Systematic Review and Network Meta-analysis

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Potassium-competitive Acid Blockers Versus Proton Pump Inhibitors for Erosive Esophagitis: A Systematic Review and Network Meta-analysis

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Background/Aims: Potassium-competitive acid blockers (P-CABs) have emerged as promising alternatives to proton pump inhibitors (PPIs) to treat erosive esophagitis (EE). This study aims to compare the efficacy and safety of P-CABs and PPIs in patients with mild to severe EE stratified by treatment phase.

Methods: A systematic literature search was conducted using PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials. Randomized controlled trials comparing the efficacy of P-CABs and PPIs for EE were included. The pooled risk ratios (RRs) and risk differences with 95% confidence intervals (CIs) were calculated. A frequentist network meta-analysis was performed, and treatment ranking was assessed using P-scores.

Results: Nineteen studies evaluating 5 P-CABs (vonoprazan, tegoprazan, keverprazan, fexuprazan, and zastaprazan) and 2 PPIs (lansoprazole and esomeprazole) were included. P-CABs demonstrated superior efficacy in healing EE during the initial phase, particularly in patients with severe EE (RR = 1.10; 95% CI, 1.00-1.20) and were also associated with a lower EE recurrence risk during maintenance treatment (RR = 0.59; 95% CI, 0.41-0.85). The efficacy was notably greater in patients with higher EE severity and among cytochrome P450 2C19 extensive metabolizers. The safety profiles of the P-CABs and PPIs were comparable. Vonoprazan consistently ranked the highest for both initial treatment (P-score = 0.68) and maintenance (P-score = 0.94).

Conclusions: P-CABs, especially vonoprazan, showed superior efficacy compared to PPIs in both the initial and maintenance treatment of EE. These findings support the use of P-CABs as a potent and reliable first-line option for EE management, particularly in high-risk populations, with acceptable safety outcomes.

Keywords: Esophagitis; Network meta-analysis; Proton pump inhibitors

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic and widespread gastrointestinal disorder caused by the reflux of gastric contents into the esophagus.[1] Common symptoms include heartburn, acid regurgitation, and extraesophageal manifestations such as chronic cough or hoarseness, which can significantly impact patients' quality of life.[2] GERD affects a substantial proportion of the global population, with an estimated prevalence ranging from 8% to 33%.[3] Erosive esophagitis (EE), characterized by visible mucosal breaks on endoscopy, accounts for approximately 25% of patients with symptomatic GERD.[4] EE is classified into mild (Los Angeles [LA] grades A and B) and severe (LA grades C and D), with severe EE being more likely to recur and progress to complications

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such as strictures, Barrett's esophagus, and esophageal cancer if not adequately treated.[5-7] Therefore, treatment strategies should consider the severity of EE because more advanced cases often require stronger and longer acid suppression to achieve mucosal healing and prevent recurrence.

Proton pump inhibitors (PPIs) have been the gold standard treatment for GERD for over 2 decades, effectively relieving symptoms and promoting mucosal healing.[8,9] However, despite their efficacy, PPIs have shown limited effectiveness in treating EE, particularly in patients with severe EE. Initial treatment with PPIs results in mucosal healing failure rates of 4-15%, and during maintenance therapy, EE recurs in up to 41% of patients, with even higher recurrence rates in those with severe EE.[10,11] These suboptimal outcomes are due to pharmacological limitations, such as delayed onset of action, meal-dependent activation, and incomplete control of nocturnal acid secretion.[12-14] Potassium-competitive acid blockers (P-CABs), a novel class of gastric acid-suppressing agents, are promising alternatives to PPIs. P-CABs competitively and reversibly inhibit H^+/K^+-ATPase, providing rapid, potent, and sustained acid suppression.[15,16] Several P-CABs, including vonoprazan, tegoprazan, fexuprazan, keverprazan, and zastaprazan, are currently available in clinical practice. These agents have shown favorable efficacy in several clinical trials, particularly for treating EE, including severe cases.[17-21]

Although clinical trials have reported favorable outcomes with P-CABs in the management of EE, the results remain heterogeneous across individual studies and agents. Treatment outcomes are also likely to be influenced by several patient- and disease-related variables,[22-25] such as cytochrome P450 2C19 (CYP2C19) metabolizer status, LA grade phenotype, and treatment phase (initial vs maintenance), which have rarely been evaluated collectively. A recent meta-analysis indicated the superior efficacy of P-CABs, particularly vonoprazan, in severe EE across both the initial and maintenance treatment phases; however, this analysis was limited primarily to patients with severe EE, restricting its applicability to a broader patient population with EE.[26] To address these limitations in the current literature, we conducted a systematic review and a network meta-analysis (NMA) to compare P-CABs and PPIs for EE management. Our analysis was stratified by disease severity (mild EE vs severe EE), treatment phase (initial vs maintenance), and CYP2C19 genotype. Outcomes, including mucosal healing, EE recurrence, and adverse events, were evaluated with the ultimate goal of informing individualized treatment strategies across GERD phenotypes.

METHODS

The protocol for this systematic review was created a priori and registered with PROSPERO (CRD420251009038). This meta-analysis was performed according to the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement.[27] As this study involved a review of the existing literature, the requirement for institutional review board approval was waived.

Literature Search Strategy and Study Selection

A comprehensive literature search was performed to identify relevant studies that compared the efficacy of PPIs and P-CABs in patients with GERD. We systematically searched PubMed, Embase, and the Cochrane Library from their inception to January 2025. The search terms included combinations of GERD-related terms ("gastroesophageal reflux disease," "gastro-esophageal reflux disease," "non-erosive reflux disease," "reflux esophagitis," "erosive reflux disease," "peptic esophagitis," "erosive esophagitis," and "endoscopy-negative reflux disease"), PPI-related terms ("proton pump inhibitor," "PPI," "lansoprazole," "omeprazole," "esomeprazole," "dexlansoprazole," "rabeprazole," "pantoprazole," and "ilaprazole"), and P-CAB-related terms ("potassium-competitive acid blocker," "P-CAB," "vonoprazan," "tegoprazan," "fexuprazan," "revaprazan," "zastaprazan" and "keverprazan"). For treatment duration, we included terms related to "initial," "short-term," "maintenance," and "long-term" therapy. Detailed, reproducible search strategies are presented in Supplementary Methods 1-8.

