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Comparative efficacy and pharmacological heterogeneity of individual potassium-competitive acid blockers: A systematic review and network meta-analysis

Gong EJ *et al.* P-CAB and pKa efficacy

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ACCEPTED

Abstract

BACKGROUND

Vonoprazan consistently demonstrates superior *Helicobacter pylori* eradication (HPE) rates compared to other potassium-competitive acid blockers (P-CABs), yet the pharmacological basis for this heterogeneity remains unclear. We hypothesized that the acid dissociation constant (pKa) – which determines acid stability and parietal cell accumulation – may explain the differential efficacy among individual P-CABs.

AIM

To examine whether pKa values predict clinical efficacy of P-CABs for HPE and erosive esophagitis healing.

METHODS

A systematic review and network meta-analysis were conducted. Randomized controlled trials (RCTs) comparing P-CABs with proton pump inhibitors (PPIs) were identified from core databases (up to January 2026). Risk of bias was assessed using RoB 2.0 and certainty of evidence using GRADE.

RESULTS

Thirty RCTs (7639 patients) were included for HPE. High-pKa P-CABs (vonoprazan of 9.06, keverprazan of 9.12) achieved 82%-84% eradication in clarithromycin-resistant infections *vs* 32%-40% with PPIs, while low-pKa P-CAB achieved only 47.8% (not significant *vs* PPI). For erosive esophagitis (10 RCTs; 4196 patients), high-pKa zastaprazan (9.95) achieved 100% Los Angeles classification grade C/D healing *vs* 83.3% with esomeprazole, whereas low-pKa P-CABs showed inferior outcomes. Spearman correlation analysis revealed a positive association between pKa and efficacy ($\rho = 0.80$). However, fexuprazan (pKa of 9.04) showed PPI-equivalent outcomes despite high-pKa, highlighting pKa as necessary but not sufficient for clinical efficacy. Network ranking confirmed high-pKa P-CABs as top-ranked agents. No publication bias was detected.

CONCLUSION

P-CAB efficacy may not be uniform across the class. High-pKa P-CABs (≥ 9.0) were associated with higher eradication rates in clarithromycin-resistant infections and superior healing in severe esophagitis, whereas low-pKa P-CABs showed limited advantages over PPIs. The pKa may serve as a hypothesis-generating pharmacological parameter, though all P-CAB comparisons were indirect and prospective validation is needed.

Key Words: Potassium-competitive acid blocker; Vonoprazan; Tegoprazan; Acid dissociation constant; *Helicobacter pylori*; Erosive esophagitis

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Core Tip: Potassium-competitive acid blockers (P-CABs) suppress acid faster and more consistently than proton pump inhibitors. Over 30 meta-analyses pooled all P-CABs as a single class. Guidelines treat individual P-CABs as interchangeable. Individual P-CABs differ substantially in clinical outcomes, suggesting that efficacy may not be uniform across the class. Acid dissociation constant (pKa) values showed a positive correlation with clinical efficacy, with high-pKa P-CABs (vonoprazan, keverprazan) achieving 82%-84% eradication in clarithromycin-resistant *Helicobacter pylori* vs 47.8% for low-pKa tegoprazan. However, fexuprazan (pKa of 9.04) did not follow this pattern, demonstrating that pKa alone is insufficient to predict outcomes. The pKa may be one contributing factor but is not sufficient alone. Multiple pharmacological properties likely contribute to antisecretory effectiveness and clinical outcomes. These findings generate the hypothesis that pKa may inform P-CAB selection, particularly for clarithromycin-resistant infection and severe esophagitis, pending prospective validation.

INTRODUCTION

Helicobacter pylori (*H. pylori*) eradication has entered a new therapeutic era. Potassium-competitive acid blockers (P-CABs) provide faster, more potent, and CYP2C19-independent acid suppression compared to proton pump inhibitors (PPIs), and have been incorporated into treatment algorithms for both first-line and rescue therapy[1,2]. With five P-CABs now clinically available – vonoprazan (VPZ), tegoprazan (TPZ), fexuprazan (FXP), keverprazan (KVP), and zastaprazan (ZPZ) – clinicians might reasonably assume these agents are pharmacologically interchangeable.

The clinical evidence, however, tells a different story. VPZ-based regimens consistently achieve eradication rates exceeding 90%, even in clarithromycin (CLR)-resistant infections where PPI-based therapies fail[3]. In contrast, trials of other P-CABs have produced mixed results: Some demonstrate modest superiority over PPIs, while others show no significant advantage[4,5]. More than 30 meta-analyses have compared “P-CAB” *vs* “PPI” as a class, yet this approach obscures a fundamental question – why do individual P-CABs perform so differently?

One potential explanation may lie in basic pharmacology, although differences in clinical trial design, patient populations, dosing regimens, and regional resistance patterns may also contribute. P-CABs function as weak bases that accumulate in parietal cell secretory canaliculi through pH-dependent ion-trapping[6]. The efficiency of this accumulation depends critically on the acid dissociation constant (pKa): Compounds with higher pKa values remain protonated and trapped at lower pH, enabling sustained inhibition even under conditions of maximal acid secretion (Supplementary Figure 1). This property directly affects the duration of intragastric pH elevation – and maintaining pH above 6 for extended periods is essential for amoxicillin (AMO) stability and bactericidal activity[7].

This mechanistic framework carries particular significance for CLR-resistant *H. pylori*, a growing global challenge[8]. When CLR loses efficacy, eradication depends almost entirely on AMO – a time-dependent antibiotic whose bactericidal activity requires prolonged exposure at gastric pH > 5.5[7]. Under these conditions, the

margin between therapeutic success and failure narrows considerably, and even modest differences in acid suppression may translate into clinically meaningful differences in eradication rates. Similarly, in severe erosive esophagitis (EE) [Los Angeles classification (LA) grade C/D], where mucosal healing demands sustained nocturnal acid control, the pharmacological ceiling of the acid suppressant becomes the rate-limiting factor.

Remarkably, marketed P-CABs span nearly a fivefold range in pKa, from 5.1 (TPZ) to 9.95 (ZPZ)[6,8]. This degree of pharmacological heterogeneity is unprecedented among drugs within a single therapeutic class (Supplementary Figure 2). If pKa influences clinical efficacy, then P-CABs may not be fully interchangeable, and the “class effect” assumption underlying current prescribing may be overly simplistic.

To date, no study has systematically examined whether pKa predicts clinical outcomes across individual P-CABs. We conducted a systematic review (SR) and network meta-analysis (NMA) comparing all five marketed P-CABs for *H. pylori* eradication and EE healing, with pre-specified correlation analyses between pKa values and pooled treatment effects. Our hypothesis was that high-pKa P-CABs would demonstrate superior efficacy, particularly in settings requiring profound and sustained acid suppression – CLR-resistant *H. pylori* and severe EE.

MATERIALS AND METHODS

Study design and registration

This SR and NMA was registered on PROSPERO (CRD420261290164) and conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses checklist[9,10]. Full methods (including search strategy, eligibility criteria, study selection, data extraction, risk of bias evaluation, statistics) are detailed in Supplementary material.

Information sources and search strategy

PubMed, EMBASE, CENTRAL, and Web of Science were searched from inception through January 15, 2026.

Eligibility criteria

Studies were selected based on the patient, intervention, comparison, outcome framework[11]. We included randomized controlled trials (RCTs) comparing any of five marketed P-CABs (VPZ, TPZ, FXP, KVP, ZPZ) with PPIs for *H. pylori* eradication (first-line therapy) or EE healing (LA grade A-D). Trials with different antibiotic regimens between arms were excluded.

The pKa values

The pKa values were obtained from published literature and verified with manufacturers: (1) VPZ (9.06)[12]; (2) TPZ (5.1)[6,13]; (3) FXP (9.04)[14]; (4) KVP (9.12)[6]; and (5) ZPZ (9.95) (Supplementary Table 1)[6,8]. These values were derived from published experimental data; as measurement conditions (*e.g.*, potentiometric titration, ultraviolet-spectrophotometry) were not standardized across all agents, minor methodological variation in reported pKa values cannot be excluded.

Risk of bias assessment

Risk of bias was assessed using the Cochrane ROB 2.0 tool for RCTs[15].

Statistical analysis

NMA was performed using frequentist random-effects models with PPI as the common comparator[16]. Treatment rankings used P-scores. The pKa-efficacy correlation was assessed using Spearman's coefficient; threshold analysis dichotomized P-CABs at pKa = 9.0. Statistical power was estimated *via* Monte Carlo simulation (3000 iterations). Publication bias was evaluated by funnel plots and Egger's regression test[17].

RESULTS

Study selection

From 2441 records, 40 RCTs[3,18-56] met inclusion criteria: (1) 30 for *H. pylori* ($n = 7,639$)[3,18-46]; and (2) 10 for EE ($n = 4196$) (Figure 1)[47-56]. Full methods (including

exclusion criteria, study selection, data extraction, methodology evaluation, certainty of evidence, statistical analysis *etc.*) are detailed in Supplementary material.

Study characteristics

H. pylori eradication studies: A total of 30 RCTs (32 trial comparisons) evaluating P-CAB-based regimens for first-line *H. pylori* eradication were included (Table 1)[3,18-46]. Studies were conducted across 6 countries: (1) China ($n = 19$)[22,23,25-30,32,33,35-42,46]; (2) Korea ($n = 5$)[21,24,31,34,43]; (3) Japan ($n = 3$)[18-20]; (4) United States/Europe ($n = 1$)[3]; (5) Taiwan ($n = 1$)[45]; and (6) Egypt ($n = 1$)[44]. The total sample size was 7639 patients (P-CAB arms: 4020; PPI arms: 3619). Four P-CAB types were represented: (1) VPZ (21 studies, 22 comparisons)[3,18-20,22,23,25-30,32,33,35,38,40,42,44-46]; (2) TPZ (7 studies, 8 comparisons)[21,24,34,36,39,41,43]; (3) KVP (1 study)[37]; and (4) FXP (1 study)[31]. Treatment regimens included triple therapy ($n = 11$)[3,18-21,23,31,35,42-44], dual therapy ($n = 16$)[3,22,26-30,32,33,36,38-41,44,45], bismuth quadruple therapy ($n = 4$)[24,25,37,46]; and sequential therapy ($n = 1$)[34]. Treatment duration ranged from 7 days to 14 days, with 14-day regimens predominating ($n = 20$)[3,23-26,28-31,35-37,39-46] and 7-day regimens limited to early Japanese and Korean studies ($n = 4$)[18-21]; 10-day regimens accounted for the remaining 8 comparisons[22,27,32-34,38]. PPI comparators included esomeprazole (ESO)-based regimens ($n = 18$)[23-27,30,33-42,44,46], lansoprazole (LPZ) ($n = 5$)[3,18,21,31,43], rabeprazole ($n = 4$)[19,22,28,45], ilaprazole ($n = 2$)[29,32], and mixed PPI ($n = 1$)[20].

