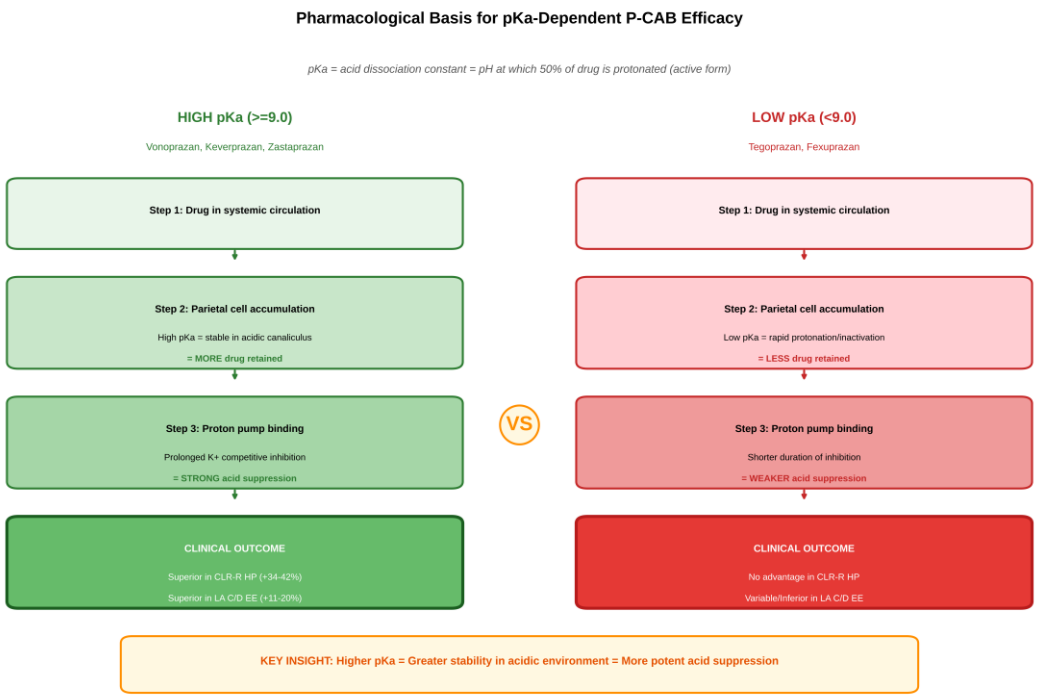
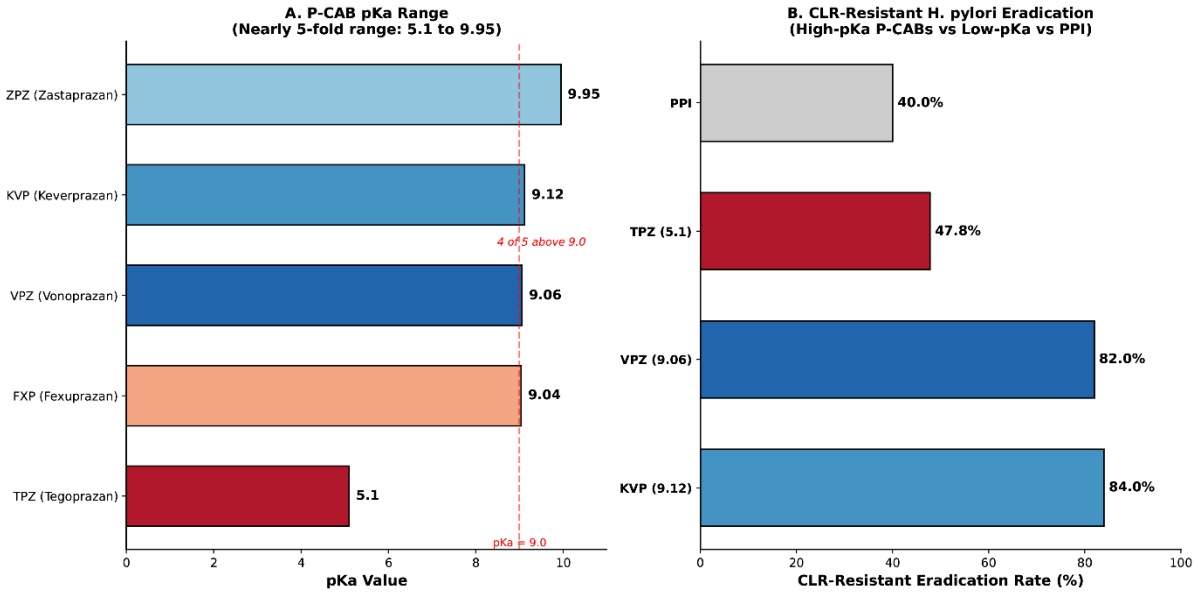
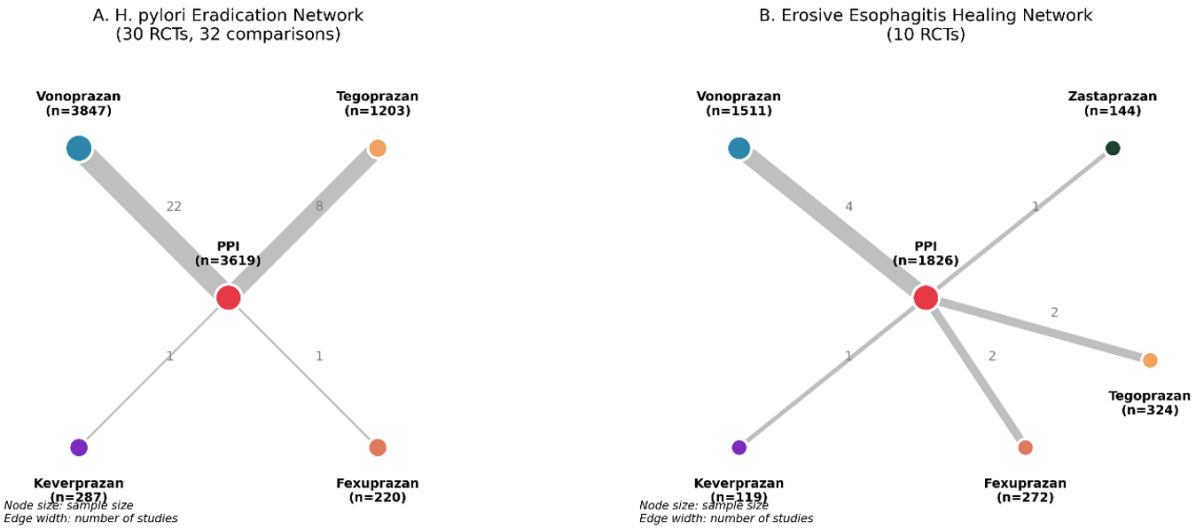


Supplementary Figure 1 Mechanism of pKa-dependent acid suppression. Schematic illustrating the pharmacological mechanism. Potassium-competitive acid blockers are weak bases that accumulate *via* pH-dependent ion-trapping. Higher pKa enables greater protonation at low pH, leading to more sustained H+, K+-ATPase inhibition.

