analysis and leave-one-out sensitivity tests were also conducted under the fixed-effect framework. To evaluate the robustness of findings, a DerSimonian–Laird random-effects model was applied as a secondary analysis, with the between-study variance (τ^2) derived from Cochran's Q statistic. Statistical heterogeneity was quantified using the Q statistic and I^2 metric.

While Excel provides transparent cell-based calculations, it has notable limitations, including manual data entry, absence of automated meta-analytic diagnostics, and susceptibility to formula-based errors. Dedicated statistical software such as RevMan, STATA, or R (meta for) was not used because the dataset was relatively small, effect-size calculations were straightforward, and the analysis plan relied primarily on standard inverse-variance pooling procedures. To minimise computational error, all worksheets containing raw data, formulas, and pooled estimates were independently cross-checked by two reviewers.

Ethics Statement: There was no need for ethical approval since this was an extrapolation of data that had already been published.

RESULTS:

PRISMA Flow Description: A total of 105 records were retrieved from PubMed, Scopus, Embase, MEDLINE and ClinicalTrials.gov databases. After removal of duplicates and screening of abstracts, 27 full-text articles were assessed for eligibility. Following exclusion of studies for reasons like non-homogenous samples, unrelated outcomes and insufficient extractable data, finally, seven RCTs met all inclusion criteria and were incorporated into both the qualitative and quantitative synthesis **Fig. 1.**

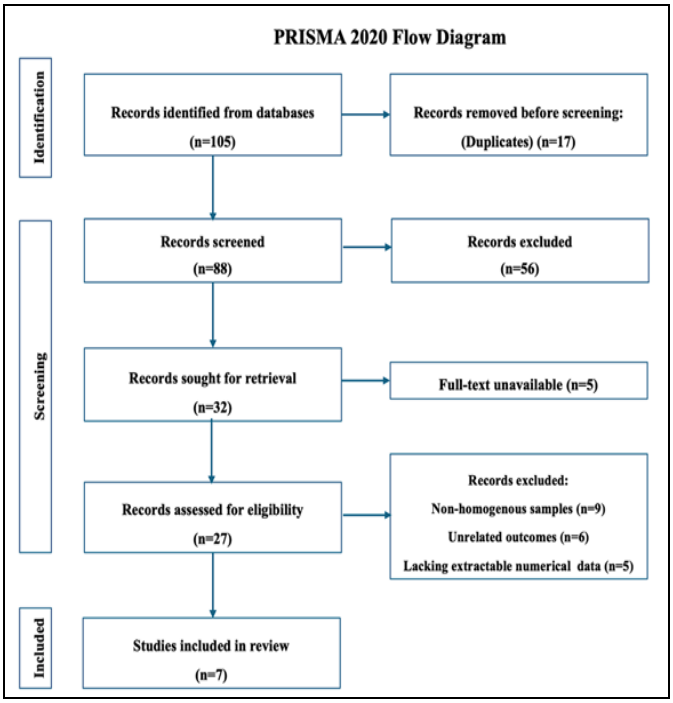

FIG. 1: PRISMA FLOW DIAGRAM DEPICTING THE SYSTEMATIC SELECTION OF STUDIES INCLUDED IN THE META-ANALYSIS

Study Characteristics Summary: This meta-analysis comprised of seven randomised controlled trials encompassing 3,289 participants with ARUGDs, specifically duodenal ulcer, gastric ulcer, or erosive oesophagitis. These studies directly contrasted PPIs, mainly lansoprazole, with PCABs, including vonoprazan, keverprazan, and tegoprazan. In every study, endoscopically verified mucosal healing was the main result/outcome. Characteristics of the included studies are summarized in **Table 1.**

TABLE 1: SUMMARY OF INCLUDED STUDIES

Study ID*	First author (year)	Condition	Intervention (dose in mg/day)	Comparator (dose in mg/day)	Sample size of intervention group showing the desired outcome (endoscopic healing of ulcer)	Total sample size (intervention group)	Sample size of comparator group showing the desired outcome (endoscopic healing of ulcer)	Total sample size (comparator group)	Duration (weeks)
S1	Ashida et al. (2016)[17]	Erosive oesophagitis	Vonoprazan (20)	Lansoprazole (30)	203	205	190	199	8
S2	Miwa et al. (2017)[18]	Gastric ulcer	Vonoprazan (20)	Lansoprazole (30)	216	231	211	225	8
S3	Miwa et al. (2017)[18]	Duodenal ulcer	Vonoprazan (20)	Lansoprazole (30)	170	178	177	180	6
S4	Tan et al. (2023)[19]	Duodenal ulcer	Keverprazan (20)	Lansoprazole (30)	170	180	166	178	6
S5	Hou et al. (2022)[20]	Duodenal ulcer	Vonoprazan (20)	Lansoprazole (30)	222	249	222	251	4
S6	Cho et al. (2020)[21]	Gastric ulcer	Tegoprazan (50)	Lansoprazole (30)	91	96	89	93	8
S7	Laine et al. (2023)[22]	Erosive oesophagitis	Vonoprazan (20)	Lansoprazole (30)	477	514	431	510	8

*Note: Study IDs (S1–S7) correspond to first author (year) as indicated in Table 1.