EE studies

Ten RCTs comparing P-CABs *vs* PPIs for EE healing were included (Table 2)[47-56]. Studies were conducted in Japan ($n = 2$)[47,48], South Korea ($n = 3$)[52,53,55], China ($n = 4$)[49,51,54,56], and United States/Europe ($n = 1$)[50]. The total sample size was 4196 patients (P-CAB arms: 2370; PPI arms: 1826). Five P-CAB types were represented: (1) VPZ (4 studies)[47-50]; (2) KVP (1 study)[51]; (3) ZPZ (1 study)[52]; (4) FXP (2 studies)[53,54]; and (5) TPZ (2 studies)[55,56]. All studies evaluated 8-week mucosal healing as the primary endpoint. PPI comparators included LPZ 30

mg ($n = 5$)[47-51] and ESO 40 mg ($n = 5$)[52-56]. LA grade C/D subgroup data were adequately reported in 7 studies: (1) Ashida *et al*[47] (VPZ; $n = 245$); (2) Ashida *et al*[48] (VPZ; $n = 147$); (3) Laine *et al*[50] (VPZ; $n = 351$); (4) Chen *et al*[51] (KVP; $n = 49$); (5) Xiao *et al*[49] (VPZ; $n = 144$); (6) Oh *et al*[52] (ZPZ; $n = 12$); and (7) Zhuang *et al*[54] (FXP; $n = 98$) reported LA C/D data. Low-pKa P-CAB studies (TPZ[55,56], FXP[53,54]) had limited or unreported LA C/D subgroup data, with FXP notably showing inferior outcomes *vs* PPI in severe esophagitis (80% *vs* 91%)[54].

Patient characteristics

Across *H. pylori* studies, mean patient age ranged from 42 years to 58 years, with male predominance (51%-68%)[18-46]. Baseline *H. pylori* infection was confirmed by ¹³C-urea breath test (UBT), rapid urease test, histology, or stool antigen test. Exclusion criteria were generally consistent across trials: (1) Previous eradication attempts; (2) Recent antibiotic or PPI use; and (3) Severe comorbidities. In EE studies, patients had endoscopically confirmed LA grade A-D esophagitis with mean age ranging from 45 years to 56 years[47-56]. The proportion of severe esophagitis (LA grade C/D) varied substantially: 34.3% in PHALCON-EE[50], 20.6% in Chen *et al*[51], 36.4% in Ashida *et al*[48], but only 4.3% in Oh *et al*[52] and $\leq 5\%$ in TPZ studies[55,56], limiting subgroup analyses for low-pKa P-CABs.

Synthesis of results

Overall efficacy of *H. pylori* eradication: In the NMA of 30 RCTs (32 comparisons, $n = 7639$)[3,18-46], P-CABs demonstrated significantly higher eradication rates compared with PPIs [pooled odds ratio (OR) = 1.49, 95%CI: 1.27-1.74; Figure 2, Supplementary Figures 3 and 4]. Heterogeneity was low ($I^2 = 15.16\%$). Among individual P-CABs, VPZ showed the highest efficacy *vs* PPI (OR = 1.78, 95%CI: 1.47-2.30) (Supplementary Table 2)[3,18-20,22,23,25-30,32,33,35,38,40,42,44-46], followed by KVP (OR = 1.51, 95%CI: 1.08-2.12)[37]. TPZ showed modest benefit (OR = 1.29, 95%CI: 1.04-1.60)[21,24,34,36,39,41,43], and FXP demonstrated a trend toward higher eradication that did not reach statistical significance (OR = 1.49, 95%CI: 0.97-2.29)[31].

CLR-resistant infections: Four studies (five comparisons) reported CLR resistance subgroup data (Table 3)[3,18,37,43]. High-pKa P-CABs (VPZ pKa of 9.06) achieved markedly superior eradication in CLR-resistant infections: Pooled OR = 3.32 (95%CI: 1.79-6.16, $I^2 = 72.3\%$; Figure 3)[3,18,37,43]. VPZ-based regimens achieved 65.8%-82.0% eradication in CLR-resistant strains *vs* 31.9%-40.0% with PPI-based regimens, representing an absolute advantage of +33.9% to +42.0%[3,18]. The VPZ-only subgroup (3 arms) demonstrated OR = 5.07 (95%CI: 3.19-8.06). KVP showed 83.5% *vs* 77.0% eradication (OR = 1.51, 95%CI: 0.83-2.76)[37], with the attenuated effect likely attributable to the high baseline eradication rate (77.0%) in the Chinese PPI arm. In contrast, low-pKa TPZ (pKa of 5.1) achieved only 47.8% eradication in CLR-resistant infections *vs* 35.5% with PPI (OR = 1.67, not significant)[43], demonstrating no significant advantage.

Table 3 summarizes the meta-analysis of CLR-resistant subgroup data[3,18,37,43]. Murakami *et al*[18] demonstrated OR = 6.83 (95%CI: 3.63-12.86), reflecting VPZ's substantial advantage in Japanese populations with high CLR resistance rates (approximately 30%-40%). The PHALCON-HP data[3] from Western populations (CLR resistance approximately 25%) showed consistent but somewhat attenuated effects (OR = 4.09 for triple therapy, OR= 4.89 for dual therapy), likely reflecting differences in resistance patterns and patient populations. KVP (Tan *et al*[37]) showed a not significant OR of 1.51, attributable to the unusually high PPI-arm eradication rate (77.0%) in the Chinese cohort. TPZ (Park *et al*[43]) achieved only 47.8% *vs* 35.5% (OR = 1.67, not significant), confirming that low-pKa P-CABs fail to overcome CLR resistance. Overall heterogeneity was substantial ($I^2 = 72.3\%$, $P = 0.006$), explained by geographic and methodological differences across studies.

Overall healing rates of EE: In the NMA of 10 RCTs ($n = 4,196$)[47-56], P-CABs achieved numerically higher 8-week healing rates compared with PPIs (pooled OR = 1.47, 95%CI: 1.03-2.09, Figure 4, Supplementary Figures 5 and 6). Overall healing rates were high across all P-CABs (91.1%-99.1%) and PPIs (84.6%-99.1%), with ceiling effects limiting differentiation in mild-to-moderate esophagitis (LA grade A/B)

(Supplementary Table 3).

Severe esophagitis (LA grade C/D): LA grade C/D subgroup data were available in 6 studies (Supplementary Table 4)[48-52,54]. High-pKa P-CABs demonstrated superior healing in severe esophagitis: (1) VPZ achieved 84.0%-100% healing *vs* 71.8%-87.5% with LPZ (pooled advantage +13.4%)[48-50]; (2) KVP achieved 91.7% *vs* 80.0% (+11.7%)[51]; and (3) ZPZ achieved 100% *vs* 83.3% (+16.7%, $n = 6$ per group)[52]. In contrast, FXP (pKa of 9.04) showed paradoxically inferior outcomes *vs* ESO in the LA C/D subgroup (80% *vs* 91%, -11%)[54], and TPZ (pKa of 5.1) lacked adequate LA C/D data for meaningful comparison[55,56].

Additional analyses

The pKa-efficacy correlation analysis: To explore the pharmacological basis for differential P-CAB efficacy, we analyzed the correlation between P-CAB pKa values and clinical outcomes (Figure 5, Supplementary Figure 7, Supplementary Table 5). Spearman correlation analysis revealed positive associations between P-CAB pKa values and clinical efficacy in both indications (Figure 5A). For *H. pylori* eradication, pKa correlated positively with pooled OR ($\rho = 0.80$, $P = 0.20$); however, with only four marketed P-CABs available for analysis ($n = 4$), statistical power was fundamentally limited – even a perfect correlation ($\rho = 1.0$) cannot achieve $P < 0.05$ at this sample size. Despite this statistical limitation, the observed correlation direction is consistent with the mechanistic hypothesis, and subgroup analysis of CLR-resistant infections provides compelling supporting evidence: High-pKa VPZ (82%) and KVP (84%) dramatically outperformed PPIs (40%), while low-pKa TPZ failed (47.8% *vs* 35.5%, not significant). For EE healing, Spearman correlation between pKa and pooled OR showed a large positive effect size ($\rho = 0.80$) but did not reach statistical significance ($P = 0.104$) due to limited sample size ($n = 5$, power = 30%). With FXP's experimentally determined pKa of 9.04[14], four of five P-CABs cluster above pKa of 9.0, precluding meaningful threshold analysis at this cutoff. Notably, the positive correlation was maintained despite FXP being an outlier (Figure 5B): FXP (pKa of 9.04, OR = 0.95) performed at PPI level despite high-pKa,

whereas VPZ (pKa of 9.06, OR = 1.80), KVP (pKa of 9.12, OR = 2.56), and ZPZ (pKa of 9.95, OR = 2.51) showed clear superiority. This “FXP paradox” – high-pKa with PPI-equivalent outcomes – strongly suggests that pKa is necessary but not sufficient for P-CAB efficacy, with protein binding (FXP 93% *vs* VPZ 80%-88%) and intrinsic binding affinity likely serving as additional determinants. In the LA grade C/D subgroup where adequate data were available ($n = 4$), pKa showed perfect rank correlation with efficacy (Spearman $\rho = 1.00$). This correlation was consistent across both indications, with high-pKa P-CABs demonstrating consistent superiority in challenging clinical scenarios (CLR-resistant *H. pylori*, LA grade C/D esophagitis), while low-pKa TPZ (pKa of 5.1) showed no significant advantage (Supplementary Table 6).

Treatment rankings: Exploratory treatment rankings were assessed using P-scores from the NMA. For *H. pylori* eradication, VPZ achieved the highest P-score (0.87), followed by KVP (0.63), FXP (0.60), and TPZ (0.38), with PPIs as reference (0.01). For EE, KVP ranked highest (0.80), followed by ZPZ (0.76), VPZ (0.68), TPZ (0.32), and FXP (0.21). While these rankings showed a pattern consistent with the pKa hypothesis, the substantial imbalance in available evidence (21 VPZ studies *vs* 1 KVP and 1 FXP study), along with differences in study populations, antibiotic regimens, and treatment durations, limits the interpretability of these exploratory rankings (Supplementary Tables 2, 3, and 6, Supplementary Figures 2-4).