Studies were included if they met the following criteria: (1) randomized controlled trials (RCTs) evaluating patients diagnosed with EE, as defined by endoscopic evidence of mucosal breaks; (2) comparisons between PPI and P-CAB treatment as either initial or maintenance treatment; (3) available full-text articles; and (4) studies written in English. The exclusion criteria were as follows: (1) abstract-only publications, conference proceedings, or study protocols without full data; (2) case reports, narrative reviews, or editorials; (3) previously published systematic reviews or meta-analyses; and (4) studies with inadequate or insufficient data on treatment outcomes. After removing duplicates, the titles and abstracts were screened to exclude irrelevant studies. The full texts of potentially eligible articles were reviewed based on pre-

defined inclusion and exclusion criteria. Disagreements were resolved through discussion. In cases of missing or unclear data, attempts were made to contact the authors of the original study.

Outcome Measures

The primary efficacy outcomes were the endoscopic healing rate of EE during initial treatment at 8 weeks and the recurrence rate of EE during maintenance treatment at 24 weeks. Secondary outcomes included improvement in GERD-related symptoms and the incidence of treatment-emergent adverse events (TEAEs). The pooled healing rates and risk ratios (RRs) were calculated from the extracted data.

Data Extraction

Data were independently extracted as dichotomous outcomes by 2 reviewers (J.W.C and D.H.J) using a prespecified standardized data collection form in Microsoft Excel. Discrepancies were resolved through discussion with a senior investigator (C.W.H.). We extracted the following data from each trial: author, year of publication, country and region, number of study centers, age, sex, CYP2C19 genotype, treatment arms and dosages, treatment durations, number of patients with mild EE (LA grade A/B) and severe EE (LA grade C/D), and number of participants who failed to achieve endoscopic healing during initial treatment or recurrence during maintenance therapy. The outcomes were classified as primary (endoscopic healing or recurrence of EE) or secondary (symptom relief and safety). Safety data, including the number of patients with adverse events, serious adverse events, treatment-related withdrawals, and TEAEs, were extracted from the reported safety population. A detailed summary of the analysis population for each trial is provided in Supplementary Table 1.

Quality Assessment

The risk of bias in the included studies was assessed independently by 2 reviewers using the Cochrane Risk of Bias 2 (RoB 2.0) tool for RCTs. The tool evaluates 5 major domains: (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of reported results. Each domain was rated as "low risk," "some concerns," or "high risk," and an overall RoB judgment was derived. Any disagreements were resolved by consensus. A summary of the RoB assessments is presented in Supplementary Figures 1 and 2. Publication bias was qualitatively assessed using funnel plot symmetry.

Statistical Analyses

This study was conducted in accordance with the PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Network Meta-analyses) guidelines for network meta-analyses. An NMA using a frequentist approach was performed to compare various PPIs and P-CABs, enabling both direct and indirect comparisons. The analysis focused on P-CABs (vonoprazan, tegoprazan, keverprazan, fexuprazan, and zastaprazan) compared with PPIs, and the RRs and 95% confidence intervals (CIs) were calculated for the efficacy and adverse events of each drug. In addition, the P-score (a value between 0 and 1) was used to compare the relative efficacy of the drugs, and the results were presented according to the duration of drug administration (8 weeks and 24 weeks) and mild and severe EE. A meta-regression analysis was performed to confirm the change in effect when mild EE progressed to severe EE. Participants in each study were classified as mild or severe and were included in the analysis. This analysis contributed to a more accurate estimation of the true effect by considering the standard error of each study based on the observed effect size. Additionally, a pairwise meta-analysis (PMA) comparing PPIs and P-CABs without subdividing the P-CABs used a random-effects model. This method is considered an appropriate analytical approach as it reflects the heterogeneity between studies when estimating the relative risk of dichotomous outcomes. The primary outcome was the efficacy of PPIs and P-CABs, whereas the secondary outcome was TEAEs, both reported as RRs with 95% CIs. Heterogeneity was assessed using the I^2 statistic, which indicates the proportion of the total variability attributable to heterogeneity. Generally, an I^2value of < 25% is considered low, 50% moderate, and ≥ 75% high. Funnel plots were used to assess publication bias in the included studies, with the x-axis representing the effect size and the y-axis representing the standard error. If the studies were symmetrically distributed within the funnel shape, publication bias was considered absent. All meta-analyses were performed using R software (version 4.5.0, R Foundation for Statistical Computing, Vienna, Austria), and the 'meta' (version 8.1.0), 'metafor' (version 4.8-0), and 'netmeta' (version 3.2.0) packages were used for the analysis.

RESULTS

Study Selection

A flow diagram of the selection process is shown in

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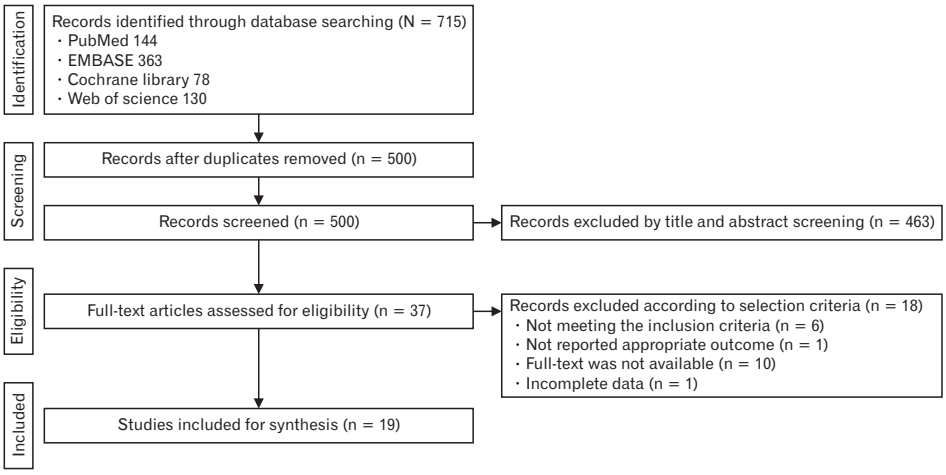

Figure 1. Flow diagram of study selection for the systematic review and network meta-analysis.