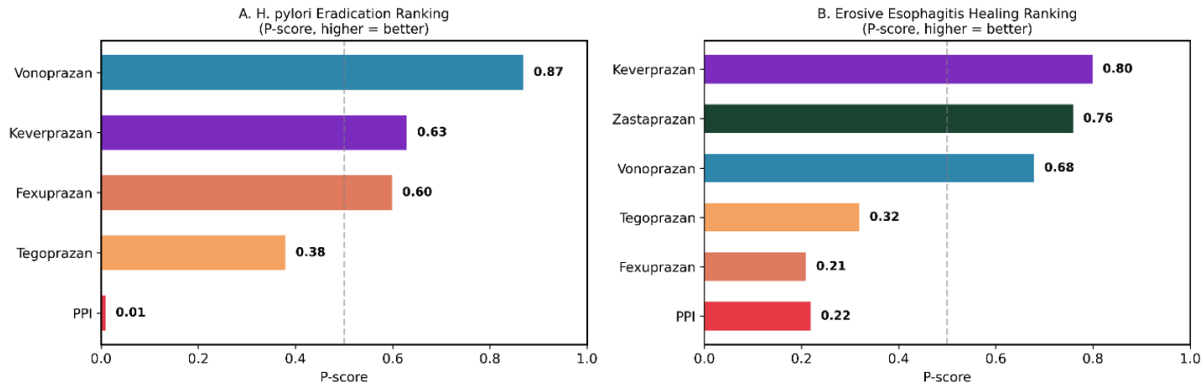


Supplementary Figure 2 Potassium-competitive acid blocker pKa range and efficacy heterogeneity. A: Potassium-competitive acid blocker (P-CAB) pKa range; B: Clarithromycin (CLR)-resistant *Helicobacter pylori* eradication. Wide pKa range (5.1-9.95)

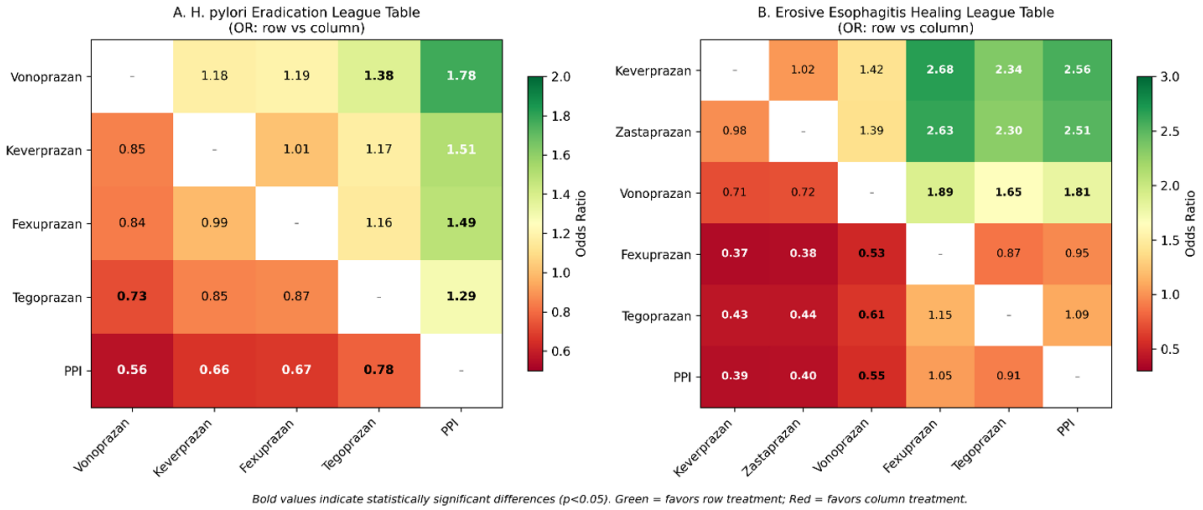
among P-CABs corresponds to heterogeneous clinical outcomes. The pKa values: Tegoprazan 5.1, fexuprazan 9.04, vonoprazan 9.06, keverprazan 9.12, zastaprazan 9.95. High-pKa P-CABs (vonoprazan 82%, keverprazan 84%) dramatically outperform proton pump inhibitors (40%) in CLR-resistant *Helicobacter pylori*; low-pKa tegoprazan (47.8%) shows no significant advantage. Notably, fexuprazan (pKa 9.04) clusters with high-pKa agents yet shows proton pump inhibitor-equivalent efficacy, highlighting pKa as necessary but not sufficient. P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor; CLR: Clarithromycin; *H. pylori*: *Helicobacter pylori*.



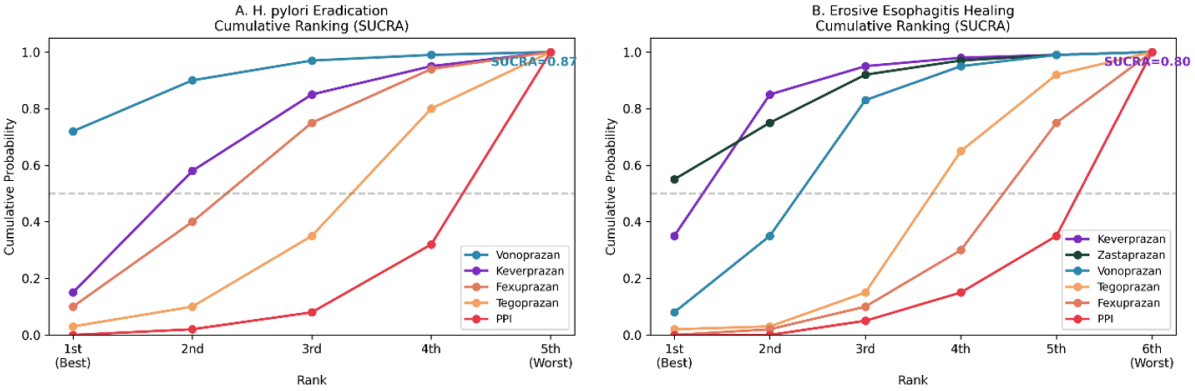
Supplementary Figure 3 Network geometry plots. Network geometry plots illustrating the evidence structure for network meta-analysis. Node size represents the number of patients randomized to each treatment. Edge thickness represents the number of direct comparisons between treatments. All potassium-competitive acid blocker s are connected to proton pump inhibitors (common comparator), forming a star-shaped network. A: *Helicobacter pylori* eradication (30 randomized controlled trial s, 32 comparisons, n = 7639); B: Erosive esophagitis healing (10 randomized controlled trials, n = 4196).