Pooled Effect Estimates and Sensitivity Analysis: Using the prespecified fixed-effect model, PCABs produced a pooled RR of 1.02 with a 95% CI of 1.00–1.04, indicating a small but statistically significant improvement in mucosal healing compared with PPIs. When the between-study variance was incorporated using the DerSimonian–Laird random-effects model, the pooled RR was 1.02 (95% CI 0.98–1.05), indicating that the statistical significance observed under the fixed-effect model was not retained after accounting for between-study heterogeneity **Table 2.**

TABLE 2: POOLED EFFICACY OUTCOMES

Study ID	Relative risk (RR)	Log (RR)	Standard error (SE)	95% Confidence interval (CI)	Fixed effect (Primary model)		Random-effects (Sensitivity model)	
					Pooled relative risk (RR)	95% Confidence interval (CI)	Pooled relative risk (RR)	95% Confidence interval (CI)
S1	1.04	0.04	0.02	1.00–1.07	1.02	1.00–1.04	1.02	0.98–1.05
S2	1	0	0.02	0.95–1.05				
S3	0.97	-0.03	0.02	0.94–1.01				
S4	1.01	0.01	0.03	0.96–1.07				
S5	1.01	0.01	0.03	0.95–1.07				
S6	0.99	-0.01	0.03	0.93–1.06				
S7	1.1	0.09	0.02	1.05–1.15				

Forest Plot: When looking at both forest plots together, the overall pattern becomes clear. All studies lean in the same direction, suggesting that PCABs generally perform slightly better than PPIs for promoting mucosal healing. However, the size of this benefit is small. In the fixed-effect plot **Fig. 2**, this small advantage reaches statistical significance because the model assumes that all studies are estimating essentially the same underlying effect.