Figure 1. A total of 715 records were identified through an electronic database search, of which 500 remained after duplicates were removed. After screening titles and abstracts, 463 records were excluded as irrelevant. Full texts of the remaining 37 articles were assessed for eligibility. Of these, 19 RCTs met the inclusion criteria and were included in the final analyses of this systematic review and NMA.

Characteristics of Included Studies

A total of 19 RCTs were included in this analysis, encompassing a broad range of P-CABs and PPIs with varied doses and treatment phases (initial and maintenance). Among these, vonoprazan has been widely investigated at various doses (5-40 mg) and compared with PPIs.[15,19-21,28-33] For instance, Ashida et al[20] assessed vonoprazan at 5, 10, 20, and 40 mg versus lansoprazole 30 mg for the initial healing of EE, while another trial[31] assessed 10 mg and 20 mg vonoprazan versus lansoprazole 15 mg for maintenance treatment over 24 weeks. Tegoprazan was evaluated in 5 studies, including 4 studies on initial treatment and 1 on maintenance treatment.[34-38] In the initial treatment studies, 50 mg and 100 mg of tegoprazan were compared with PPIs such as esomeprazole 20 mg and 40 mg, and lansoprazole 30 mg. The maintenance treatment study compared tegoprazan 25 mg with lansoprazole 15 mg, both of which are half-dose regimens. Other evaluated P-CABs included fexuprazan (40 mg),[39,40] keverprazan (20 mg),[41] and zastaprazan (20 mg),[16] each compared with standard-dose PPIs (esomeprazole 40 mg or lansoprazole 30 mg) over 8 weeks of initial treatment. In our NMA, the doses of P-CABs and PPIs were selected according to current guideline recommendations,[18,42] which advocate standard-dose regimens for initial treatment and half-dose regimens for maintenance treatment, consistent with previous studies by Laine et al.[19] Thus, the standard doses were defined as vonoprazan 20 mg, tegoprazan 50 mg, fexuprazan 40 mg, keverprazan 20 mg, zastaprazan 20 mg, and the corresponding PPI comparators (esomeprazole 40 mg and lansoprazole 30 mg). Half-doses were defined as vonoprazan 10 mg, tegoprazan 25 mg, and PPI comparators, such as lansoprazole 15 mg or esomeprazole 20 mg.

Most of the included studies were conducted in East Asia (Japan, Korea, and China), with a few Western-based trials such as those by Laine et al.[19] The study designs varied from open-label to double-blind, with durations ranging from 4 to 52 weeks and sample sizes ranging from 32 to over 1000 patients. Several studies[29,32] included multinational populations, adding to the geographic diversity. Table provides the characteristics of the included RCTs, including study design, population, treatment regimens, and outcome measures.

Risk of Bias and Publication Bias

Of the 19 included RCTs, 13 clearly reported a method for generating the randomization sequence. Most studies adequately addressed allocation concealment and protocol adherence, with 18 studies rated as having a low risk of deviation from intended interventions. Regarding the completeness of the outcome data, 17 studies were judged as low-risk. Outcome measurements were considered to have a low risk of bias in 18 studies, and 18 studies had no concerns related to selective reporting. Overall, 13 studies were assessed as having a low risk of bias, 5 as having some concerns, and 1 was judged to have a high risk of bias. Supplementary Figures 1A and 2A summarize the risk-of-bias evaluations.

Publication bias was qualitatively assessed using funnel plots for 8-week and 24-week analyses (Sup-