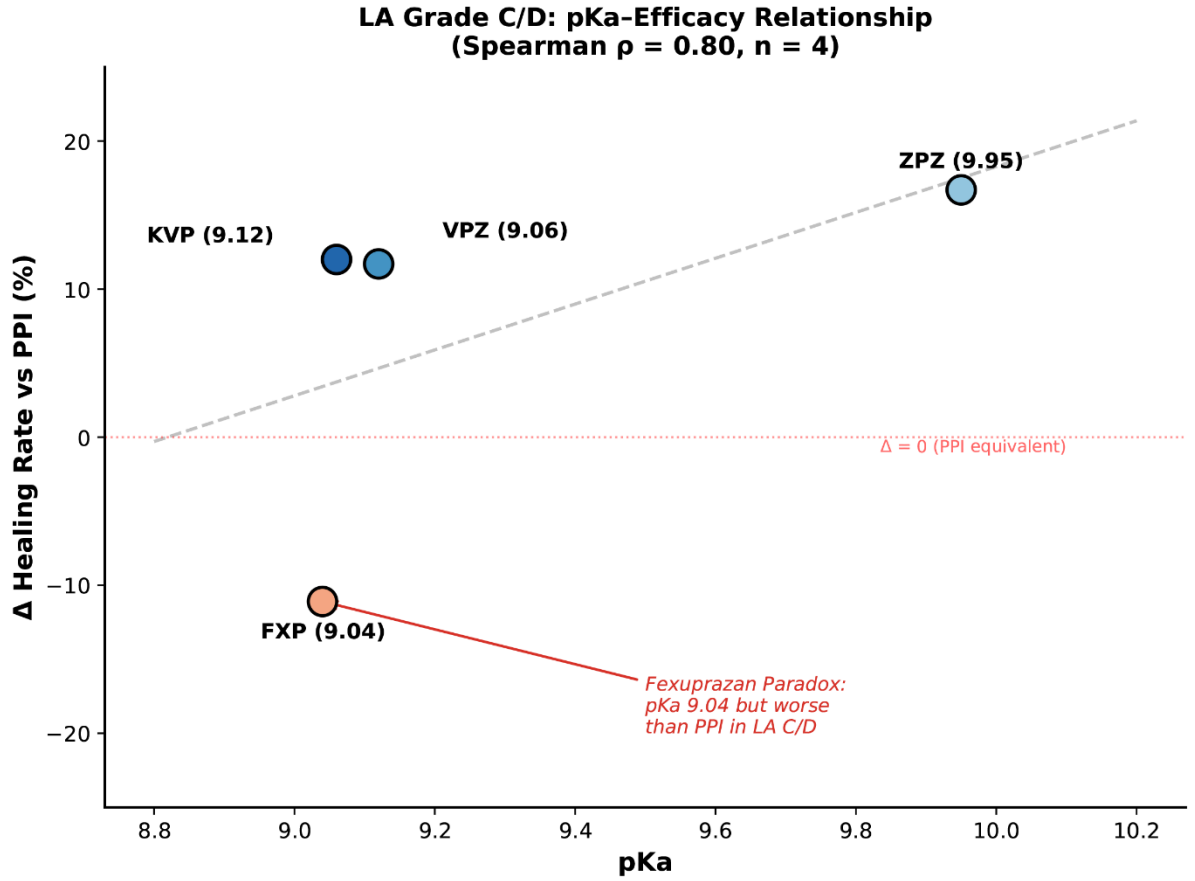
Supplementary Figure 4 Treatment ranking plots (P-scores). A and B: P-scores represent the probability that a treatment is better than all competing treatments, ranging from 0 (worst) to 1 (best). For *Helicobacter pylori* eradication, vonoprazan achieved the highest P-score (0.87), followed by keverprazan (0.63), fexuprazan (0.60), and tegoprazan (0.38). The ranking pattern closely follows pKa values.



Supplementary Figure 5 League tables. A and B: League tables present all pairwise comparisons from the network meta-analysis. Each cell shows the odds ratio (OR) (95%CI) for the row treatment versus the column treatment. For *Helicobacter pylori* eradication, vonoprazan demonstrated significant superiority over proton pump inhibitor (OR = 1.78) and over tegoprazan (OR = 1.29), while tegoprazan showed no significant difference from proton pump inhibitor (OR = 1.29, 95%CI: 1.04-1.60).