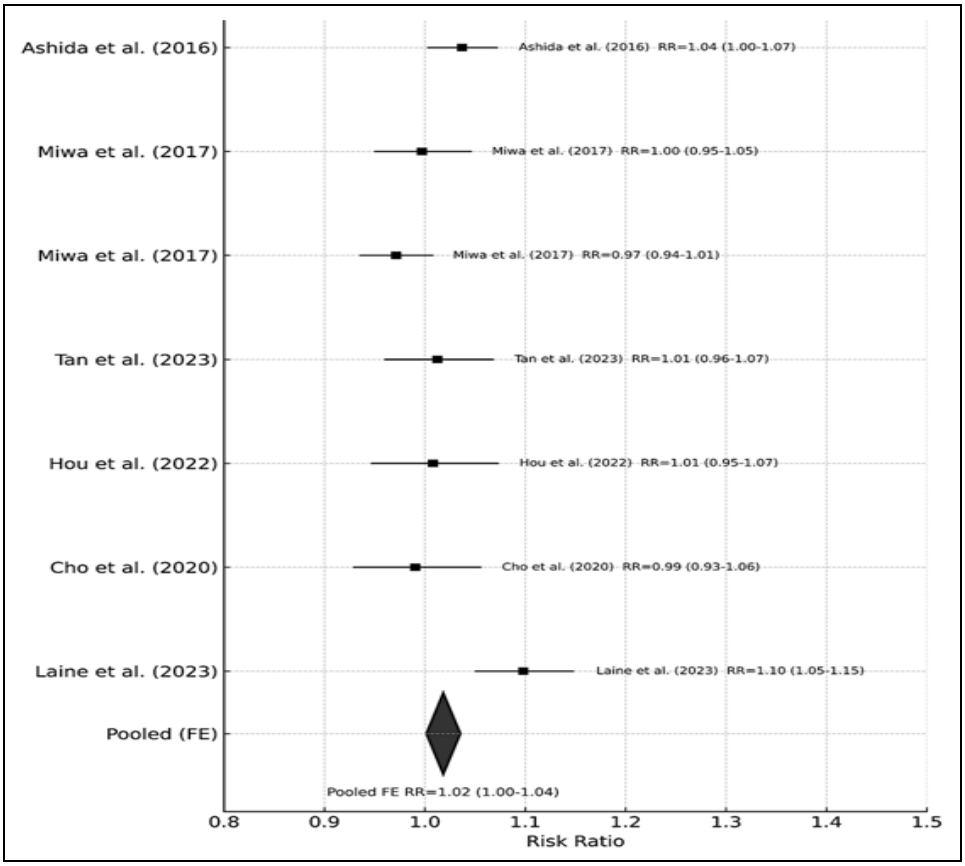

FIG. 2: FOREST PLOT (FIXED-EFFECT INVERSE-VARIANCE MODEL). [SQUARE = STUDY RR; HORIZONTAL LINES = 95% CIS; DIAMOND = POOLED RR WITH 95% CI (FIXED-EFFECT)]

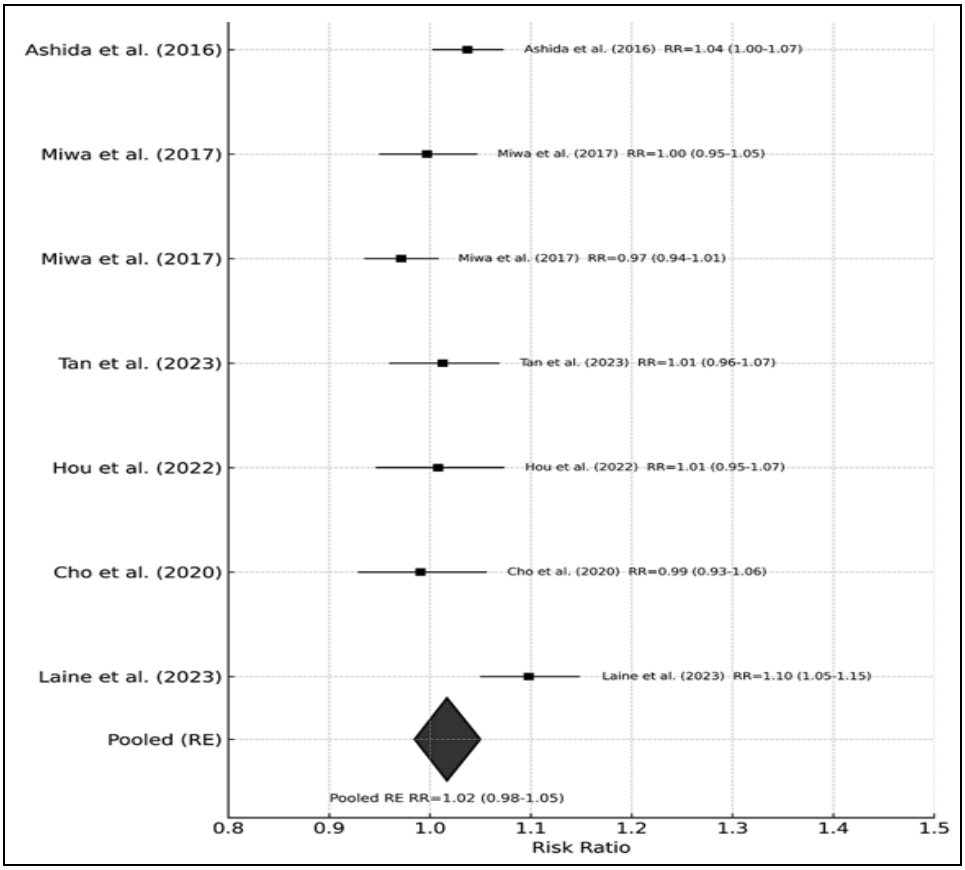

FIG. 3: FOREST PLOT (DERSIMONIAN–LAIRD RANDOM-EFFECTS MODEL; SENSITIVITY ANALYSIS). [SQUARE = STUDY RR; HORIZONTAL LINE = 95% CIS; DIAMOND = POOLED RR WITH 95% CI (RANDOM EFFECT)].

Taken together, these findings imply that while PCABs may offer a slight improvement over PPIs, the advantage is modest and sensitive to differences across studies. The clinical meaning of this effect should therefore be interpreted with caution and within the context of the diversity among the included trials.

Heterogeneity Assessment: Between-study heterogeneity was evaluated using Cochran's Q test and quantified by the I^2 statistic, which represents the proportion of total variation across studies due to true differences rather than chance. Following Cochrane conventions, I^2 values of 0–40% were regarded as low, 30–60% moderate, 50–90% substantial and above 75% considerable heterogeneity. In this meta-analysis, I^2 was 70.28% with a Q statistic of 20.19[degrees of freedom (df) = 6], signifying substantial heterogeneity. To explore possible sources of heterogeneity, subgroup analysis (by disease type, treatment duration and class of PCAB used), and leave-one-out sensitivity analysis were performed.