Table. Summary of Selected Randomized Controlled Trials

Author (yr)	Location	Drug administration	Patients	Duration	Outcome
Ashida et al,[20] (2015)	Japan	Vonoprazan 5, 10, 20, 40 mg vs Lansoprazole 30 mg	732 randomized (578 Vonoprazan, 154 Lansoprazole)	8 wk	Primary: EE healing at week 4 (endoscopy) Secondary: healing at week 2 and 8, symptoms, safety
Ashida et al,[21] (2016)	Japan	Vonoprazan 20 mg vs Lansoprazole 30 mg	409 randomized (207 Vonoprazan, 202 Lansoprazole)	8 wk (initial), 52 wk (maintenance)	Primary: EE healing up to week 8; Maintenance: recurrence over 52 wk; Safety
Ashida et al,[31] (2018)	Japan	Vonoprazan 10, 20 mg vs Lansoprazole 15 mg	607 randomized (204 Vonoprazan 20 mg, 202 Vonoprazan 10 mg, 201 Lansoprazole 15 mg)	24 wk	Primary: EE recurrence at 24 wk; Secondary: EE recurrence at 12 wk; Secondary endpoints: heartburn/acid reflux incidence, safety outcomes
Oshima et al,[28] (2019)	Japan	Vonoprazan 20 mg vs Lansoprazole 30 mg	32 randomized (16 Vonoprazan, 16 Lansoprazole)	14 day	Primary: first day of complete day and night heartburn relief for 7 consecutive days Secondary: FSSG scores, PSQI scores
Sakurai et al,[15] (2019)	Japan	Vonoprazan 20 mg vs Esomeprazole 20 mg	60 randomized (30 Vonoprazan, 30 Esomeprazole)	4 wk	Primary: symptom relief by GerdQ at 4 wk Secondary: FSSG and GOS scores
Lee et al,[34] (2019)	Korea	Tegoprazan 50 mg, 100 mg vs Esomeprazole 40 mg	302 randomized (100 Tegoprazan 50 mg vs 102 Tegoprazan 100 mg vs 100 Esomeprazole 40 mg)	8 wk	Primary: EE healing rate at 8 wk; Secondary: symptom improvement (RDQ), HRQoL, safety
Xiao et al,[29] (2020)	China, South Korea, Taiwan, Malaysia	Vonoprazan 20 mg vs Lansoprazole 30 mg	481 randomized (244 Vonoprazan 20 mg, 235 Lansoprazole 30 mg)	8 wk	Primary: EE healing at 8 weeks. Secondary: EE healing at 2 wk and 4 wk, safety (TEAEs), QoL, symptom relief
Lee et al,[40] (2022)	Korea	Fexuprazan 40 mg vs Esomeprazole 40 mg	263 randomized (107 Fexuprazan, 111 Esomeprazole)	8 wk	Primary: EE healing at week 8 Secondary: EE healing at week 4, RDQ, GERD-HRQoL, TEAEs, serum gastrin
Chen et al,[41] (2022)	China	Keverprazan 20 mg vs Lansoprazole 30 mg	240 randomized (119 Keverprazan, 121 Lansoprazole)	8 wk	Primary: EE healing rate at 8 wk; Secondary: EE healing at 4 wk, symptom improvement, safety
Matsuda et al,[30] (2022)	Japan	Vonoprazan 10 mg vs Lansoprazole 15 mg (crossover 4 + 4 wk)	122 randomized (63 Vonoprazan-Lansoprazole, 59 Lansoprazole-Vonoprazan)	8 wk	Proportion of asymptomatic or well-controlled patients; FSSG, GSRS, serum gastrin
Cho et al,[38] (2022)	Korea	Tegoprazan 25 mg vs Lansoprazole 15 mg	351 randomized (174 Tegoprazan, 177 Lansoprazole)	24 wk	Primary: endoscopic remission at 24 wk; Secondary: remission at 12 wk, symptom-free days, GERD-HRQoL, safety
Laine et al,[19] (2023)	USA and Europe	Vonoprazan 20 mg vs Lansoprazole 30 mg (healing); Vonoprazan 10/20 mg vs Lansoprazole 15 mg (maintenance)	1027 randomized (514 Vonoprazan 20 mg, 513 Lansoprazole 30 mg)	8 wk (healing), 24 wk (maintenance)	Primary: healing by week 8, maintenance of healing at week 24 Secondary: heartburn-free days, sustained resolution of heartburn
Zhuang et al,[39] (2024)	China	Fexuprazan 40 mg vs Esomeprazole 40 mg	332 randomized (165 Fexuprazan 40 mg, 163 Esomeprazole 40 mg)	8 wk	Primary: EE healing at 8 wk Secondary: EE healing at 4 wk, symptom resolution, GERD-HRQoL, TEAEs
Oh et al,[16] (2024)	Korea	Zastaprazan 20 mg vs Esomeprazole 40 mg	300 randomized (149 Zastaprazan vs 151 Esomeprazole)	8 wk	Primary: proportion with healed EE at 8 wk (endoscopy). Secondary: healing at week 4, symptom response (RDQ), GERD-HRQoL, safety, serum gastrin
Zhu et al,[35] (2024)	China	Tegoprazan 50 mg vs Esomeprazole 40 mg	261 randomized (132 Tegoprazan vs 129 Esomeprazole)	8 wk	Primary: endoscopic healing at week 8 Secondary: RDQ and GERD-HRQoL scores, symptom-free days, time to symptom resolution, safety endpoints

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Table. Continued

Author (yr)	Location	Drug administration	Patients	Duration	Outcome
Xiao et al,[32] (2024)	China, South Korea, and Malaysia	Vonoprazan 10 mg, 20 mg vs Lansoprazole 15 mg	703 randomized (235 Vonoprazan 10 mg, 226 Vonoprazan 20 mg, 242 Lansoprazole)	24 wk	Primary: endoscopic recurrence of EE over 24 wk; Secondary: TEAEs, symptom diaries
Uemura et al[33] (2024)	Japan	Healing phase – Vonoprazan 20 mg vs Lansoprazole 30 mg/Maintenance phase – Vonoprazan 10 mg vs Lansoprazole 15 mg	208 randomized (139 Vonoprazan vs 69 Lansoprazole)	260 wk	Primary: histological changes in gastric mucosa Secondary: EE healing and recurrence, adverse events, serum gastrin, and chromogranin A levels
Kang et al,[36] (2025)	Korea	Tegoprazan 50 mg vs Esomeprazole 20 mg	69 randomized (36 Tegoprazan vs 33 Esomeprazole)	8 wk	Primary: patient satisfaction with on-demand therapy (5-point Likert scale) Secondary: time to symptom improvement, number of doses used, symptom severity and frequency, and adverse events
Shin et al,[37] (2025)	Korea	Tegoprazan 50 mg vs Lansoprazole 30 mg	218 randomized (109 Tegoprazan vs 109 Lansoprazole)	4 wk	Primary: cumulative proportion of patients with healed EE (up to week 4); Secondary: Healed EE at week 2, healing by CYP2C19 genotype and EE severity, symptom response (RDQ), and safety (TEAE)

EE, erosive esophagitis; FSSG, frequency scale for the symptoms of gastroesophageal reflux disease (GERD); PSQI, Pittsburgh sleep quality index; GerdQ, gastroesophageal reflux disease questionnaire; GOS, global overall symptom; RDQ, reflux disease questionnaire; HRQoL, health-related quality of life; TEAEs, treatment-emergent adverse events; QoL, quality of life; GSRS, gastrointestinal symptom rating scale; CYP2C19, cytochrome P450 2C19 (an enzyme affecting drug metabolism).

plementary Fig. 1B and 2B). Studies included within a symmetrical inverted triangular shape based on effect size indicated a low publication bias. Caution is required when interpreting the results from fewer than 10 studies.

Network Synthesis

A network evidence plot of the efficacy and safety analyses is shown in Supplementary Figure 3. A total of 3684 participants with EE were included in the initial efficacy analysis,[16,19-21,29,34,35,39-41] 1661 in the maintenance efficacy analysis,[19,31,32,38] 2834 in the short-term TEAE analysis,[15,16,19-21,28,29,34-37,39-41] and 1813 in the long-term TEAE analysis.[16,19-21,29,31,32,34-41] The specific randomized controlled trials contributing to each analysis are summarized in Supplementary Table 2.