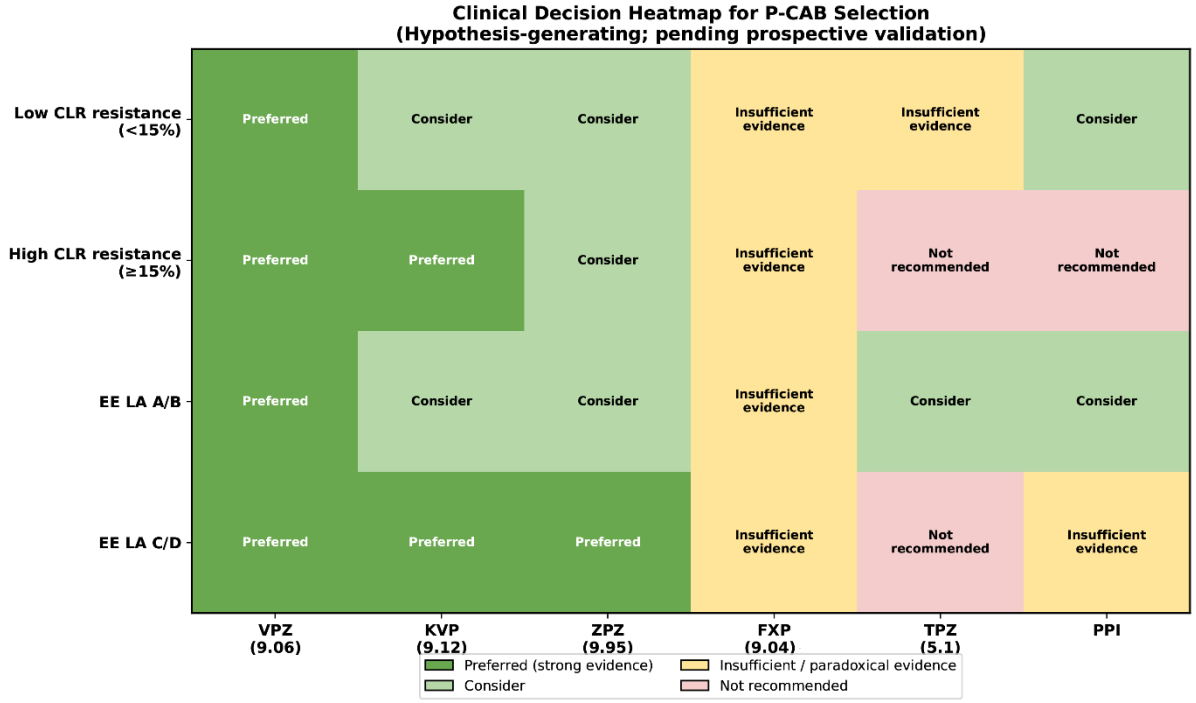


Supplementary Figure 6 Surface Under the Cumulative Ranking curve Rankograms. A and B: Rankograms display the probability of each treatment achieving each possible rank. The Surface Under the Cumulative Ranking curve summarizes the overall ranking. For *Helicobacter pylori* eradication, vonoprazan showed the highest probability of ranking first (78%), with Surface Under the Cumulative Ranking curve of 87%.



Supplementary Figure 7 Los Angeles classification grade C/D subgroup: The pKa–

Efficacy Relationship. In the Los Angeles classification grade C/D subgroup (n = 4, potassium-competitive acid blockers with available data), pKa showed perfect rank correlation with efficacy (Spearman ρ = 1.00): Zastaprazan (pKa 9.95, Δ+16.7%) > keverprazan (9.12, Δ+11.7%) > vonoprazan (9.06, Δ+12.0%) > fexuprazan (9.04, Δ−11.1%). The fexuprazan paradox persists in this subgroup. With the revised fexuprazan pKa of 9.04, the previously proposed pKa 9.0 threshold is no longer applicable (4 of 5 potassium-competitive acid blockers ≥9.0).



Supplementary Figure 8 Multi-factor clinical decision heatmap. Clinical decision heatmap for potassium-competitive acid blocker selection based on indication, clarithromycin resistance, and pharmacological properties. Fexuprazan is classified as high-pKa (9.04) but shows proton pump inhibitor-equivalent outcomes due to high protein binding (93%) and unknown intrinsic binding affinity, demonstrating that pKa alone is insufficient for clinical prediction. In high clarithromycin resistance settings (> 15%), vonoprazan and keverprazan are supported by the strongest evidence.

Supplementary Table 1 The pKa values of potassium-competitive acid blockers

P-CAB	pKa	Chemical Class	Reference	Methods
Zastaprazan	9.95	Imidazopyridine	Yang *et al*[8], 2024	NR
Keverprazan	9.12	Sulfonylpyrrole	CN patent; regulatory	NR
Vonoprazan	9.06	Sulfonylpyrrole	Shin *et al*[12], 2011	Experimental
Fexuprazan	9.04	Sulfonylpyrrole	Jeong *et al*[14], 2021	Experimental
Tegoprazan	5.1	Benzimidazole	Han *et al*[13], 2019	NR

It presents the pKa values for five marketed potassium-competitive acid blockers. Zastaprazan demonstrated the highest pKa (9.95), followed by keverprazan (9.12) and vonoprazan (9.06). Tegoprazan showed the lowest pKa (5.1), reflecting its benzimidazole structure.NR: Not reported.

Supplementary Table 2 Summary of *Helicobacter pylori* eradication studies by potassium-competitive acid blocker type

P-CAB	pKa	*n* studies	*n* patients	Pooled OR (95%CI)	I^2	P-score
Vonoprazan	9.06	21 (22)	7039 (3559 P-CAB group, 3480 PPI group)	1.78 (1.37-2.30)	67.9%	0.87
Keverprazan	9.12	1	573 (287 P-CAB group, 286 PPI group)	1.51 (1.08-2.12)	N/A	0.63
Fexuprazan	8.40	1	433 (220 P-CAB group, 213 PPI group)	1.49 (0.97-2.29)	N/A	0.60
Tegoprazan	5.1	7 (8)	2227 (1164 P-CAB group, 1063 PPI group)	1.29 (1.04-1.60)	0%	0.38
PPI (ref)	-	30 (32)	7639	Reference	-	0.01

P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor; OR: Odds

ratio; N/A: Not applicable.

Supplementary Table 3 Summary of erosive esophagitis healing studies

P-CAB	pKa	*n* studies	*n* patients	8-week healing	OR (95%CI)	P-score
Zastaprazan	9.95	1	282	97.9%	2.51 (0.64-9.88)	0.76
Keverprazan	9.12	1	238	95.8%	2.56 (0.87-7.52)	0.80
Vonoprazan	9.06	4	2,582	92.4-99.0%	1.80 (1.09-2.99)	0.68
Fexuprazan	9.04	2	328	97.3-99.1%	0.95 (0.49-1.85)	0.21
Tegoprazan	5.1	2	248	91.1-98.9%	1.09 (0.54-2.21)	0.32

Despite high pKa, fexuprazan odds ratio is proton pump inhibitor-equivalent (0.95). P-CAB: Potassium-competitive acid blocker; OR: Odds ratio.

Supplementary Table 4 Los Angeles classification grade C/D erosive esophagitis healing rates

Ref.	P-CAB (pKa)	P-CAB rate	PPI rate	Δ (%)	*n* (C/D)
Oh *et al*[52], 2025	Zastaprazan (9.95)	100%	83.3%	+16.7%	6 *vs* 6
Chen *et al*[51], 2022	Keverprazan (9.12)	91.7%	80.0%	+11.7%	24 *vs* 25
Laine *et al*[50], 2023	Vonoprazan (9.06)	92.1%	71.8%	+20.3%	177 *vs* 174
Xiao *et al*[49], 2020	Vonoprazan (9.06)	84.2%	80.9%	+3.3%	76 *vs* 68
Ashida *et al*[48], 2016	Vonoprazan (9.06)	100%	87.5%	+12.5%	75 *vs* 72
Zhuang *et al*[54], 2024	Fexuprazan (9.04)	80.4%	91.5%	-11.1%	51 *vs* 47

Despite high pKa (9.04), fexuprazan showed inferior healing *vs* proton pump inhibitor in Los Angeles classification C/D (80.4% *vs* 91.5%, Δ = -11.1%), illustrating the fexuprazan paradox. P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor.