Subgroup Analysis: Subgroup analyses demonstrated that the modest overall advantage of PCABs was not uniform across all conditions. The benefit was primarily driven by trials in erosive oesophagitis, where PCABs showed a meaningful advantage over PPIs (k = 2 RCTs; pooled RR = 1.06; 95% CI 1.03–1.09; I^2 = 75.59%). This pattern is consistent with the pharmacodynamic profile of PCABs, which provide rapid and sustained acid suppression, an important determinant of healing in reflux-related mucosal injury. In contrast, healing rates for gastric and duodenal ulcers were nearly identical between groups, suggesting that ulcer repair, which depends more on mucosal defence mechanisms than rapid acid neutralisation, does not substantially benefit from the enhanced potency of PCABs.

Treatment duration also influenced outcomes. A small advantage of PCABs emerged only with regimens lasting ≥6 weeks (k = 4 RCTs; RR = 1.04; 95% CI 1.01–1.06; I^2 = 72.73%), whereas shorter courses (<6 weeks) yielded no observable difference. This indicates that any incremental benefit of PCABs requires sustained exposure and may not be clinically meaningful in short-term therapy.

Drug-specific findings further supported this interpretation. Vonoprazan-based regimens (k = 5) demonstrated a slight superiority (RR = 1.02; 95% CI 1.00–1.04; I^2 = 79.28%), whereas other PCABs showed no clear advantage. This suggests that the observed effects may reflect the greater potency and real-world evidence base for vonoprazan rather than a uniform class effect. Overall, these subgroup findings indicate that PCABs offer a clinically relevant benefit only in specific contexts, particularly erosive oesophagitis, longer treatment durations, and vonoprazan regimens while providing no substantial improvement over PPIs in uncomplicated gastric or duodenal ulcer healing.

Leave-One-Out Sensitivity Analysis: Although heterogeneity was high (I^2 = 70.28%), this was driven predominantly by a single large influential study (Laine *et al.,* 2023). Leave-one-out sensitivity analysis excluding Laine *et al.,* 2023 reduced I^2 to 29.72%. Since Laine *et al.,* 2023 met all eligibility criteria and had acceptable methodological quality, it was retained in the primary analysis. The observed heterogeneity likely reflects differences in disease type, sample sizes, and PCAB types across studies **Table 3.**

TABLE 3: LEAVE-ONE-OUT SENSITIVITY ANALYSIS OF INCLUDED RESEARCH STUDIES

Removed study ID	Pooled log (RR)	Q statistic	I^2statistic (%)
S1	0.01	18.60	73.12
S2	0.02	19.33	74.14
S3	0.03	12.25	59.19
S4	0.02	20.14	75.18
S5	0.02	20.08	75.10
S6	0.02	19.40	74.23
S7	0.01	7.11	29.72

Publication Bias: Egger's test was non-significant (t = −0.28; degrees of freedom (df) = 5; p = 0.79) and visual inspection of funnel plot did not reveal clear asymmetry **Fig. 4,** which indicates no evidence of publication bias.