Efficacy

Initial treatment

Overall erosive esophagitis

In the 8-week treatment phase, vonoprazan 20 mg demonstrated statistically significant superiority in healing EE compared to standard dose PPIs (RR = 1.77; 95% CI, 1.30-2.43) and ranked third among all treatments based on the P-score (0.68) (Fig. 2A). Although keverprazan and zastaprazan showed higher point estimates (P-score 0.81 and 0.77, respectively), their 95% CIs were wide and did not reach statistical significance. Tegoprazan (RR = 1.05; 95% CI, 0.50-2.21; P-score = 0.29) and fexuprazan (RR = 0.95; 95% CI, 0.49-1.86; P-score = 0.22) showed comparable efficacy to PPIs. The PMA supported this finding, showing a statistically significant benefit over PPIs in the overall population (RR = 1.03; 95% CI, 1.00-1.05; $P = 0.020$; $I^2 = 47\%$) (Supplementary Fig. 4A).

Mild erosive esophagitis

Among patients with mild EE, the NMA showed that the effects of P-CABs overlapped with those of PPIs. Vonoprazan, keverprazan, and zastaprazan had P-scores ranging from 0.38 to 0.69, indicating no meaningful difference in treatment ranking (Fig. 2B). Similarly, PMA showed no statistically significant difference in healing rates between P-CABs and PPIs (RR = 1.00; 95% CI, 0.99-1.02; $P = 0.902$; $I^2 = 0\%$) (Supplementary Fig. 4B).

Severe erosive esophagitis

P-CABs showed a trend toward higher efficacy in patients with severe EE. Vonoprazan demonstrated significantly superior healing efficacy compared with standard-dose PPIs, ranking second among all treatments based on the P-score (0.72). Although keverprazan and zastaprazan did not reach statistical significance, their P-scores (0.64 and 0.76, respectively) suggested a po-

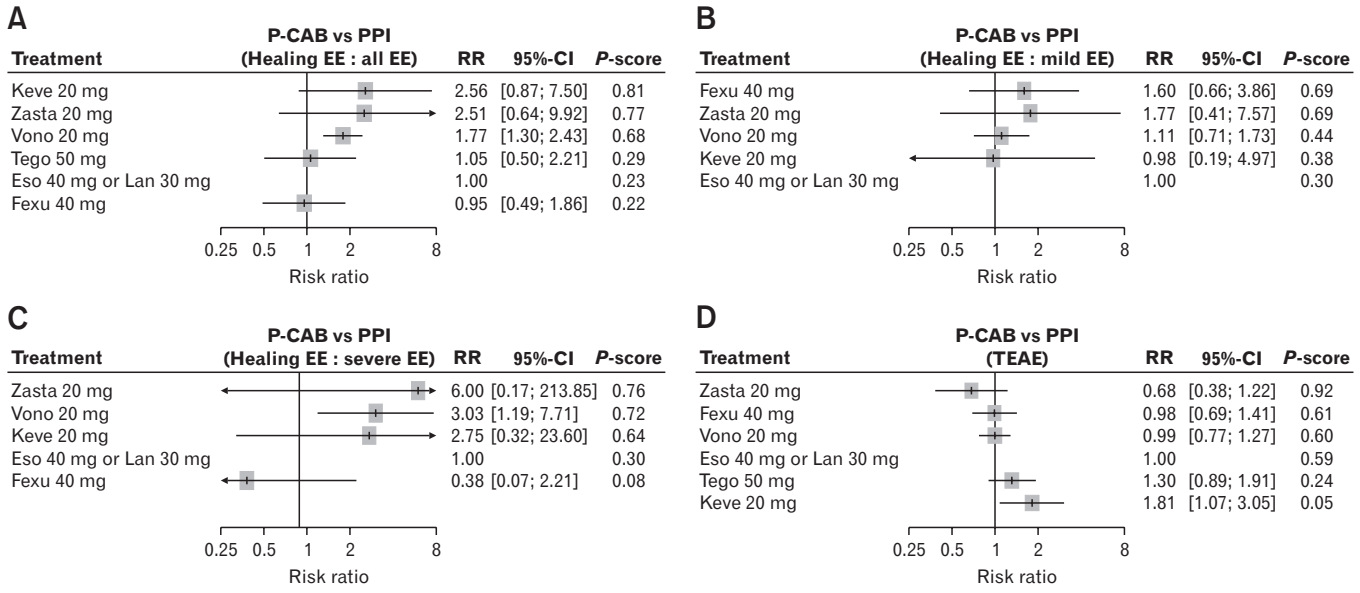

Figure 2. Network meta-analysis results for efficacy (healing of erosive esophagitis [EE]) and safety (treatment-emergent adverse events [TEAEs]) at 8 weeks of initial treatment. Relative risk estimates and P-scores are presented for each intervention. (A) Healing of EE in the overall population. (B) Healing of EE in patients with mild EE. (C) Healing of EE in patients with severe EE. (D) TEAEs in the overall population. P-CABs, potassium-competitive acid blockers; PPI, proton pump inhibitor; Keve, keverprazan; Zasta, zastaprazan; Vono, vonoprazan; Tego, tegoprazan; Eso, esomeprazole; Fexu, fexuprazan.