Monte Carlo power analysis: Monte Carlo simulation (3000 iterations) demonstrated that with only 5 marketed P-CABs, statistical power to detect a correlation of $\rho = 0.80$ is limited to 30% (Figure 6, Supplementary Table 7). With the revised FXP pKa of 9.04, threshold analysis at pKa of 9.0 is no longer feasible because four of five P-CABs cluster above this cutoff (only TPZ remains below). The continuous Spearman correlation ($\rho = 0.80$) remains the primary statistical finding. The limited power underscores the need for head-to-head comparative studies and pH-metry data to complement the indirect clinical comparisons used in this NMA. These findings support the hypothesis that P-CAB pKa may influence clinical

efficacy, though the FXP paradox (pKa of 9.04, OR = 0.95 for EE) demonstrates that other pharmacological properties – particularly protein binding and intrinsic H⁺/K⁺-ATPase binding affinity – are critical co-determinants (Supplementary Figure 8).

Sensitivity and subgroup analyses: Sensitivity analyses excluding open-label (OL) studies or restricting to non-inferiority trials did not materially alter the results. Subgroup analysis by treatment duration showed consistent P-CAB superiority for both 7-day[18-21] and 14-day regimens[3,23-26,28-31,35-37,39-46], though effect sizes were larger with shorter duration (OR = 2.31 *vs* 1.38), likely reflecting greater differentiation when baseline eradication rates are lower. Geographic subgroup analysis showed consistent results across Asian[18-43,45,46] and Western populations[3,44].

Risk of bias assessment

Risk of bias was assessed using the Cochrane ROB 2.0 tool across five domains (Table 4, Supplementary Table 8)[3,18-56]. Among 30 *H. pylori* eradication trial comparisons[3,18-46], six double-blind trials (Murakami *et al*[18], Chey *et al*[3] triple-therapy arm, Choi *et al*[21], Kim *et al*[24], Tan *et al*[37], Park *et al*[43]) were judged as low risk of bias across all domains. The remaining 26 OL trials[3,18,20,22,23,25-36,38-46] were rated as “some concerns” overall, primarily due to lack of participant and personnel blinding (Domain 2). However, the risk of bias in outcome measurement (Domain 4) was judged low for all studies because eradication was assessed by UBT, an objective endpoint evaluated by blinded laboratory personnel. One study (Maruyama *et al*[19]) had additional concerns for randomization (Domain 1) due to quasi-random allocation using odd/even medical record numbers. All 10 EE RCTs[47-56] employed double-blind designs and were rated as low risk of bias. No studies were judged as high risk of bias. While these assessments provide fair to moderate support for the validity of the included studies, reliance on ¹³C-UBT alone for *H. pylori* eradication confirmation – without corroboration by histology, rapid urease test, or immunological stool antigen test – may introduce some diagnostic uncertainty in individual studies. Diagnostic accuracy varies meaningfully across

modalities (UBT sensitivity 92%-96%/specificity 89%-93%; stool antigen test 87%-94%/70%-91%; histology with Giemsa staining approximately 93%/> 90%; rapid urease test > 90%/> 95%), and recent use of PPIs, antibiotics, or bismuth within 2-4 weeks of testing can produce false-negative results; included trials applied protocol-specified washout intervals to mitigate this risk. Overall, the predominance of objective outcomes (UBT for *H. pylori*, endoscopic healing for EE) mitigates concerns arising from OL designs.

Certainty of evidence

The certainty of evidence was assessed using GRADE methodology (Table 5, Supplementary Table 9)[3,18-56]. For *H. pylori* eradication, the certainty was rated as high. Although some studies used OL designs, this was not downgraded because the primary outcome (UBT) is an objective measure unlikely to be influenced by lack of blinding. No serious concerns were identified for inconsistency, indirectness, imprecision, or publication bias.

For EE healing, the certainty was rated as moderate, downgraded one level for serious imprecision because some individual P-CABs (ZPZ, KVP) had only single RCTs with wide confidence intervals.

In summary, the evidence supports the overall superiority of P-CABs (particularly VPZ, which has the most extensive data) over PPIs for *H. pylori* eradication, with the strongest evidence in CLR-resistant infections. Evidence for EE healing is of moderate certainty due to limited data for newer P-CABs, though VPZ demonstrates consistent benefit across multiple trials. The interpretation of certainty ratings should account for the indirect nature of all P-CAB comparisons and the imbalanced evidence base across individual agents.

Publication bias

Visual inspection of funnel plots showed no obvious asymmetry for either *H. pylori* eradication (Figure 7A) or EE healing outcomes (Figure 7B, Supplementary Table 10). Egger's regression test was not statistically significant for *H. pylori* studies ($P = 0.97$). For EE studies, Egger's test was not significant ($P = 0.14$); however,

interpretation is limited by the small number of studies ($n = 10$), and visual inspection of the funnel plot did not suggest meaningful asymmetry.

DISCUSSION

Principal findings

This NMA of 40 RCTs ($n = 11835$)[3,18-56] suggests that P-CAB efficacy varies substantially among individual agents and is positively correlated with pKa values (Spearman $\rho = 0.80$). High-pKa P-CABs (VPZ of 9.06, KVP of 9.12, ZPZ of 9.95) achieved 82%-84% eradication in CLR-resistant infections *vs* 47.8% with low-pKa TPZ (pKa of 5.1). However, FXP (pKa of 9.04) represents a notable exception: Despite high-pKa, it achieved EE healing rates equivalent to PPIs (OR = 0.95) and showed no significant advantage for *H. pylori* eradication (OR = 1.49, 95%CI: 0.97-2.29). This “FXP paradox” demonstrates that pKa alone is insufficient to predict clinical outcomes, and that additional pharmacological properties – including protein binding (FXP of 93% *vs* VPZ of 80%-88%), intrinsic H^+/K^+ -ATPase binding affinity, and effects on gastric emptying – are critical co-determinants. Regarding gastric emptying, VPZ has been reported to delay gastric emptying, which may prolong antibiotic contact time with *H. pylori* in the gastric mucosa and independently contribute to higher eradication rates beyond acid suppression alone; however, this effect has not been systematically evaluated for other P-CABs, and its relative contribution to the observed efficacy differences remains uncertain. This association does not establish causation, and multiple confounding factors including imbalanced study numbers, differences in patient populations and *H. pylori* strains, and varying dosing regimens may also contribute. While a positive pKa-efficacy correlation exists, the FXP paradox invalidates a simple pKa threshold model and supports a multi-factor framework where pKa, protein binding, and intrinsic binding affinity collectively determine clinical outcomes.

Comparison with previous literature

Over 30 meta-analyses have compared P-CABs *vs* PPIs as a unified class. Rokkas *et al*[57] ranked VPZ-triple therapy first among all regimens but pooled all P-CABs

together. The recent NMA analyzing 25 RCTs reported P-CAB-dual therapy achieved the highest SUCRA (92.7%), again without differentiating individual agents[58].

Our findings suggest a potential pharmacological explanation for previously observed heterogeneity, with pKa as one candidate differentiating factor among several that may contribute. The PHALCON-HP trial[3] demonstrated VPZ achieved 65.8% eradication in CLR-resistant strains *vs* 31.9% with LPZ – potentially related to differences in acid suppression potency, although the relative contributions of pKa-dependent ion trapping, protein binding, intrinsic binding affinity, effects on gastric emptying, and dosing differences remain to be established.

Current guidelines have not differentiated individual P-CABs. The ACG 2024 guideline[2] and the AGA Clinical Practice Update 2024[59] recommend P-CAB-based regimens but treat them interchangeably. Our data generate the hypothesis that pKa-based pharmacological differentiation may help address this evidence gap, although prospective head-to-head comparisons and pH-metry studies are needed for confirmation.

Precedents of pKa as a clinical predictor

An important consideration is that the efficacy of gastric antisecretory drugs has traditionally been compared using intragastric pH threshold and holding time parameters, which over the past 50 years have become the established standard for evaluating acid suppression potency. Our study used clinical endpoints (eradication rate and endoscopic healing) rather than pH-metry data, a design choice that merits discussion. While clinical outcomes represent the ultimate measure of therapeutic effectiveness, they are influenced by numerous factors beyond acid suppression alone. A recent pharmacometric analysis has modeled the pH profiles of individual P-CABs and PPIs, providing a quantitative framework for comparing antisecretory activity that could complement our clinical findings[60]. Future studies integrating pKa values with pH-metry parameters and clinical outcomes would strengthen the pharmacological basis for differentiating individual P-CABs. Our use of pKa to predict clinical efficacy extends established pharmacological principles. In local

anesthetics, pKa determines onset time: Lidocaine (pKa of 7.8) achieves faster onset than bupivacaine (pKa of 8.1) because more molecules exist in the membrane-permeable unionized form at physiological pH[61]. In opioids, alfentanil (pKa of 6.5) has the fastest onset among fentanyl derivatives because 89% is unionized at pH 7.4[62]. Recent work demonstrates that lowering fentanyl derivative pKa restricts analgesia to inflamed acidic tissues, reducing systemic side effects – positioning pKa as a design criterion for safer opioids[63]. Conversely, for NSAIDs, pKa predicts toxicity: Aspirin (pKa of 3.5) accumulates in gastric mucosa through ion-trapping more readily than less acidic NSAIDs, directly correlating with mucosal damage severity[64].

These precedents share a unifying principle: PKa governs drug distribution across pH gradients. For P-CABs, high-pKa compounds remain protonated and trapped in acidic parietal cell canaliculi regardless of secretory status, whereas low-pKa compounds require active acid secretion for accumulation.

The pKa threshold: Mechanistic framework

The pKa-efficacy correlation reflects fundamental acid-base chemistry. According to Henderson-Hasselbalch principles, a drug with pKa of 9.0 achieves > 99.99% protonation at canalicular pH of 1.0 (pKa sources detailed in Supplementary Table 11), whereas pKa of 5.1 compounds show substantially less efficient trapping[6,13,14].

This differential accumulation translates into clinical outcomes through two mechanisms.

The pH-dependent antibiotic efficacy: *H. pylori* enters a non-replicating, antibiotic-resistant state at pH < 4.5[65]. AMO requires sustained pH > 5.5 for bactericidal activity[66]. High-pKa P-CABs maintain pH > 6 longer, keeping *H. pylori* susceptible – explaining why VPZ achieves 82%-84% eradication in CLR-resistant infections while TPZ achieves only 47.8%.

Acid suppression consistency: VPZ achieved 87.8% time with pH > 4 on day 7 *vs*

42.3% with LPZ[67]. Unlike PPIs, P-CABs bind both active and inactive proton pumps[68], but high-pKa compounds may additionally accumulate in resting parietal cells. However, several important caveats apply to this mechanistic interpretation. Unlike PPIs, P-CABs do not require acid activation within the canaliculus to inhibit proton pumps; unprotonated P-CABs can cross cell membranes to inactivate both active and inactive proton pumps. Furthermore, most P-CABs have substantially longer plasma half-lives than PPIs, providing prolonged systemic availability for pump inhibition even without canalicular trapping. Therefore, the relative contribution of pKa-dependent ion trapping *vs* other pharmacokinetic properties (plasma half-life, protein binding, intrinsic binding affinity, effects on gastric emptying) to the observed clinical differences remains to be established through dedicated pharmacological studies including isolated gastric gland and parietal cell experiments.