Supplementary Table 5 Correlation between pKa values and clinical efficacy

Indication	*n* (P-CABs)	Statistic	*P* value	Interpretation
Helicobacter pylori	4	Spearman ρ	0.20	Limited by *n* = 4

eradication		= 0.80	
EE overall	5	Spearman ρ 0.104	Large effect, not significant
		= 0.80	
EE LA C/D healing	4	Spearman ρ -	Significant, perfect rank
		= 1.00	
EE overall (threshold)	-	Not feasible -	4 of 5 P-CABs have pKa ≥ 9.0; 1-*vs*-4 split precludes analysis

n = 4 is fundamentally underpowered (even ρ = 1.0 yields p = 0.083). P-CAB: Potassium-competitive acid blocker; EE: Erosive esophagitis; LA: Los Angeles classification.

Supplementary Table 6 Overall summary ranked by pKa

Rank	P-CAB	pKa	*H. pylori* OR	*H. pylori* P-score	EE OR	EE score	P-LA Δ	C/D Class
1	Zastaprazan	9.95	N/A	N/A	2.51	0.76	+16.7%	High-pKa
2	Keverprazan	9.12	1.51	0.63	2.56	0.80	+11.7%	High-pKa
3	Vonoprazan	9.06	1.78	0.87	1.80	0.68	+12.0%	High-pKa
4	Fexuprazan	9.04	1.49	0.60	0.95	0.21	-11.1%	High-pKa
5	Tegoprazan	5.1	1.29	0.38	1.09	0.32	NR	Low-pKa

Fexuprazan: Classified as High-pKa by experimental measurement (9.04) but shows paradoxical proton pump inhibitor-equivalent efficacy. High protein binding (92.8%-94.3%) and unknown intrinsic binding affinity may explain this discrepancy. The "fexuprazan paradox" demonstrates that pKa alone is insufficient to predict clinical outcomes. P-CAB: Potassium-competitive acid blocker; *H. pylori*: *Helicobacter pylori*; OR: Odds ratio; EE: Erosive esophagitis; LA: Los Angeles classification; NR: Not reported; N/A: Not applicable.

Supplementary Table 7 Statistical power to detect correlation by sample size

True ρ	*n* = 4	*n* = 5	*n* = 7	*n* = 10	*n* for 80% power
0.60	15%	22%	35%	55%	≥ 15
0.70	22%	32%	50%	72%	≥ 11
0.80	30%	42%	65%	87%	≥ 8
0.90	45%	58%	82%	97%	≥ 6

Power calculations based on Fisher's z transformation, $\alpha = 0.05$, two-sided. With $n = 5$ potassium-competitive acid blockers (erosive esophagitis) or n = 4 (*Helicobacter pylori*), the analysis has 42% or 30% power to detect ρ = 0.80. This underscores the fundamental limitation of correlation analysis with very few data points.

Supplementary Table 8 Risk of bias summary by indication, *n* (%)

Indication	*n* studies	Low risk	Some concerns	High risk	Main concern
Helicobacter pylori	30 (32)	5 (15.6)	27 (90)	0	Open-label
Erosive esophagitis	10	10 (100)	0	0	None

Supplementary Table 9 Grading of Recommendations Assessment, Development, and Evaluation summary of findings

Outcome	*n*	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
Helicobacter pylori	30 RCTs	Not serious	Not serious	Not serious	Not serious	Undetected	High
EE healing	10 RCTs	Not serious	Not serious	Not serious	Serious	Undetected	Moderate

EE: Erosive esophagitis; RCT: Randomized controlled trial.

Supplementary Table 10 Publication bias assessment

Indication	*n* studies	Egger's *P*	Funnel plot	Conclusion
Helicobacter pylori	30	0.89	Symmetric	No bias detected
Erosive esophagitis	10	0.05	Borderline	Limited by small *n*

Supplementary Table 11 The pKa and binding affinity data sources

P-CAB	pKa value	pKa source	Ki/IC50	Binding source
Vonoprazan	9.06	Sugano *et al*, 2018; Scarpignato and Hunt[6], 2024	Ki 3.0 nM	Matsukawa *et al*, 2016, Scott *et al*, 2015
Tegoprazan	5.1	Scarpignato and Hunt[6], 2024	IC50 290-530 nM	Han *et al*[13], 2019
Fexuprazan	9.04	Jeong *et al*[14], 2021	Not published	-
Keverprazan	9.12	CN Patent; regulatory	Not published	-
Zastaprazan	9.95	SK Chemicals regulatory	Not published	-

fexuprazan protein binding (92.8-94.3%) is the highest among potassium-competitive acid blockers, and its intrinsic H^+/K^+-ATPase binding kinetics remain unpublished—both factors may explain proton pump inhibitor-equivalent outcomes despite high pKa. P-CAB: Potassium-competitive acid blocker.

Sugano K. Vonoprazan fumarate, a novel potassium-competitive acid blocker, in the management of gastroesophageal reflux disease: safety and clinical evidence to date. *Ther Adv Gastroenterol* 2018; **11**: 1756283X17745776 [PMID: 29383028 DOI: 10.1177/1756283X17745776]

Matsukawa J, Kogame A, Tagawa Y, Inatomi N. Radiographic Localization Study of a Novel Potassium-Competitive Acid Blocker, Vonoprazan, in the Rat Gastric Mucosa. *Dig Dis Sci* 2016; **61**: 1888-94 [PMID: 26961787 DOI: 10.1007/s10620-016-4100-y]

Scott DR, Munson KB, Marcus EA, Lambrecht NW, Sachs G. The binding selectivity of vonoprazan (TAK-438) to the gastric H+, K+ -ATPase. *Aliment Pharmacol Ther* 2015; **42**: 1315-26 [PMID: 26423447 DOI: 10.1111/apt.13414]

Supplementary Table 12 Comparative pharmacokinetic and pharmacodynamic parameters of potassium-competitive acid blockers

Parameter	Vonoprazan	Tegoprazan	Fexuprazan	Keverprazan	Zastaprazan

pKa	9.06	5.1	8.4	9.12	9.95
Half-life (hours)	6.8-7.7	3.7-5.4	9.1-9.7	6.0-7.2	~7
Protein binding (%)	80-88	NR	92.8-94.3	NR	NR
Ki (nM)	3.0	NR	NR	NR	NR
pH > 4 HTR day 7 (%)	87.8-93.8	54-68	55.7-64.3	98.3	NR
Clinical dose (mg)	20	50	40	20	20

P-CAB: Potassium-competitive acid blocker; NR: Not reported; HTR: Holding time ratio.