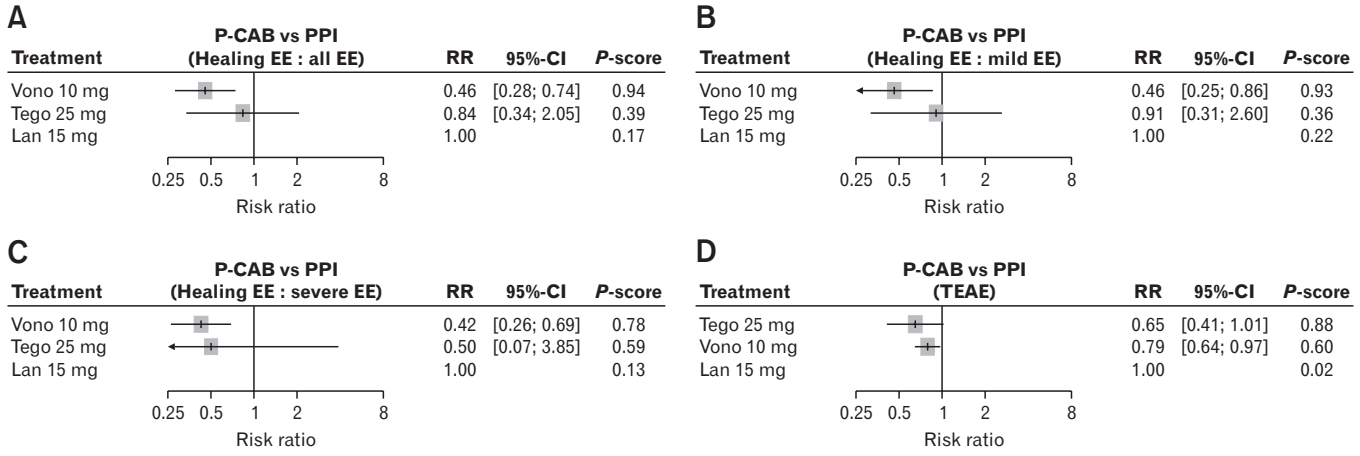

Figure 3. Network meta-analysis results for efficacy (recurrence) and safety (treatment-emergent adverse events [TEAEs]) during 24-week maintenance therapy. (A) Recurrence of erosive esophagitis (EE) in the overall population. (B) Recurrence of EE in patients with mild EE. (C) Recurrence of EE in patients with severe EE. (D) TEAEs in the overall population. P-CABs, potassium-competitive acid blockers; PPI, proton pump inhibitor; Vono, vonoprazan; Tego, tegoprazan; Lan, lansoprazole.

tential advantage of P-CABs, particularly in patients with more severe disease (Fig. 2C). Similarly, PMA showed that P-CABs were associated with significantly higher healing rates compared to PPIs (RR = 1.10; 95% CI, 1.00-1.20; $P = 0.040$; $I^2 = 64\%$) (Supplementary Fig. 4C).

Maintenance treatment

Overall erosive esophagitis

For 24-week maintenance treatment, vonoprazan 10 mg significantly reduced the risk of EE recurrence compared to lansoprazole 15 mg (RR = 0.46; 95% CI, 0.28-0.74), with the highest P-score (0.94) (Fig. 3A). Tegoprazan 25 mg showed a favorable result but did not reach statistical significance (RR = 0.84; 95% CI, 0.34-2.05;

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P-score = 0.39). PMA showed that P-CABs showed significantly lower recurrence rates compared to PPIs (RR = 0.59; 95% CI, 0.41-0.85; P = 0.005; I^2 = 60%) (Supplementary Fig. 5).

Mild erosive esophagitis

In patients with mild EE, vonoprazan significantly reduced recurrence risk compared to PPI (RR = 0.46; 95% CI, 0.25–0.86; P-score = 0.93), whereas tegoprazan showed no significant effect (Fig. 3B). PMA showed lower recurrence rates with P-CABs in mild EE (RR = 0.60; 95% CI, 0.38-0.94; P = 0.026; I^2 = 56%) (Supplementary Fig. 5).

Severe erosive esophagitis

In patients with severe EE, vonoprazan showed a statistically significant reduction in recurrence risk (RR = 0.42; 95% CI, 0.26-0.69; P-score = 0.78), whereas tegoprazan had a favorable point estimate but a wide CI (RR = 0.50; 95% CI, 0.07-3.85; P-score = 0.59) (Fig. 3C). PMA also supported a lower recurrence rate with P-CABs in severe EE (RR = 0.60; 95% CI, 0.44-0.83; P = 0.002; I^2 = 0%) (Supplementary Fig. 5C).

Safety

Initial treatment

Safety profiles during the initial 8-week treatment phase were comparable across P-CABs and PPIs. As shown in Figure 2, most agents had a similar incidence of TEAEs with no significant differences. However, keverprazan 20 mg was associated with a significantly increased risk of TEAEs compared to PPIs (RR = 1.81; 95% CI, 1.07-3.05), with the lowest P-score (0.05). Zastaprazan 20 mg showed a favorable safety profile (P-score = 0.90), although the difference was not statistically significant. Similarly, PMA showed that the overall incidence of TEAEs was comparable between the P-CABs and PPIs (Supplementary Fig. 6).

Maintenance treatment

Regarding long-term TEAEs, P-CABs demonstrated a similar or lower risk than PPIs (Fig. 3). Tegoprazan 25 mg had the highest safety ranking (P-score = 0.88), although the difference was not statistically significant (RR = 0.65; 95% CI, 0.41-1.01). Vonoprazan 10 mg also showed a favorable safety profile (RR = 0.79; 95% CI, 0.64–0.97; P-score = 0.60). Similarly, PMA showed no significant difference in the overall incidence of TEAEs between the P-CAB and PPI groups (Supplementary Fig. 7). A comprehensive summary of safety data across all included trials is presented in Supplementary Table 3.

Sensitivity analysis

Initial treatment (2 weeks and 4 weeks)

Supplementary Figure 8 shows the 4-week EE healing rates. P-CABs were significantly more effective than PPIs at 4 weeks (RR = 1.04; 95% CI, 1.01-1.06; P = 0.002; I^2 = 1%). Subgroup analysis according to severity revealed no statistically significant difference in patients with mild EE (RR = 1.01; 95% CI, 0.97-1.06; P = 0.591; I^2 = 59%). However, in patients with severe EE, P-CABs were associated with significantly higher healing rates compared to PPIs (RR = 1.14; 95% CI, 1.03-1.26; P = 0.009; I^2 = 39%). These findings indicate the consistent superiority of P-CABs over PPIs in endoscopic healing, particularly among patients with severe EE, at both the 4-week and 8-week treatment durations.

Additionally, in an analysis of 2-week outcomes, 4 RCTs of vonoprazan 20 mg and 1 RCT of tegoprazan 50 mg were available. P-CABs demonstrated a significantly higher healing rate compared with PPIs (RR = 1.08; 95% CI, 1.04-1.13; P < 0.001; I^2 = 0%) (Supplementary Fig. 9).

Symptom relief

Supplementary Figure 10 shows the results of the PMA on symptom improvement at 8 weeks. P-CABs were associated with a statistically significant improvement in symptoms compared to PPIs (RR = 1.06; 95% CI, 1.00-1.11; P = 0.038; I^2 = 0%).