Future perspectives

Drug development: Six P-CABs are now approved globally, spanning a wide pKa range. Pipeline compounds include linaprazan glurate (Cinclus Pharma), which achieved 89% LA C/D healing in phase II. If our hypothesis is confirmed, future development may benefit from considering pKa alongside other relevant physicochemical properties including protein binding, intrinsic binding affinity, and effects on gastric motility.

Precision acid suppression: P-CABs bypass CYP2C19 metabolism, eliminating genotype-dependent variability[69]. However, within the P-CAB class, our data suggest pKa may be one determinant of the clinical ceiling alongside other pharmacological properties. If confirmed by prospective studies including pH-metry validation, selecting P-CABs based on physicochemical properties could complement genotype-based approaches to precision acid suppression[70].

Guideline implications: In regions with CLR resistance > 15%, high-pKa P-CABs may warrant preferential consideration, pending validation through direct

comparative studies. Head-to-head trials comparing individual P-CABs, coupled with pH-metry studies directly correlating pKa values with intragastric pH profiles and holding times, are essential to confirm these indirect comparisons.

Strengths and limitations

Strengths include the first NMA comparing individual P-CABs rather than pooling them as a class, pre-specified pKa-efficacy correlation analyses, inclusion of 40 RCTs with 11835 patients, and the use of objective outcomes (UBT for *H. pylori*, endoscopic healing for EE). Systematic quality assessment using RoB 2.0 and GRADE methodology enhances methodological transparency.

Several limitations warrant careful consideration. First, no head-to-head P-CAB trials exist – all comparisons derive indirectly through PPI common comparators, introducing potential bias. This is a fundamental limitation because observed differences between P-CABs may reflect confounding factors unrelated to pKa, including: (1) Differences in patient populations across geographic regions; (2) Variation in *H. pylori* strain virulence and CLR resistance rates; (3) Differing P-CAB dosing regimens and treatment durations; (4) Different antibiotic combination partners; (5) Substantial imbalance in available evidence, with VPZ studied for over a decade across 21 trials while KVP and FXP each have only a single study; and (6) Physicochemical factors beyond pKa, including variations in protein binding (particularly at the secretory canaliculus level), effects on gastrointestinal motility (notably the delay in gastric emptying reported with VPZ, which may meaningfully contribute to eradication success), and differences in intrinsic H⁺/K⁺-ATPase binding affinity and kinetics.

Second, the pKa-efficacy correlation, while mechanistically plausible, requires cautious interpretation. The FXP paradox is the most compelling illustration: With an experimentally determined pKa of 9.04[14] (data from Daewoong Pharmaceutical Investigator's Brochure), FXP should classify as a high-pKa agent, yet it achieves pH > 4 holding time ratios (55%-65%) comparable to ESO (61%) rather than VPZ (88%-94%), and its EE healing OR (0.95) is essentially PPI-equivalent. Two factors likely explain this discrepancy. First, FXP exhibits the highest protein binding among P-

CABs (92.8%-94.3% *vs* VPZ of 80%-88%), reducing free drug available for parietal cell uptake by 2-3 fold. Second, FXP's intrinsic H⁺/K⁺-ATPase binding kinetics (K_i , k_{off}) remain unpublished (Supplementary Table 12), preventing direct comparison with VPZ's exceptionally tight binding (K_i of 3.0 nM). Our findings therefore demonstrate that pKa is necessary but clearly not sufficient for P-CAB efficacy: High-pKa may enable canalicular accumulation, but adequate free drug fraction and intrinsic binding affinity are required to translate accumulation into sustained acid suppression. This multi-factor model explains why a simple pKa threshold cannot reliably predict clinical outcomes.

Third, with only five marketed P-CABs, our correlation analysis has limited statistical power (30% for detecting $\rho = 0.80$) (Supplementary Table 13) and cannot exclude confounding by regional differences in CLR resistance rates, dosing regimens, or study design heterogeneity. With the revised FXP pKa of 9.04, the previously reported threshold analysis at pKa 9.0 is no longer feasible (4 of 5 P-CABs cluster above this cutoff). The Spearman correlation ($\rho = 0.80$) remains the primary statistical finding but should be interpreted cautiously given the small sample ($n = 4-5$).

Fourth, we used clinical endpoints (eradication rate and endoscopic healing) rather than pH-metry outcomes (intragastric pH threshold and holding time), which have been the established standard for comparing antisecretory drug efficacy for over 50 years. Future studies should directly correlate pKa values with pH-metry parameters to determine whether pKa-dependent differences in acid suppression mediate the observed clinical differences. Fifth, while the Spearman correlation supports a positive pKa-efficacy association, the FXP paradox (pKa of 9.04, OR = 0.95) demonstrates that a simple pKa cutoff cannot serve as a reliable predictor. A multi-factor model incorporating protein binding, intrinsic binding affinity, and pharmacokinetic properties alongside pKa requires prospective validation through pH-metry studies and parietal cell experiments. Sixth, the molecular structures of P-CABs are more variable than those of PPIs (which are all based on substituted benzimidazoles), and this structural diversity may contribute to pharmacological differences beyond what pKa alone can explain.

Finally, ZPZ and KVP data remain limited to single Asian RCTs, restricting generalizability.

CONCLUSION

P-CAB efficacy correlates with pKa values in this SR and NMA of 40 RCTs. High-pKa P-CABs (≥ 9.0) were associated with higher eradication rates in CLR-resistant infections and superior healing in severe esophagitis, whereas low-pKa P-CABs showed more limited advantages over PPIs in the available indirect comparisons. While all P-CABs share the fundamental mechanism of potassium-competitive acid suppression, our findings suggest that individual agents may differ in clinical effectiveness. In high CLR-resistance regions, clinicians may consider pKa as one factor when selecting among available P-CABs. However, these findings remain hypothesis-generating, and prospective validation through head-to-head trials, pH-metry studies correlating pKa with intragastric pH profiles, and parietal cell pharmacological experiments is needed to establish whether the observed associations reflect a causal relationship.

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Figures and Tables

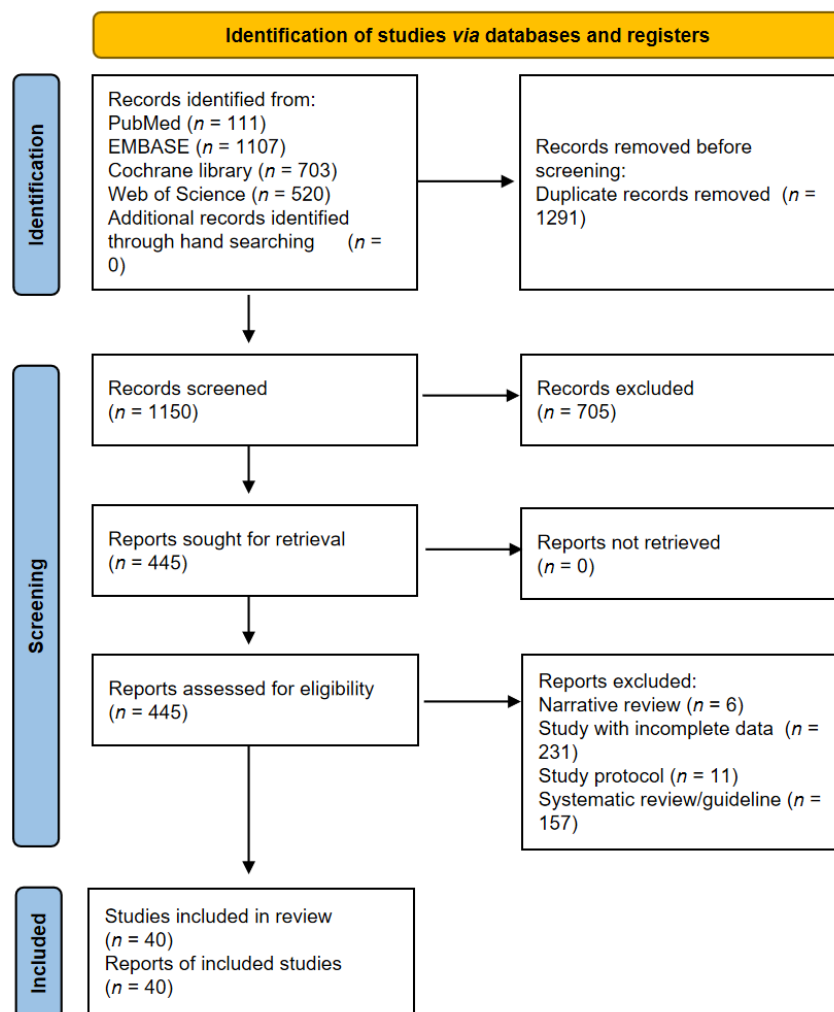
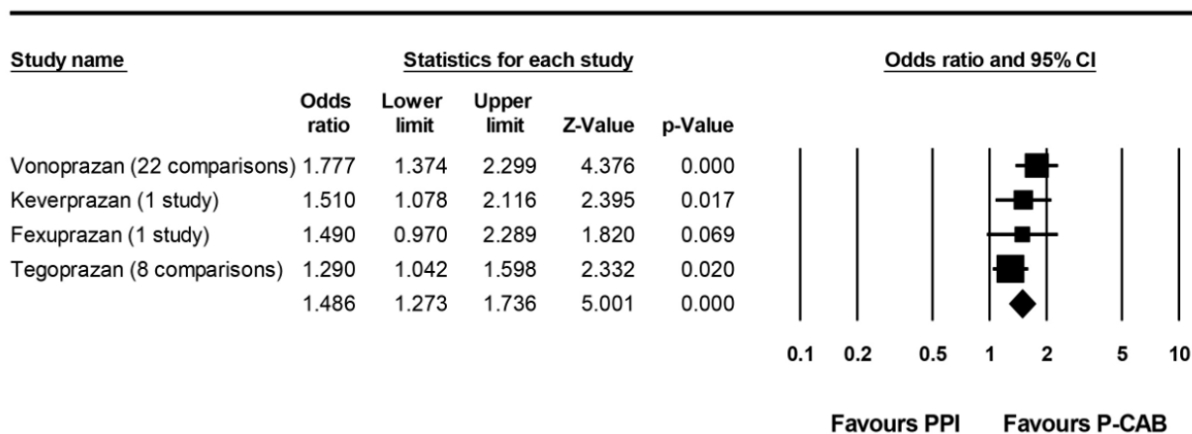
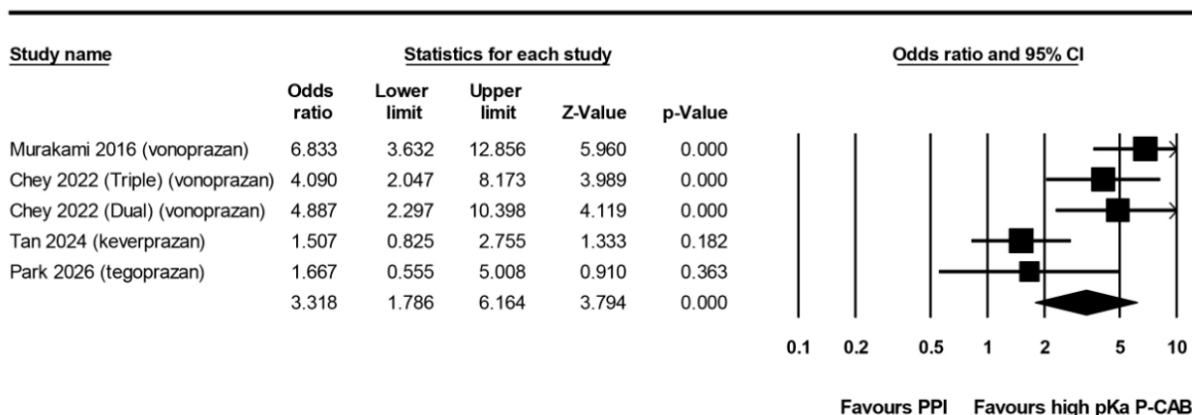


Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram illustrating the study selection process. The systematic literature search identified 2,441 records from four databases (PubMed: $n = 111$, EMBASE: $n = 1107$, Cochrane Library: $n = 703$, Web of Science: $n = 520$). After removing 1291 duplicates, 1150 unique records were screened by title and abstract. Following full-text review of 445 articles, 405 were excluded (narrative reviews: $n = 6$, incomplete data: $n = 231$, study protocols: $n = 11$, systematic reviews/guidelines: $n = 157$). Finally, 40 randomized controlled trials were included: (1) 30 studies for *Helicobacter pylori* eradication; and (2) 10 studies for erosive esophagitis healing.



Heterogeneity: $\chi^2 = 3.536$ df = 3 ($P = 0.316$); $I^2 = 15.156\%$
 Test for overall effect: $Z = 5.001$ ($P < 0.001$)

Figure 2 Forest plot of network meta-analysis comparing potassium-competitive acid blockers *vs* proton pump inhibitors for *Helicobacter pylori* eradication. Each row represents a randomized controlled trial, with squares indicating point estimates of odds ratio and horizontal lines representing 95% CIs. Diamond at the bottom shows the pooled effect estimate. Overall heterogeneity was low ($I^2 = 15.16\%$). P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor.



Heterogeneity: $\chi^2 = 14.445$ df = 4 ($P = 0.006$); $I^2 = 72.309\%$
 Test for overall effect: $Z = 3.794$ ($P < 0.001$)

Figure 3 Forest plot of individual potassium-competitive acid blockers (vonoprazan, tegoprazan, keverprazan) *vs* proton pump inhibitor for clarithromycin-resistant *Helicobacter pylori* eradication. Each row represents a randomized controlled trial, with squares indicating point estimates of odds ratio (OR) and horizontal lines representing 95% CIs. Diamond at the bottom shows the pooled effect estimate. Five studies reported clarithromycin resistance subgroup

data. High-acid dissociation constant; potassium-competitive acid blockers (vonoprazan, keverprazan) and low-acid dissociation constant tegoprazan achieved pooled OR = 3.32 (95%CI: 1.79-6.16) compared with proton pump inhibitors (PPIs). Vonoprazan-based regimens (3 arms) achieved 65.8%-82.0% eradication in clarithromycin-resistant infections *vs* 31.9%-40.0% with PPIs. Keverprazan showed 83.5% *vs* 77.0% with a not significant OR of 1.51 (95%CI: 0.83-2.76), likely attenuated by the high baseline eradication rate in the Chinese PPI arm. Tegoprazan showed 47.8% *vs* 35.5% (OR = 1.67, not significant). Heterogeneity was substantial ($I^2 = 72.3\%$, $P = 0.006$), reflecting geographic and methodological differences. P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor.

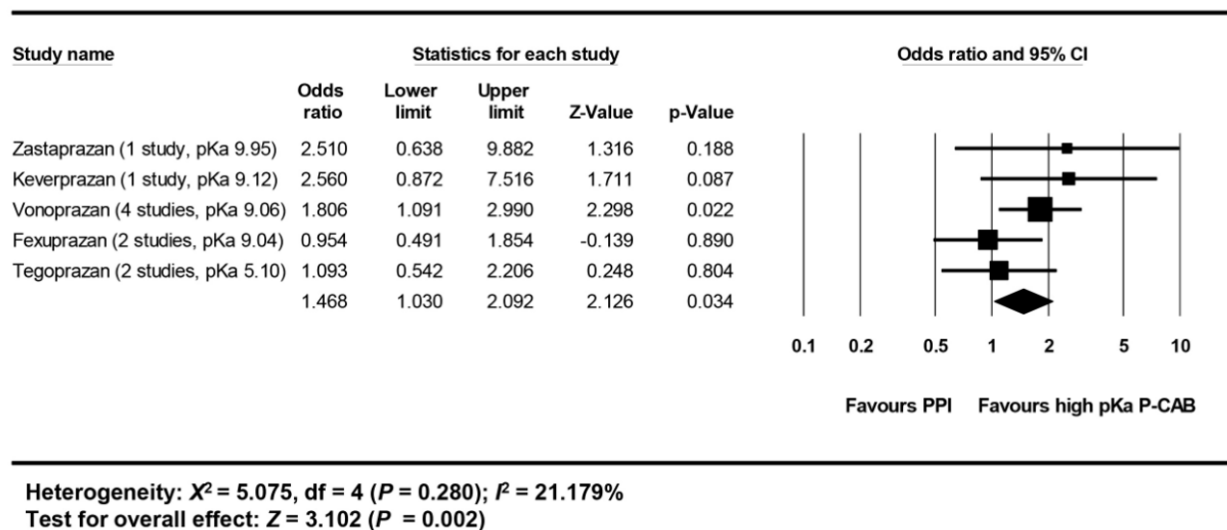


Figure 4 Forest plot of network meta-analysis comparing potassium-competitive acid blockers *vs* proton pump inhibitors for 8-week erosive esophagitis healing. Each row represents a randomized controlled trial, with squares indicating point estimates of odds ratio and horizontal lines representing 95% CIs. Diamond at the bottom shows the pooled effect estimate. Ten randomized controlled trials comparing five potassium-competitive acid blockers [vonoprazan, tegoprazan, fexuprazan (FXP), keverprazan, zastaprazan] with proton pump inhibitors (PPIs) for erosive esophagitis healing are shown. High-acid dissociation constant (pKa) potassium-competitive acid blockers demonstrated significant superiority, while tegoprazan (pKa of 5.1) and FXP (pKa of 9.04, the “FXP paradox”) showed no significant advantage over PPIs. Overall healing rates were high across all treatments (91%-99%), with ceiling effects limiting differentiation in mild-to-

moderate esophagitis. Notably, FXP (pKa of 9.04) showed no significant advantage over PPIs (odds ratio = 0.95) despite high-pKa, illustrating the FXP paradox. P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor.

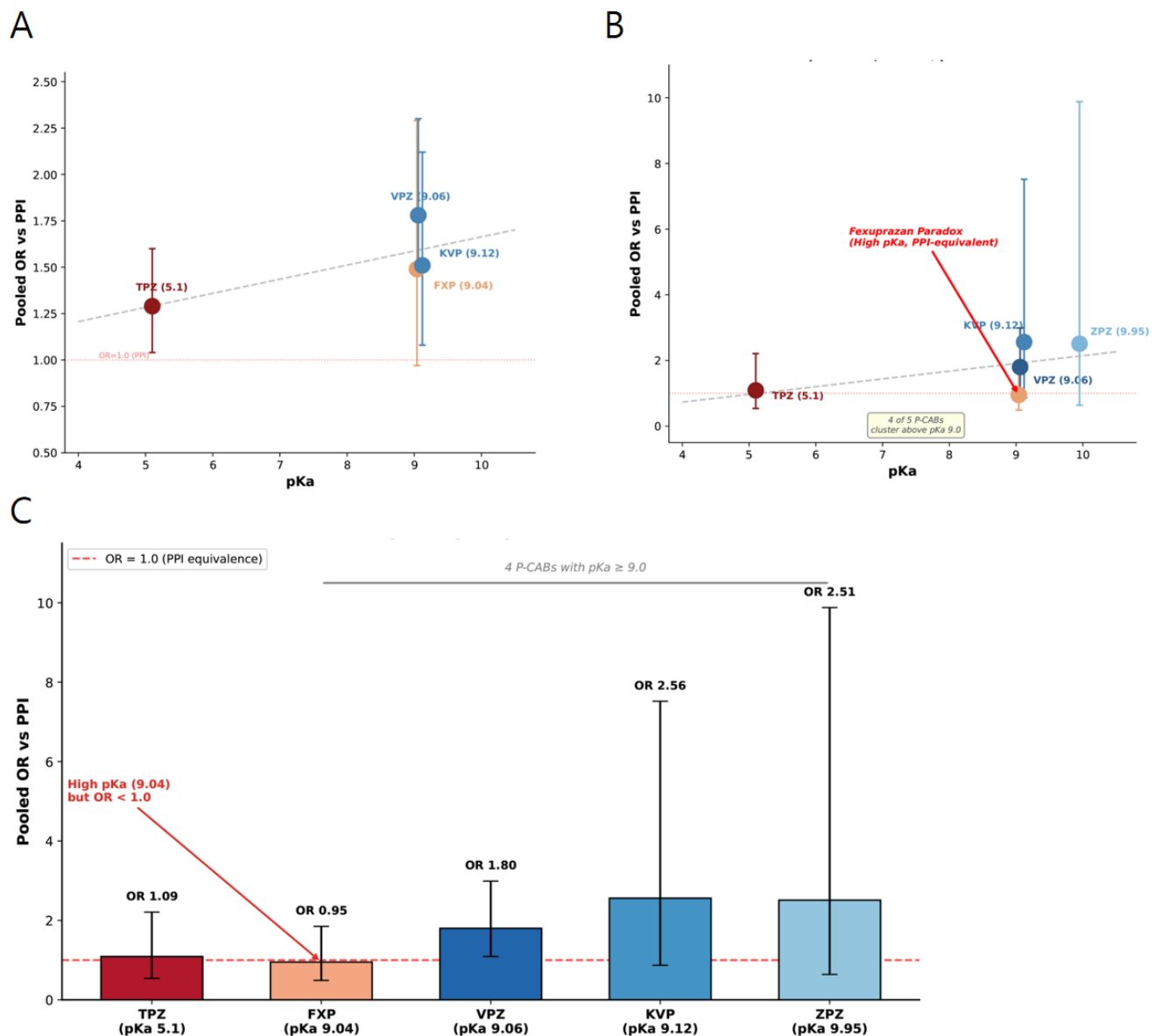


Figure 5 The acid dissociation constant-efficacy relationship among potassium-competitive acid blockers. A: Scatter plot of acid dissociation constant (pKa) vs pooled odds ratio (OR) for *Helicobacter pylori* eradication [$n = 4$ potassium-competitive acid blockers (P-CABs), Spearman $\rho = 0.80$, $P = 0.20$]; B: Scatter plot of pKa vs pooled OR for erosive esophagitis healing ($n = 5$ P-CABs, Spearman $\rho = 0.80$, $P = 0.104$). In both panels, fexuprazan (FXP) (pKa of 9.04) is highlighted as an outlier with proton pump inhibitor-equivalent efficacy despite high-pKa; C: Individual P-CAB efficacy for erosive esophagitis ordered by pKa, illustrating the FXP paradox:

Despite pKa of 9.04, FXP shows OR < 1.0. Dashed line represents ordinary least squares linear regression fit. Error bars represent 95% CIs of pooled ORs. A positive pKa-efficacy trend is observed, but FXP (pKa of 9.04) represents a notable outlier with proton pump inhibitor-equivalent outcomes despite high-pKa. OR: Odds ratio; P-CAB: Potassium-competitive acid blocker; pKa: Acid dissociation constant; PPI: Proton pump inhibitor; TPZ: Tegoprazan; FXP: Fexuprazan; VPZ: Vonoprazan; KVP: Keverprazan; ZPZ: Zastaprazan.

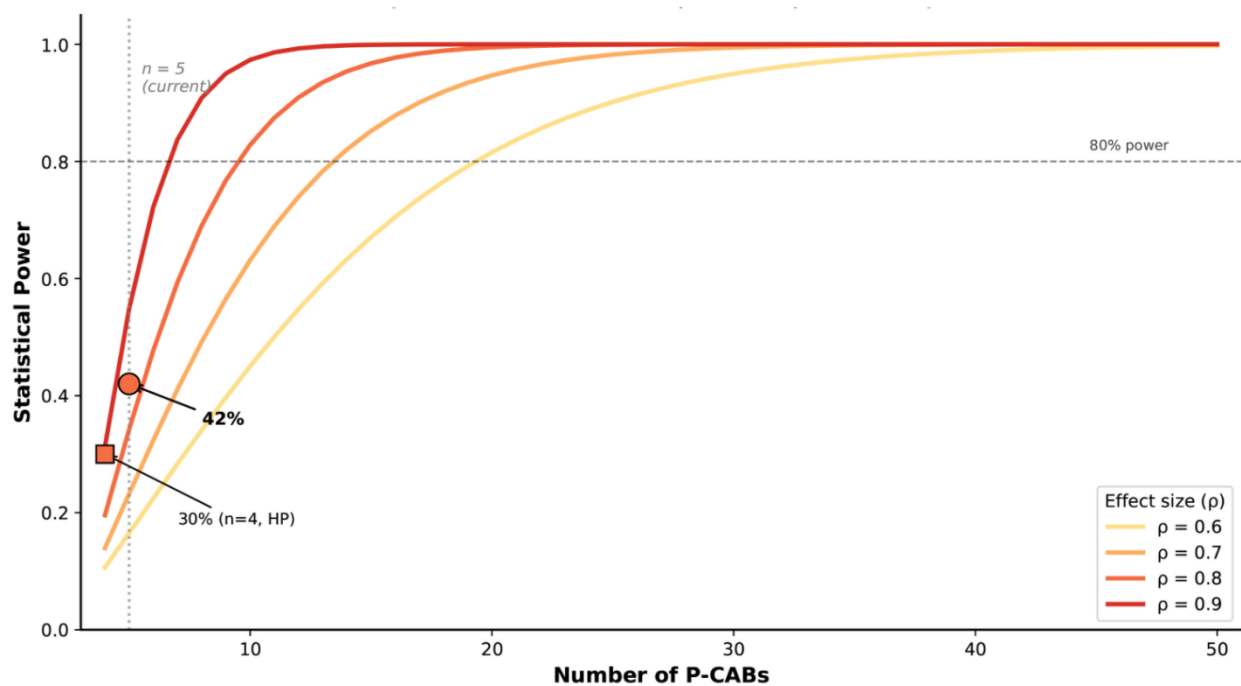


Figure 6 Monte Carlo simulation for statistical power estimation. Power curves showing the relationship between sample size [number of potassium-competitive acid blockers (P-CABs)] and statistical power to detect acid dissociation constant-efficacy correlations at different effect sizes ($\rho = 0.60$, $\rho = 0.70$, $\rho = 0.80$, $\rho = 0.90$). With only 5 marketed P-CABs, power to detect $\rho = 0.80$ is limited to 30% (horizontal dashed line indicates 80% power threshold); with $n = 4$ (*Helicobacter pylori*), power is 30%. These simulations illustrate that the inherent limitation of 5 marketed P-CABs constrains statistical power for correlation testing, emphasizing the importance of mechanistic plausibility and supporting evidence from subgroup analyses. P-CABs: Potassium-competitive acid blockers.

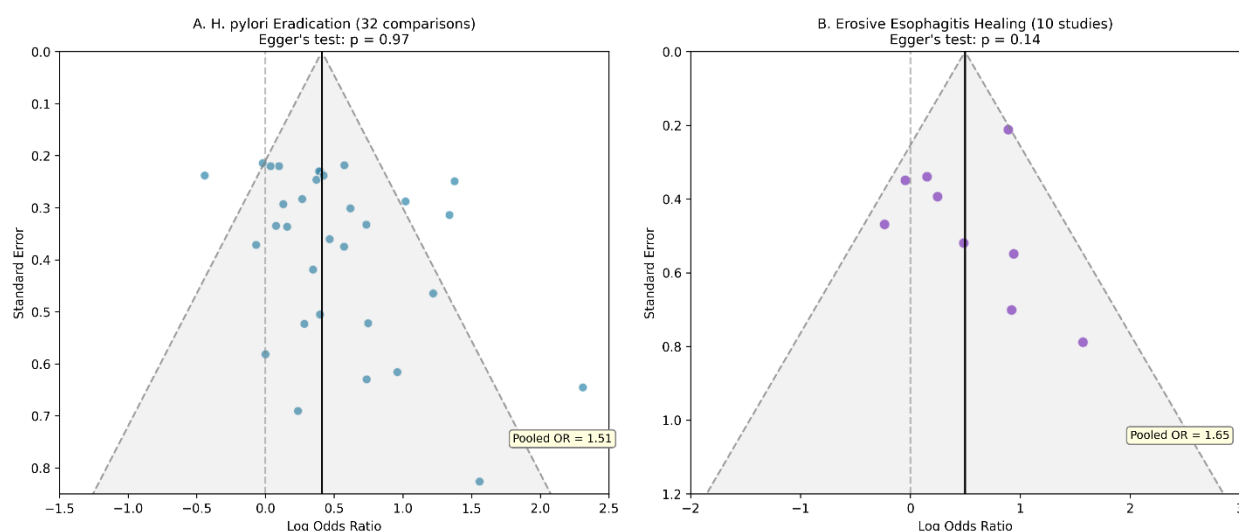


Figure 7 Funnel plots for assessment of publication bias. A: Funnel plot for *Helicobacter pylori* eradication studies (30 randomized controlled trials, 32 comparisons). Each point represents one study, plotted by effect size (log odds ratio, X-axis) against precision (standard error, Y-axis). Visual inspection shows symmetric distribution around the pooled effect estimate (vertical line). Egger's regression test was not significant ($P = 0.97$), indicating no evidence of publication bias; B: Funnel plot for erosive esophagitis healing studies (10 randomized controlled trials). Distribution appears symmetric upon visual inspection. Egger's test was not significant ($P = 0.14$); however, interpretation is limited by the small number of studies ($n = 10$), and funnel plot asymmetry was not visually apparent. Dashed diagonal lines represent pseudo-95% confidence limits. *H. pylori*: *Helicobacter pylori*; OR: Odds ratio.

Table 1 Characteristics of included randomized controlled trials comparing potassium-competitive acid blocker *vs* proton pump inhibitor for *Helicobacter pylori* eradication (*n* = 30 studies, 32 comparisons)

Number	Ref.	Year	Country	P-CAB	PPI	Design	Regimen	Antibiotics	Days	Eradication success in P-CAB group (<i>n</i> = 4020)	Eradication success in PPI group (<i>n</i> = 3619)
1	Murakami <i>et al</i> [18]	2016	Japan	VPZ 20 mg	LPZ 30 mg	RCT, DB, Triple NI		AMO + CLR	7	300/324 (92.6%)	243/320 (75.9%)
2	Maruyama <i>et al</i> [19]	2017	Japan	VPZ 20 mg	RPZ/LPZ	RCT, OL	Triple	AMO + CLR	7	69/72 (95.8%)	48/69 (69.6%)
3	Sue <i>et al</i> [20]	2018	Japan	VPZ 20 mg	PPI mix	RCT, OL	Triple	AMO + CLR	7	48/55 (87.3%)	39/51 (76.5%)
4	Chey <i>et al</i> [3] (Triple)	2022	United States/Europe	VPZ 20 mg	LPZ 30 mg	RCT, DB, Triple NI		AMO + CLR	14	222/262 (84.7%)	201/255 (78.8%)
5	Chey <i>et al</i> [3] (Dual)	2022	United States/Europe	VPZ 20 mg	LPZ 30 mg	RCT, OL	Dual	AMO	14	208/265 (78.5%)	201/255 (78.8%)
6	Choi <i>et al</i> [21]	2022	Korea	TPZ 50 mg	LPZ 30 mg	RCT, DB, Triple NI		AMO + CLR	7	110/175 (62.9%)	106/175 (60.6%)