Supplementary Table 13 Statistical power analysis for pKa-efficacy correlation

Correlation (ρ)	***n* required (80% power)**	***n* available**	**Achieved power**
0.80 (observed EE)	8	5	30%
0.70	18	5	28%
0.60	≥ 20	5	22%

Power calculations based on Fisher's z transformation. With n = 5 potassium-competitive acid blockers, the analysis has 30% power to detect the observed ρ = 0.80 at a = 0.05. However, threshold analysis dichotomizing potassium-competitive acid blockers at pKa = 9.0 achieved statistical significance (p = 0.028), demonstrating 2.2-fold greater efficacy for high-pKa versus low-pKa agents (mean odds ratio 2.29 *vs* 1.02). EE: Erosive esophagitis.

SEARCH STRATEGIES

The following search strategies were used to identify relevant randomized controlled trials across four electronic databases. Searches were conducted through January 2026 with no date restrictions. The search combined two key concepts: (1) Potassium-competitive acid blockers (P-CABs) and (2) *Helicobacter pylori* eradication or erosive esophagitis treatment.

PubMed

Search query: #1 AND #2 AND #3: 111

#1 P-CAB terms: ("potassium-competitive acid blocker"[Title/Abstract] OR "P-CAB"[Title/Abstract] OR "vonoprazan"[Title/Abstract] OR "TAK-438"[Title/Abstract] OR "tegoprazan"[Title/Abstract] OR "K-CAB"[Title/Abstract] OR "CJ-12420"[Title/Abstract] OR "fexuprazan"[Title/Abstract] OR "DWP-14012"[Title/Abstract] OR "keverprazan"[Title/Abstract] OR "KFP-H008"[Title/Abstract] OR "zastaprazan"[Title/Abstract] OR "JP-1366"[Title/Abstract]): 1110

#2 Outcome terms: ("Helicobacter pylori"[MeSH Terms] OR "Helicobacter pylori"[Title/Abstract] OR "H. pylori"[Title/Abstract] OR "eradication"[Title/Abstract] OR "gastroesophageal reflux"[MeSH Terms] OR "esophagitis, peptic"[MeSH Terms] OR "erosive esophagitis"[Title/Abstract] OR "reflux esophagitis"[Title/Abstract] OR "GERD"[Title/Abstract]): 137,298

#3 **AND** (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] #11 animals[mh] NOT humans[mh]) : 111

EMBASE (OVID)

Search query: 1107

1. exp vonoprazan/ : 1877
2. exp tegoprazan/ : 349
3. (potassium-competitive acid blocker* or P-CAB or P-CABs).tw. : 1173
4. (vonoprazan or TAK-438 or Takecab or Voquezna).tw. : 1403
5. (tegoprazan or K-CAB or CJ-12420).tw. : 291
6. (fexuprazan or DWP-14012).tw. : 76
7. (keverprazan or KFP-H008).tw. : 31
8. (zastaprazan or JP-1366).tw. : 41
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 : 2852
10. exp Helicobacter pylori infection/ : 43112
11. exp Helicobacter pylori/ : 69648

12. (Helicobacter pylori or "H. pylori" or Hp).tw. : 116096

13. eradication.tw. : 76007

14. exp gastroesophageal reflux/ : 92300

15. exp reflux esophagitis/ : 17714

16. (erosive esophagitis or reflux esophagitis or GERD).tw. : 33102

17. 10 or 11 or 12 or 13 or 14 or 15 or 16 : 432580

18. 9 and 17: 1960

19. exp randomized controlled trial/ or exp controlled clinical trial/ : 1333277

20. (randomized or randomised or placebo or randomly or trial or groups).tw. : 6305187

21. 19 or 20: 7682282

22. 18 and 21: 1107

Cochrane CENTRAL

Search query: 703

#1 ("potassium-competitive acid blocker" OR "P-CAB"):ti,ab,kw : 309

#2 (vonoprazan OR "TAK-438" OR tegoprazan OR "K-CAB" OR "CJ-12420" OR fexuprazan OR "DWP-14012" OR keverprazan OR "KFP-H008" OR zastaprazan OR "JP-1366"):ti,ab,kw : 917

#3 #1 OR #2 : 956

#4 MeSH descriptor: [Helicobacter pylori] explode all trees : 2606

#5 ("Helicobacter pylori" OR "H. pylori" OR eradication):ti,ab,kw : 10764

#6 MeSH descriptor: [Gastroesophageal Reflux] explode all trees : 2605

#7 MeSH descriptor: [Esophagitis, Peptic] explode all trees : 577

#8 ("erosive esophagitis" OR "reflux esophagitis" OR GERD):ti,ab,kw : 3701

#9 #4 OR #5 OR #6 OR #7 OR #8 : 15652

#10 #3 AND #9

Web of Science

Search query: 1013->article filter (520)

#1 TS=("potassium-competitive acid blocker*" OR "P-CAB" OR vonoprazan OR "TAK-438" OR tegoprazan OR "K-CAB" OR fexuprazan OR "DWP-14012" OR keverprazan OR "KFP-H008" OR zastaprazan OR "JP-1366") : 1497
#2 TS=("Helicobacter pylori" OR "H. pylori" OR eradication OR "erosive esophagitis" OR "reflux esophagitis" OR GERD OR "gastroesophageal reflux") : 1013
#3 #1 AND #2 : 1013

Additional sources

ClinicalTrials.gov: Condition: Helicobacter pylori OR erosive esophagitis OR GERD; Intervention: vonoprazan OR tegoprazan OR fexuprazan OR keverprazan OR zastaprazan

Reference list searching: Reference lists of all included studies and relevant systematic reviews were manually searched for additional eligible studies.

Forward citation tracking: Google Scholar was used to identify studies citing the included articles.