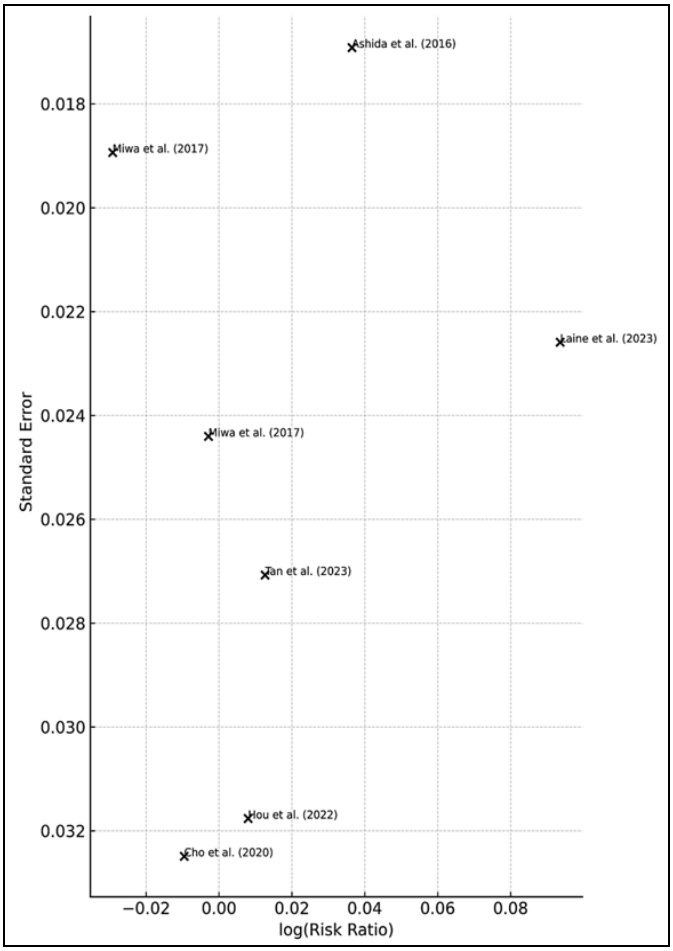

FIG. 4: FUNNEL PLOT OF INCLUDED RANDOMISED CONTROLLED TRIALS

Risk of Bias and GRADE Assessment: Risk of bias was assessed using the revised Cochrane RoB2 tool. Most studies [Ashida *et al.* (2016) (S1), Miwa *et al.* (2017, gastric ulcer) (S2), Miwa et al. (2017, duodenal ulcer) (S3), and Cho *et al.* (2020) (S6)] were judged to have some concerns mainly related to allocation concealment and blinding in a subset of trials. No study was judged to have high risk of bias. The certainty of evidence for the outcome was rated as moderate due to inconsistency ($I^2 > 50\%$) and imprecision of the pooled effect.

DISCUSSION: This meta-analysis evaluated the comparative healing efficacy of PCABs and PPIs across acid-related upper gastrointestinal disorders. Although the fixed-effect model suggested a slight advantage for PCABs, this benefit disappeared under the random-effects model, indicating that the overall effect is small, sensitive to heterogeneity, and unlikely to reflect a clinically meaningful difference for most patients. The modest superiority observed is consistent with the pharmacologic profile of PCABs, which achieve rapid and sustained acid suppression independent of CYP2C19 metabolism [17]. Recent evidence supports these findings. Zhou *et al.* (2024) reported higher efficacy and comparable safety of PCABs versus PPIs in GERD [5]. Yang *et al.* (2022) observed superior mucosal healing with vonoprazan, and Simadibrata *et al.* (2024) demonstrated improved maintenance of healed oesophagitis, confirming durable acid control [23, 24]. In the present review, subgroup analysis PCABs showed a measurable benefit only in erosive oesophagitis, a condition in which rapid and potent acid suppression is critical for restoring mucosal integrity. In contrast, gastric and duodenal ulcer healing processes strongly supported by mucosal defence mechanisms did not differ between treatment groups, suggesting that the enhanced potency of PCABs does not translate into superior ulcer healing. The benefit associated with prolonged treatment and with vonoprazan-based regimens reinforces the notion that the clinical impact of PCABs is situational rather than universal.

These findings align with broader evidence showing improved acid control and symptom resolution with PCABs, especially vonoprazan, but relatively comparable ulcer-healing outcomes [25, 26]. This review's strength lies in its inclusion of randomised trials, structured risk of bias assessment and adherence to PRISMA-2020 and GRADE frameworks. Clinically, this meta-analysis suggests that PCABs may be most useful in patients with severe erosive oesophagitis, rapid metaboliser phenotypes, or inadequate response to PPIs, while standard-dose PPIs remain appropriate for uncomplicated ulcer disease. Future research should include larger, multinational trials, stratification by disease subtype, evaluation of long-term outcomes, and exploration of pharmacogenomic and cost-effectiveness considerations to better define the clinical role of PCABs in acid-related disease management.

Limitations: This meta-analysis has several important limitations that should be considered when interpreting the findings. First, substantial statistical heterogeneity was present ($I^2 = 70\%$), largely influenced by one large erosive-oesophagitis trial, indicating variability in study populations, disease severity, and PCAB agents.

Second, most included trials were conducted in East Asian countries, which may limit generalisability to other regions with different genetic, dietary, and healthcare profiles. Third, although a fixed-effect model was prespecified based on similar clinical outcomes and comparator regimens across studies, this approach may underestimate between-study variability; therefore, results should be interpreted alongside the random-effects sensitivity analysis. Finally, all calculations were performed using Microsoft Excel, which, while transparent and adequate for small datasets, lacks the automated diagnostic tools and error-checking capabilities of more advanced meta-analytic software. These limitations suggest that the observed effects should be interpreted cautiously, and further high-quality, multinational trials using robust analytical platforms are warranted.

CONCLUSION: This meta-analysis shows that PCABs provide healing outcomes broadly comparable to PPIs, with only small differences observed across included trials. While certain subgroups demonstrated slightly higher healing rates with PCAB therapy, the overall magnitude of benefit remains limited.

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