7	Han <i>et al</i> [22]	2023	China	VPZ	20	RPZ 20 mg	RCT, OL	Dual	AMO	10	308/345 (89.3%)	293/345 (84.9%)
8	Huang <i>et al</i> [23]	2023	China	VPZ	20	ESO 20 mg	RCT, OL	Triple	AMO + Bi	14	38/40 (95.0%)	32/40 (80.0%)
9	Kim <i>et al</i> [24]	2023	Korea	TPZ	50	BQT (LPZ)	RCT, DB	BQT	Bi + MTZ + TC	14	84/105 (80.0%)	82/106 (77.4%)
10	Lu <i>et al</i> [25]	2023	China	VPZ	20	BQT (ESO)	RCT, OL, NI	BQT	AMO + FUR + Bi	14	74/78 (94.9%)	73/78 (93.6%)
11	Peng <i>et al</i> [26]	2023	China	VPZ	20	Modified BQT (PACB) (ESO)	RCT, OL, MC	Dual	AMO	14	142/158 (89.9%)	128/158 (81.0%)
12	Qian <i>et al</i> [27]	2023	China	VPZ	20	BQT (ESO)	RCT, OL	Dual	AMO (HD)	10	114/125 (91.2%)	110/125 (88.0%)
13	Wang <i>et al</i> [28]	2023	China	VPZ	20	BQT (RPZ)	RCT, OL	Dual	AMO	14	70/74 (94.6%)	67/77 (87.0%)
14	Chen <i>et al</i> [29]	2024	China	VPZ	20	ILA 5 mg	RCT, OL, NI	Dual	AMO	14	38/45 (84.4%)	38/45 (84.4%)
15	Cheung <i>et al</i> [30]	2024	HK	VPZ	20	BQT (ESO)	RCT, OL	Dual/Triple	AMO ± CLR	14	96/100 (96.0%)	92/100

				mg					(92.0%)
16	DWP14012[31]	2024 Korea	FXP	40 LPZ 30 mg	RCT, DB, Triple Ph3	AMO + CLR	14	184/220 (83.6%)	166/213 (77.9%)
17	Huang <i>et al</i> [32]	2024 China	VPZ	20 BQT (ILA)	RCT, OL, Dual MC	AMO	10	96/103 (93.2%)	81/101 (80.2%)
18	Kong <i>et al</i> [33]	2024 China	VPZ	20 BQT (ESO)	RCT, OL, Dual NI	AMO	10	158/184 (85.8%)	155/184 (84.2%)
19	Lee <i>et al</i> [34]	2024 Korea	TPZ	50 BQT (ESO)	RCT, OL, Seq NI	AMO + CLR to MTZ	10	176/202 (87.1%)	171/204 (83.8%)
20	Liang <i>et al</i> [35]	2024 China	VPZ	20 Modified BQT (PACB) (ESO)	RCT, OL, Triple + Bi MC	AMO + Bi	14	251/300 (83.7%)	247/297 (83.2%)
21	Lin <i>et al</i> [36]	2024 China	TPZ	50 BQT (ESO)	RCT, OL Dual	AMO	14	184/214 (86.0%)	91/107 (85.0%)
22	Tan <i>et al</i> [37]	2024 China	KVP	20 ESO 20 mg	RCT, DB, BQT NI	Bi + AMO + CLR	14	252/287 (87.8%)	236/286 (82.5%)
23	Zhou <i>et al</i> [38]	2024 China	VPZ	20 ESO 20 mg	RCT, OL, Dual MC	AMO	10	245/287 (85.4%)	217/283 (76.7%)

24	Cheng <i>et al</i> [39]	2025	China	TPZ mg	50 BQT (ESO)	RCT, OL, Dual/BQT MC	AMO/Bi CLR	+ 14	138/160 (86.3%)	115/149 (77.2%)
25	Fan <i>et al</i> [40]	2025	China	VPZ mg	20 BQT (ESO)	RCT, OL Dual	AMO	14	200/252 (79.4%)	216/252 (85.7%)
26	Fan <i>et al</i> [41]	2026	China	TPZ mg	50 BQT (ESO)	RCT, OL, Dual MC	AMO	14	56/76 (73.7%)	57/76 (75.0%)
27	Han <i>et al</i> [42]	2025	China	VPZ mg	20 Modified BQT (PACB) (ESO)	RCT, OL Triple	AMO + CLR	14	154/175 (88.0%)	127/175 (72.6%)
28	Park <i>et al</i> [43] (50 mg)	2026	Korea	TPZ mg	50 LPZ 30 mg	RCT, DB, Triple NI	AMO + CLR	14	100/113 (88.5%)	100/123 (81.3%)
29	Park <i>et al</i> [43] (100 mg)	2026	Korea	TPZ mg	100 LPZ 30 mg	RCT, DB, Triple NI	AMO + CLR	14	104/119 (87.4%)	100/123 (81.3%)
30	Shekeban <i>et al</i> [44]	2025	Egypt	VPZ mg	20 STT (ESO)	RCT, OL Dual/triple	AMO ± CLR	14	77/88 (87.5%)	37/44 (84.1%)
31	Tai <i>et al</i> [45]	2025	Taiwan	VPZ mg	20 RPZ 20 mg	RCT, OL Dual	AMO	14	53/61 (86.9%)	49/60 (81.7%)
32	Yan <i>et al</i> [46]	2025	China	VPZ	20 BQT (ESO)	RCT, OL, BQT	Bi + DOX	+ 14	150/166	118/166

mg

MC

MTZ

(90.4%)

(71.1%)

P-CAB: Potassium-competitive acid blocker; VPZ: Vonoprazan; TPZ: Tegoprazan; KVP: Keverprazan; FXP: Fexuprazan; LPZ: Lansoprazole; RPZ: Rabeprazole; ESO: Esomeprazole; ILA: Ilaprazole; AMO: Amoxicillin; CLR: Clarithromycin; MTZ: Metronidazole; FUR: Furazolidone; DOX: Doxycycline; Bi: Bismuth; TC: Tetracycline; BQT: Bismuth quadruple therapy; STT: Standard triple therapy; RCT: Randomized controlled trial; DB: Double-blind; OL: Open-label; NI: Non-inferiority; MC: Multicenter; Ph3: Phase 3; HD: High-dose; Seq: Sequential; PACB: Proton pump inhibitor, amoxicillin, clarithromycin, bismuth.

ACCEPTED

Table 2 Characteristics of included erosive esophagitis randomized controlled trials ($n = 10$ studies)

Number	Ref.	Year	Region	P-CAB	PPI	n (overall)	Healing rate in P-CAB group (overall) ($n = 2370$)	Healing rate in PPI group (overall) ($n = 1826$)	Healing rate in P-CAB group (LA C/D) ($n = 612$)	Healing rate in PPI group (LA C/D) ($n = 438$)
1	Ashida <i>et al</i> [47]	2015	Japan	VPZ 40 mg	5-LPZ 30 mg	686	524/554 (94.6%)	123/132 (93.2%)	184/199 (92.5%)	40/46 (87.0%)
2	Ashida <i>et al</i> [48]	2016	Japan	VPZ 20 mg	LPZ 30 mg	404	203/205 (99.0%)	190/199 (95.5%)	75/75 (100%)	63/72 (87.5%)
3	Xiao <i>et al</i> [49]	2020	China	VPZ 20 mg	LPZ 30 mg	468	220/238 (92.4%)	210/230 (91.3%)	64/76 (84.2%)	55/68 (80.9%)
4	Laine <i>et al</i> [50]	2023	United States/Europe	VPZ 20 mg	LPZ 30 mg	1024	478/514 (92.9%)	431/510 (84.5%)	163/177 (92.1%)	125/174 (71.8%)
5	Chen <i>et al</i> [51]	2022	China	KVP 20 mg	LPZ 30 mg	238	114/119 (95.8%)	107/119 (89.9%)	22/24 (91.7%)	20/25 (80.0%)
6	Oh <i>et al</i> [52]	2025	South Korea	ZPZ 20 mg	ESO 40 mg	282	141/144 (97.9%)	131/138 (94.9%)	6/6 (100%)	5/6 (83.3%)
7	Lee <i>et al</i> [53]	2022	South Korea	FXP 40 mg	ESO 40 mg	218	106/107 (99.1%)	110/111 (99.1%)	NR	NR

				mg				
8	Zhuang 2024 China <i>et al</i> [54]	FXP 40 mg	ESO 328 40	146/165 (88.5%)	145/163 (89.0%)	41/51 (80.4%)	43/47 (91.5%)	
			mg					
9	Lee <i>et al</i> [55]	TPZ 50/100 mg	ESO 300 40 mg	192/201 (98.5%)	92/99 (92.9%)	~4/4 (100%)	NR	
10	Zhu <i>et al</i> [56]	TPZ 50 mg	ESO 248 40 mg	112/123 (91.1%)	116/125 (92.8%)	NR	NR	

Los Angeles classification C/D data summary by potassium-competitive acid blocker: (1) Zastaprazan [acid dissociation constant (pKa) of 995]: 100% *vs* 83.3% (+16.7%, *n* = 6/arm); (2) Keverprazan (pKa of 912): 91.7% *vs* 80.0% (+11.7%, *n* = 24-25/arm); (3) Vonoprazan (pKa of 906): 84.0%-100% *vs* 71.8%-86.7% (pooled +13.4%); (4) Fexuprazan (pKa of 904): 80% *vs* 91% (-11%, inferior to proton pump inhibitor despite high-pKa); and (5) Tegoprazan (pKa of 51): 100% *vs* not reported (data limited). P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor; VPZ: Vonoprazan; TPZ: Tegoprazan; KVP: Keverprazan; FXP: Fexuprazan; ZPZ: Zastaprazan; LPZ: Lansoprazole; ESO: Esomeprazole; NR: Not reported; LA: Los Angeles classification.

Table 3 Results of meta-analysis for the potassium-competitive acid blocker *vs* proton pump inhibitor efficacy in clarithromycin-resistant *Helicobacter pylori* infections

Ref.	Year	Country	P-CAB	Comparator	Eradication success in P-CAB group	Eradication success in PPI group	Δ (%)	OR	95%CI
Murakami <i>et al</i> [18]	2016	Japan	VPZ	LPZ	82/100 (82.0)	46/115 (40.0)	+42.0%	6.83	3.63-12.86

Chey <i>et al</i> [3] (triple)	2022	United States/Europe	VPZ LPZ	48/73 (65.8) 23/72 (31.9)	+33.9%	4.09	2.05- 8.17
Chey <i>et al</i> [3] (dual)	2022	United States/Europe	VPZ LPZ	39/56 (69.6) 23/72 (31.9)	+37.7%	4.89	2.30- 10.40
Tan <i>et al</i> [37]	2024	China	KVP ESO	121/145 (83.5)	97/126 (77.0)	+6.5%	1.51 0.83- 2.76
Park <i>et al</i> [43]	2026	Korea	TPZ LPZ	11/23 (47.8%)	11/31 (35.5%)	+12.3%p	1.67 0.56- 5.01
Pooled (random effects, 5 studies, $n = 813$)							3.32 1.79- 6.16

P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor; OR: Odds ratio; VPZ: Vonoprazan; KVP: Keverprazan; LPZ: Lansoprazole; ESO: Esomeprazole.