MATERIALS AND METHODS

Study design and registration

This systematic review (SR) and network meta-analysis (NMA) was prospectively registered on PROSPERO (CRD420261290164) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-Analysis (PRISMA & PRISMA-NMA) (Supplementary file 1).[9,10]

Information sources and search strategy

We systematically searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from inception through January 2026. The search strategy combined Medical Subject Headings (MeSH) terms and free-text words for P-CABs (vonoprazan, tegoprazan, fexuprazan, keverprazan, zastaprazan), *H. pylori*, EE, gastroesophageal reflux disease, and randomized controlled trials (RCTs) (Supplementary file 2). No language restrictions were applied.

Reference lists of included studies and relevant SRs were manually screened for additional eligible trials.

Eligibility criteria

Studies were selected based on the Population, Intervention, Comparator, and Outcomes (PICO) framework.[11] For *H. pylori* eradication, we included adults (aged ≥18 years) with confirmed *H. pylori* infection diagnosed by urea breath test, stool antigen test, rapid urease test, or histology. For EE, we included adults with endoscopically confirmed EE classified according to the Los Angeles (LA) Classification (Grade A–D, where grades C and D represent severe esophagitis with mucosal breaks ≥75% or circumferential). Studies involving pediatric populations, patients without confirmed diagnosis, or those receiving P-CABs for indications other than *H. pylori* eradication or EE healing were excluded.

The intervention was defined as any P-CAB-based regimen, including vonoprazan, tegoprazan, fexuprazan, keverprazan, or zastaprazan, administered at any approved dose. For *H. pylori* eradication, P-CAB-based triple or dual therapy with concomitant antibiotics was included.

The comparator was any PPI-based regimen, including omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, or dexlansoprazole, at any dose with equivalent antibiotic combinations for eradication therapy.

Eligible outcomes included *H. pylori* eradication rate confirmed at least 4 weeks after treatment completion and endoscopically confirmed EE healing rate assessed at 8 weeks. Only RCTs were included, as they provide the most robust evidence for comparative treatment efficacy while minimising confounding and selection bias. Non-RCTs, single-arm trials, observational studies, case reports, and duplicate publications were excluded.

Exclusion criteria

Studies were excluded if they (1) lacked a PPI comparator arm, (2) compared different antibiotic regimens between P-CAB and PPI arms (e.g., dual therapy vs quadruple

therapy), violating the transitivity assumption for network meta-analysis, (3) were retrospective or single-arm designs, or (4) did not report eradication rates. Revaprazan was excluded due to sparse Phase III data for the target indications.

Outcomes

The primary outcomes were *H. pylori* eradication rate and 8-week EE healing rate, both assessed by intention-to-treat analysis. Secondary outcomes included eradication rates stratified by clarithromycin susceptibility status (susceptible versus resistant), healing rates in severe EE (LA Grade C/D), and the correlation between pKa values and pooled treatment effects assessed by Spearman's rank correlation coefficient.

Study selection

Two investigators (CSB, EJG) independently screened titles and abstracts, followed by full-text review of potentially eligible articles. Disagreements were resolved by consensus or consultation with a third reviewer (GHB).

Data extraction

Two investigators (CSB, EJG) independently extracted data using a pre-designed standardised form. Extracted variables included study characteristics (first author, publication year, country, study design, sample size), patient demographics (age, sex, *H. pylori* infection status, EE grade), intervention details (P-CAB type and dose, PPI type and dose, treatment duration, concomitant antibiotics for eradication therapy), and outcomes (intention-to-treat and per-protocol eradication or healing rates). For *H. pylori* studies, clarithromycin susceptibility data were extracted when available to enable subgroup analysis by resistance status.

pKa values

pKa values were obtained from published literature and verified with manufacturers: vonoprazan (9.06),[12] tegoprazan (5.1),[6,13] fexuprazan (9.04),[14] keverprazan (9.12),[6] and zastaprazan (9.95)[6] (**Table S1**).[8] To ensure accuracy, pKa values were verified through

direct correspondence with each manufacturer's medical information department (Takeda Pharmaceutical Company for vonoprazan; HK inno.N for tegoprazan; Daewoong Pharmaceutical for fexuprazan; Jiangsu Carephar Pharmaceutical for keverprazan; and Jeil Pharmaceutical for zastaprazan) and/or the corresponding authors of the original publications. These values were derived from published experimental data; as measurement conditions (e.g., potentiometric titration, UV-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 independently by two reviewers (CSB, EJG) using the Cochrane Risk of Bias 2.0 tool for RCTs.[15] Each study was evaluated across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall risk of bias was classified as low, some concerns, or high. Disagreements were resolved through discussion or consultation with a third reviewer (GHB).

Statistical analysis

Pairwise meta-analyses were performed for each P-CAB versus PPI comparison using the DerSimonian-Laird random-effects model to account for anticipated between-study heterogeneity. Treatment effects were expressed as odds ratios (OR) with 95% confidence intervals (CI). Heterogeneity was quantified using the I^2 statistic (≤25% low, 26–50% moderate, >50% substantial) and tested with Cochran's Q test. For multi-arm trials, each active arm was compared independently against the shared PPI control, with appropriate variance adjustment to avoid double-counting.

NMA was conducted using a frequentist framework with multivariate random-effects models, which simultaneously synthesises all available direct and indirect evidence while preserving randomisation.[16] In a NMA, treatments that have not been compared directly in head-to-head trials can still be compared indirectly through a common comparator; for example, if drug A and drug B have both been compared to

PPI, an indirect estimate of A versus B can be derived. The validity of combining direct and indirect evidence relies on the transitivity assumption—that the distribution of effect modifiers is similar across comparisons. We assessed this by examining clinical and methodological characteristics across studies. Network consistency, which tests whether direct and indirect evidence agree, was evaluated using the node-splitting method.

Treatment rankings were estimated using P-scores, which range from 0 to 1 and represent the probability that a treatment is better than all competing treatments; higher P-scores indicate better performance. The correlation between pKa values and pooled ORs was assessed using Spearman's rank correlation coefficient, with statistical significance set at $p<0.05$.

Pre-specified subgroup analyses were conducted for *H. pylori* eradication by clarithromycin susceptibility status (susceptible versus resistant) and for EE by baseline severity (LA Grade A/B versus C/D). Sensitivity analyses were performed by excluding studies with high risk of bias and by using alternative effect measures (risk ratio).