Cytochrome P450 2C19 genotype

Supplementary Figure 11 shows the subgroup analysis according to the CYP2C19 metabolizer status at 8 weeks. In extensive metabolizers (EMs), P-CABs were significantly more effective than PPIs in achieving mucosal healing (RR = 1.06; 95% CI, 1.02-1.11; P = 0.002; I^2 = 45%), suggesting a clinically meaningful advantage of P-CABs in patients with CYP2C19 who were EMs. In contrast, among poor metabolizers (PMs), no significant difference in healing rates was observed between P-CABs and PPIs (RR = 1.00; 95% CI, 0.94-1.06; P = 0.885; I^2 = 0%).

Meta-regression according to disease severity

To evaluate the influence of EE severity on treatment efficacy, we performed meta-regression analysis across the spectrum of EE severity (Fig. 4). In the initial treatment phase (Fig. 4A), higher EE severity was associated with greater healing efficacy of P-CABs (slope estimate,

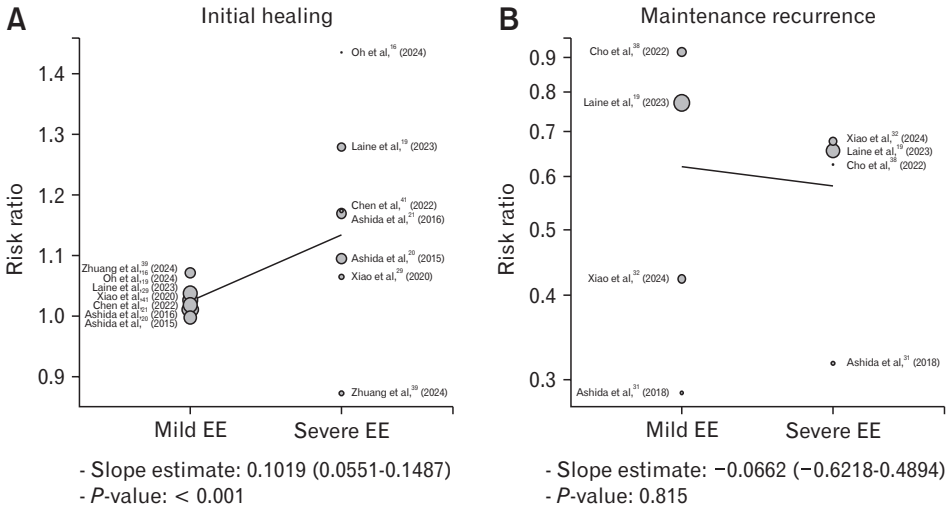

Figure 4. Meta-regression analysis evaluation the association between erosive esophagitis (EE) severity and treatment efficacy. (A) Initial treatment phase (EE healing). (B) Maintenance treatment phase (EE recurrence).

0.102; 95% CI, 0.055-0.149; $P < 0.001$). Similarly, in the 24-week maintenance phase (Fig. 4B), although not statistically significant, a trend toward greater efficacy of P-CABs was observed with higher EE severity.

DISCUSSION

This NMA evaluated the comparative efficacy and safety of P-CABs and PPIs in the treatment of EE, stratified by disease severity (mild vs severe EE) and treatment phase (initial vs maintenance). The major findings are summarized as follows: (1) In the initial treatment, P-CABs showed similar efficacy to PPIs in patients with mild EE, but demonstrated superior efficacy in those with severe EE. (2) During maintenance treatment, P-CABs were more effective than PPIs at preventing both mild and severe EE recurrence. (3) P-CABs demonstrated greater healing efficacy in patients with more severe EE, and their therapeutic advantage was more evident in CYP2C19 EMs. (4) The incidence of TEAEs was comparable between P-CABs and PPIs, indicating similar short- and long-term safety profiles.

Several RCTs have evaluated the efficacy of P-CABs in the initial treatment of EE. Vonoprazan was evaluated in the largest number of RCTs, with 7 studies involving more than 2847 participants comparing various doses of vonoprazan (5-40 mg) with lansoprazole 15-30 mg or esomeprazole 20 mg. Most trials demonstrated either superior or comparable efficacy of vonoprazan in terms of mucosal healing. In addition, other P-CABs have been compared in RCTs with esomeprazole 20-40 mg or lansoprazole 30 mg, including tegoprazan 50-100 mg (4 studies, 857 participants), fexuprazan 40 mg (2 studies, 550 participants), keverprazan 20 mg (1 study, 238 participants), and zastaprazan 20 mg (1 study, 300 participants). In these studies, P-CABs showed mucosal healing rates that were either superior or similar to those of esomeprazole 20-40 mg or lansoprazole 30 mg. Although these studies included patients with both mild and severe EE, mild EE constituted a major proportion of the enrolled population, and direct evidence focused specifically on severe EE remains relatively limited. Our study expanded upon this evidence by analyzing both direct and indirect comparisons across EE severity subgroups. In patients with severe EE (7 studies, 897 participants), P-CABs demonstrated superior efficacy compared to PPIs. Notably, vonoprazan was significantly more effective than PPIs in achieving endoscopic healing (RR = 3.03; 95% CI, 1.19-7.71) and ranked favorably based on P-score (0.72), following zastaprazan (P-score = 0.76). Although zastaprazan and keverprazan (P-score = 0.64) showed relatively favorable rankings, their statistical significance was limited by their wide CIs and small sample sizes. In mild EE (7 studies, 2,126 participants), P-CABs showed comparable efficacy to PPIs, with overlapping CIs and similar P-scores across agents. Interestingly, subgroup analysis by CYP2C19 genotype revealed a clinically relevant pattern: in EMs, P-CABs were significantly more effective than PPIs (RR = 1.06; 95% CI, 1.02-1.11), whereas no such difference was seen in PMs. This finding highlights the pharmacogenetic advantage of P-CABs, which are minimally affected by CYP2C19 variability, highlighting their potential as reliable acid-suppressive therapies in real-world populations with variable metabolisms. In addition, in an analysis of early outcomes at 2 weeks, P-CABs demonstrated significantly greater healing rates compared with PPIs. This suggests that P-CABs may

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provide faster mucosal healing, although the limited number of studies and the exploratory nature of this analysis warrant cautious interpretation. Short-term TEAEs were largely comparable between P-CABs and PPIs. While keverprazan was associated with a numerically higher TEAE rate (RR = 1.81; 95% CI, 1.07-3.05), other P-CABs showed favorable or equivalent profiles. These results support the overall short-term safety of P-CABs in the initial management of EE, although further data are needed to establish safety across diverse patient populations and over longer treatment durations, particularly for newer P-CABs, such as keverprazan.