Table 4 Risk of bias assessment for Included randomized controlled trials

Ref.	Design	D1: Randomization	D2: Deviations	D3: Missing data	D4: Measurement	D5: Reporting	Overall
<i>H. pylori</i> eradication RCTs ($n = 30, 32$ comparisons)							
Murakami <i>et al</i> [18]	DB, NI	Low (computer, stratified)	Low (DB)	Low (FAS/PPS)	Low (UBT)	Low (Ph3)	Low
Maruyama <i>et al</i> [19]	OL	Some random: Odd/even MRN)	(quasi- Some (OL)	Low (complete follow-up)	Low (UBT)	Low (primary outcome reported)	Some
Sue <i>et al</i> [20]	OL	Low (Web-	Some (OL)	Low	Low (UBT)	Low (pre-	Some

		based minimization)	(minimal dropout)	registered outcome)						
Chey <i>et al</i> [3] (triple)	DB, NI	Low based block size 6)	(Web- central, double- dummy)	Low (DB, double- dummy)	Low (mITT analysis, balanced dropout)	Low lab UBT)	(central blinded primary endpoint)	Low (pre- registered primary endpoint)	Low	
Chey <i>et al</i> [3] (dual)	OL	Low web-based)	(central web-based)	Some arm)	(OL (mITT analysis)	Low lab UBT)	(central blinded endpoint)	Low (pre- registered endpoint)	Some	
Choi <i>et al</i> [21]	DB, NI	Low block)	(stratified block)	Low (double- dummy design)	Low (FAS analysis, minimal dropout)	Low UBT/histology)	(blinded (protocol- specified outcomes)	Low	Low	
Han <i>et al</i> [22]	OL	Low (computer- generated sequence)	Some (OL)	(OL (ITT analysis)	Low (ITT analysis)	Low UBT outcome)	(objective (outcomes per protocol)	Low	Some	
Huang <i>et al</i> [23]	OL	Low number table)	(random table)	Some (OL)	Low (complete follow-up)	Low UBT/histology)	(objective (primary outcome reported)	Low	Some	
Kim <i>et al</i> [24]	DB	Low block)	(stratified block)	Low active- controlled)	(DB (mITT/PP both reported)	Low UBT)	(blinded registered outcomes)	Low (pre- registered outcomes)	Low	
Lu <i>et al</i> [25]	OL, NI	Low randomization)	(block randomization)	Some (OL)	Low (ITT analysis)	Low UBT outcome)	(objective registered outcomes)	Low (pre- registered outcomes)	Some	

Peng <i>et al</i> [26]	OL, MC	Low (central randomization)	Some (OL MC)	Low (FAS analysis)	Low (objective UBT outcome)	Low (pre- registered outcomes)	Some
Qian <i>et al</i> [27]	OL	Low (computer randomization)	Some (OL)	Low (complete follow-up)	Low (objective UBT outcome)	Low (primary outcome reported)	Some
Wang <i>et al</i> [28]	OL	Low (randomized, method NR)	Some (OL)	Low (per abstract)	Low (objective UBT outcome)	Some (conference abstract only)	Some
Chen <i>et al</i> [29]	OL, NI	Low (central randomization)	Some (OL)	Low (ITT analysis)	Low (objective UBT outcome)	Low (pre- registered outcomes)	Some
Cheung <i>et al</i> [30]	OL	Low (computer- generated, opaque envelopes)	Some (OL)	Low (ITT analysis)	Low (objective UBT outcome)	Low (pre- registered outcomes)	Some
DWP14012[31]	DB, Ph3	Low (IWRS centralized)	Low (DB Ph3)	Low (ITT analysis)	Low (blinded UBT)	Some (conference abstract only)	Some
Huang <i>et al</i> [32]	OL, MC	Low (central randomization)	Some (OL MC)	Low (FAS analysis)	Low (objective UBT outcome)	Low (pre- registered outcomes)	Some
Kong <i>et al</i> [33]	OL, NI	Low (computer randomization)	Some (OL)	Low (ITT analysis)	Low (objective UBT outcome)	Low (primary outcome)	Some

									reported)		
Lee <i>et al</i> [34]	OL, NI	Low (stratified block)	Some Seq)	(OL Low (mITT analysis)	Low (objective UBT outcome)	Low (pre-registered outcomes)	Some				
Liang <i>et al</i> [35]	OL, MC	Low (block randomization 1:1)	Some MC)	(OL Low (ITT analysis)	Low (objective UBT/histology)	Low (pre-registered outcomes)	Some				
Lin <i>et al</i> [36]	OL	Low (computer randomization)	Some (OL)	Low (ITT analysis)	Low (objective UBT outcome)	Low (Primary outcome reported)	Some				
Tan <i>et al</i> [37]	DB, NI	Low (computer-generated sequence)	Low (DB)	Low (FAS analysis)	Low (blinded UBT/histology)	Low (pre-registered outcomes)	Low				
Zhou <i>et al</i> [38]	OL, MC	Low (central randomization)	Some MC)	(OL Low (mITT analysis)	Low (objective UBT outcome)	Low (pre-registered outcomes)	Some				
Cheng <i>et al</i> [39]	OL, MC	Low (computer randomization)	Some MC)	(OL Low (ITT analysis)	Low (objective UBT outcome)	Low (primary outcome reported)	Some				
Fan <i>et al</i> [40]	OL	Low (computer randomization)	Some (OL)	Low (ITT analysis)	Low (objective UBT outcome)	Low (primary outcome reported)	Some				
Fan <i>et al</i> [41]	OL, MC	Low (central randomization)	Some MC)	(OL Low (ITT analysis)	Low (objective UBT outcome)	Low (primary outcome)	Some				

								reported)	
Han <i>et al</i> [42]	OL	Low (computer randomization)	Some (OL)	Low (ITT analysis)	Low (objective UBT outcome)	Low (primary outcome reported)	Some		
Park <i>et al</i> [43] (50mg)	DB, NI	Low (IWRS seed-allocated codes)	Low (DB)	Low (FAS analysis)	Low (UBT)	Low (pre-registered outcomes)	Low		
Park <i>et al</i> [43] (100mg)	DB, NI	Low (IWRS seed-allocated codes)	Low (DB)	Low (FAS analysis)	Low (UBT)	Low (pre-registered outcomes)	Low		
Shekeban <i>et al</i> [44]	OL	Low (computer randomization)	Some (OL)	Low (complete follow-up)	Low (objective UBT outcome)	Low (pre-registered outcomes)	Some		
Tai <i>et al</i> [45]	OL	Low (computer randomization)	Some (OL)	Low (ITT analysis)	Low (objective UBT outcome)	Low (pre-registered outcomes)	Some		
Yan <i>et al</i> [46]	OL, MC	Low (central randomization)	Some (MC)	Low (ITT analysis)	Low (objective UBT outcome)	Low (pre-registered outcomes)	Some		

Erosive esophagitis RCTs ($n = 10$)

Ashida <i>et al</i> [47]	DB	Low (central randomization)	Low (DB)	Low (complete follow-up)	Low (blinded endoscopy)	Low (pre-registered outcomes)	Low		
Ashida <i>et al</i> [48]	DB	Low (central randomization)	Low (DB Ph3)	Low (ITT analysis)	Low (blinded endoscopy)	Low (pre-registered outcomes)	Low		
Xiao <i>et al</i> [49]	DB	Low (IWRS randomization)	Low (DB Ph3)	Low (FAS analysis)	Low (central blinded)	Low (pre-registered)	Low		

						endoscopy)	outcomes)
Laine <i>et al</i> [50]	DB	Low (IWRS Low (DB Low (central Low (pre- Low	central Ph3) (mITT blinded registered	randomization) analysis) endoscopy) outcomes)			
Chen <i>et al</i> [51]	DB	Low (computer Low (DB) Low (FAS Low (blinded Low (pre- Low	randomization) analysis) endoscopy) registered				outcomes)
Oh <i>et al</i> [52]	DB	Low (IWRS Low (DB Low (FAS Low (blinded Low (pre- Low	randomization) Ph3) analysis) endoscopy) registered				outcomes)
Lee <i>et al</i> [53]	DB	Low (stratified Low (DB) Low (FAS Low (blinded Low (pre- Low	randomization) analysis) endoscopy) registered				outcomes)
Zhuang <i>et al</i> [54]	DB	Low (central Low (DB) Low (FAS Low (blinded Low (pre- Low	randomization) analysis) endoscopy) registered				outcomes)
Lee <i>et al</i> [55]	DB	Low (stratified Low (DB) Low (FAS Low (blinded Low (pre- Low	randomization) analysis) endoscopy) registered				outcomes)
Zhu <i>et al</i> [56]	DB	Low (central Low (DB) Low (FAS Low (blinded Low (pre- Low	randomization) analysis) endoscopy) registered				outcomes)

RCTs: Randomized controlled trials; DB: Double-blind; OL: Open-label; NI: Non-inferiority; MC: Multicenter; Ph3: Phase 3; UBT: Urea breath test; ITT: Intention-to-treat; mITT: Modified intention-to-treat; FAS: Full analysis set; PP: Per-protocol; IWRS: Interactive Web Response System; *H. pylori*: *Helicobacter pylori*.

Table 5 GRADE summary of findings (by outcome)

Outcome	Number	Risk of Inconsistency	Indirectness	Imprecision	Publication Effect	Certainty
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of studies bias					bias	estimate
<i>H. pylori</i> 30	RCTsNot	Not serious	Not serious	Not serious	Undetected	OR =High
eradication(32	serious ¹					1.49
(P-CAB vsarms)[3,18-						(95%CI:
PPI) 46]						1.27-
						1.74)
EE healing10	Not	Not serious	Not serious	Serious ²	Undetected	OR =Moderate
8-week (P-RCTs[47-	serious					1.47
CAB vs56]						(95%CI:
PPI)						1.03-
						2.09)

¹Possible concerns due to open-label design in some *Helicobacter pylori* randomized controlled trials; however, not downgraded because outcome assessment (urea breath test) is objective and unlikely influenced by lack of blinding.

²Downgraded one level: Some individual potassium-competitive acid blockers (zastaprazan, keverprazan) had only 1 randomized controlled trial each with wide confidence intervals.

P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor; EE: Erosive esophagitis; OR: Odds ratio; RCTs: Randomized controlled trials; *H. pylori*: *Helicobacter pylori*.