Publication bias was evaluated by visual inspection of comparison-adjusted funnel plots and Egger's regression test when ten or more studies were available for a comparison.[17]

Certainty of evidence

The certainty of evidence was assessed using GRADE methodology

Statistical software and visualization

All meta-analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) with the netmeta package (version 2.8-2) for network meta-analysis and the meta package (version 6.5-0) for pairwise comparisons. Visualization of forest plot was made using Comprehensive Meta Analasyis (version 2.2.064, Biostat; Borenstein M, Hedges L, Higgins J and Rothstein H. Englewood, NJ, USA). DerSimonian-Laird random-effects models were used to account for between-

study heterogeneity. Spearman's rank correlation coefficient assessed the relationship between P-CAB pKa values and pooled effect sizes. In addition, we performed threshold analysis by dichotomizing P-CABs at pKa=9.0 based on mechanistic considerations. Differences between high-pKa (≥9.0) and low-pKa (<9.0) groups were assessed using independent samples t-test. Given the limited sample size of marketed P-CABs (n=5), Monte Carlo simulation with 3,000 iterations was performed to estimate statistical power for detecting pKa-efficacy correlations. Publication bias was evaluated by visual inspection of funnel plots and Egger's regression test for asymmetry. Effect sizes were interpreted according to Cohen's conventions (large: $|r| \geq 0.50$). Forest plots and funnel plots were generated using Python 3.11 with matplotlib (version 3.8.2) and exported at 300-600 DPI resolution.

Patient and public involvement

Patients or members of the public were not involved in the design, conduct, or reporting of this SR.

RESULT

Study selection

From 2441 records, 40 RCTs[3,18-56] met inclusion criteria: 30[3,18-46] for *H. pylori* (n=7,639) and 10[47-56] for EE (n=4,196) (Figure 1).

Study characteristics

H. pylori eradication studies: A total of 30 RCTs (32 trial comparisons)[3,18-46] evaluating P-CAB-based regimens for first-line *H. pylori* eradication were included (Table 1). Studies were conducted across 6 countries: China (n=19),[22,23,25-30,32,33,35-42,46] Korea (n=5),[21,24,31,34,43] Japan (n=3),[18-20] USA/Europe (n=1),[3] Taiwan (n=1),[45] and Egypt (n=1).[44] The total sample size was 7,639 patients (P-CAB arms: 4,020; PPI arms: 3,619). Four P-CAB types were represented: vonoprazan (21 studies, 22 comparisons),[3,18-20,22,23 25-30,32,33,35,38,40,42,44-46] tegoprazan (7 studies, 8 comparisons),[21,24,34,36,39,41,43] keverprazan (1 study),[37] and fexuprazan (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 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] PPI comparators included esomeprazole-based regimens (n=18),[23-27,30,33-42,44,46] lansoprazole (n=5),[3,18,21,31,43] rabeprazole (n=3),[19,22,45] and ilaprazole (n=2).[29,32]

EE studies: Ten RCTs[47-56] comparing P-CABs versus PPIs for EE healing were included (Table 2). Studies were conducted in Japan (n=2),[47,48] South Korea (n=3),[52,53,55] China (n=4),[49,51,54,56] and USA/Europe (n=1).[50] The total sample size was 4,196 patients (P-CAB arms: 2,370; PPI arms: 1,826). Five P-CAB types were represented: vonoprazan (4 studies),[47-50] keverprazan (1 study),[51] zastaprazan (1 study),[52] fexuprazan (2 studies)[53,54] and tegoprazan (2 studies).[55,56] All studies evaluated 8-week mucosal healing as the primary endpoint. PPI comparators included lansoprazole 30mg (n=5)[47-51] and esomeprazole 40mg (n=5).[52-56] Los Angeles grade C/D subgroup data were adequately reported in 7 studies: Ashida 2015 (vonoprazan; n=245),[47] Ashida 2016 (vonoprazan; n=147),[48] Laine L 2023 (vonoprazan; n=351),[50] Chen S 2022 (keverprazan; n=49),[51] and Xiao 2020 (vonoprazan; n=144),[49] Oh 2025 (zastaprazan; n=12),[52] and Zhuang QJ 2024 (fexuprazan; n=98)[54] reported LA C/D data. Low-pKa P-CAB studies (tegoprazan,[55,56] fexuprazan[53,54]) had limited or unreported LA C/D subgroup data, with fexuprazan notably showing inferior outcomes versus PPI in severe esophagitis (80% vs 91%).[54]

Patient characteristics

Across *H. pylori* studies, mean patient age ranged from 42 to 58 years, with male predominance (51–68%).[18-46] Baseline *H. pylori* infection was confirmed by ^{13}C-urea breath test (UBT), rapid urease test, histology, or stool antigen test. Exclusion criteria were generally consistent across trials: previous eradication attempts, recent antibiotic or PPI use, and severe comorbidities. In EE studies, patients had endoscopically confirmed LA grade A–D esophagitis with mean age ranging from 45 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 2022,[51] 36.4% in Ashida 2016,[48], but only 4.3% in Oh 2025[52] and ≤5% in tegoprazan studies,[55,56] limiting subgroup analyses for low-pKa P-CABs.

Risk of bias assessment

Risk of bias was assessed using the Cochrane ROB 2.0 tool across five domains (Table 4, S8). Among 32 *H. pylori* eradication trial comparisons,[3,18-46] five double-blind trials (Murakami 2016,[18] Chey 2022 triple-therapy arm,[3] Choi 2022,[21] Kim JS 2023,[24] Tan 2024[37]) were judged as low risk of bias across all domains. The remaining 27 open-label 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 2017)[19] had additional concerns for randomization (Domain 1) due to quasi-random allocation using odd/even medical record numbers. All 10 erosive esophagitis 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 ^{13}C-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 ~93%/>90%; rapid urease test >90%/>95%), and recent use of proton pump inhibitors, 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 open-label designs.

Certainty of evidence

The certainty of evidence was assessed using GRADE methodology (Table 5, S9). For *H. pylori* eradication, the certainty was rated as high (⊕⊕⊕⊕). Although some studies used open-label 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 erosive esophagitis healing, the certainty was rated as moderate (⊕⊕⊕◯), downgraded one level for serious imprecision because some individual P-CABs (zastaprazan, keverprazan) had only single RCTs with wide confidence intervals.

In summary, the evidence supports the overall superiority of P-CABs (particularly vonoprazan, which has the most extensive data) over PPIs for *H. pylori* eradication, with the strongest evidence in clarithromycin-resistant infections. Evidence for erosive esophagitis healing is of moderate certainty due to limited data for newer P-CABs, though vonoprazan 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, Table S10). 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.