Only 2 P-CABs, vonoprazan and tegoprazan, have been evaluated as maintenance treatments to date. Vonoprazan has been investigated in the largest number of RCTs, with 4 trials involving over 2545 participants comparing various doses (10-20 mg) to lansoprazole 15 mg.[19,31-33] Most trials demonstrated either superior or comparable efficacy of vonoprazan in preventing EE recurrence. Additionally, a recent study comparing tegoprazan 25 mg with lansoprazole 15 mg reported comparable efficacy, although the sample size was limited (351 participants).[38] Although previous studies on P-CAB have primarily focused on initial healing, data on maintenance treatment remains limited. To address this gap, our NMA incorporated both direct and indirect comparisons to evaluate the long-term efficacy according to EE severity. In patients with mild EE (4 studies, 1287 participants), P-CABs demonstrated superior efficacy over PPIs. Vonoprazan 10 mg significantly reduced the risk of EE recurrence (RR = 0.46; 95% CI, 0.25-0.86), ranking highest in P-score analysis (0.93). Tegoprazan 25 mg also showed a favorable ranking (P-score = 0.39), suggesting potential benefit; however, statistical significance was not achieved (RR = 0.84; 95% CI, 0.34-2.05), likely due to the small sample size and wide CIs. In patients with severe EE (4 studies, 363 participants), P-CABs demonstrated superior efficacy over PPIs. Vonoprazan 10 mg significantly reduced recurrence risk (RR = 0.42; 95% CI, 0.26-0.69) and ranked highest in P-score analysis (0.78). Tegoprazan 25 mg also showed a favorable ranking (P-score = 0.59), indicating its potential benefits. Regarding safety, the TEAE rates over the 24-week maintenance period were comparable across the treatment arms. Both vonoprazan 10 mg and tegoprazan 25 mg demonstrated favorable safety profiles relative to PPIs, with P-scores of 0.60 and 0.88, respectively. These findings suggest that P-CABs are effective and well-tolerated options for the long-term maintenance treatment of EE, including in patients with severe disease.

This study had several notable strengths. First, it is the most comprehensive NMA to date that evaluated all currently available P-CABs, including newer agents, such as keverprazan and zastaprazan, in both the initial and maintenance treatment phases of EE. By focusing exclusively on RCTs and using the LA classification to stratify disease severity, our analysis ensures reliable methodology and enhances clinical relevance. While a recent meta-analysis was limited to patients with severe EE,[26] the present study extends the evidence base by incorporating both mild and severe EE and by assessing not only initial healing but also long-term recurrence during maintenance therapy. This broader scope provides a more comprehensive evaluation that complements prior reviews and enhances the clinical applicability of our findings. Second, we stratified treatment efficacy not only by treatment phase (initial vs maintenance) but also by endoscopic severity (mild vs severe EE) and further incorporated the CYP2C19 metabolizer status. This allows a more detailed understanding of how treatment responses

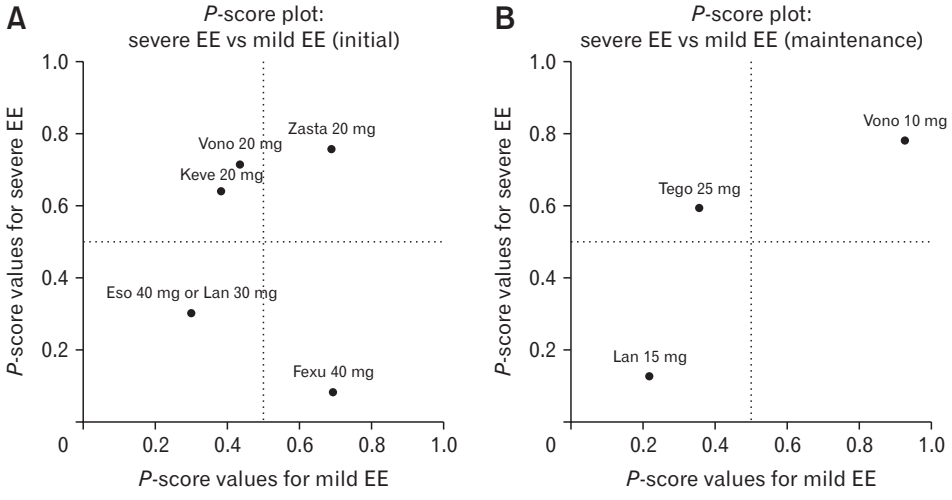

Figure 5. Summarized 2-dimensional P-score ranking plot for efficacy (mild erosive esophagitis [EE] vs severe EE) at initial (A) and maintenance (B) treatment phases. Eso, esomeprazole; Keve, keverprazan; Vono, vonoprazan; Zasta, zastaprazan; Fexu, fexuprazan; Lan, lansoprazole; Tego, tegoprazan.

differ among patient subgroups and supports the development of individualized phenotype-specific treatment strategies. Finally, the dual incorporation of NMA and PMA strengthened the robustness of our findings and enhanced their applicability in clinical decision-making. These findings may help clinicians select the optimal acid-suppressive treatment based on individual patient factors, such as disease severity and CYP2C19 genotype, particularly when considering the role of P-CABs as a first-line option for high-risk EE populations. Summarized P-score rankings for overall efficacy according to the treatment phase and EE severity are shown in Figure 5.

This study had several limitations that warrant consideration. First, although we conducted a comprehensive NMA, including both the initial and maintenance phases, we restricted our analysis to standard or half-dose doses for each agent rather than incorporating high-dose or twice-daily PPI regimens. However, these selected doses align with the current guideline recommendations and reflect real-world clinical practice, thereby enhancing the external validity of our findings. Second, most included studies were conducted in Asian populations, particularly in Japan, Korea, and China, raising concerns about the generalizability of our results to non-Asian cohorts. Considering the ethnic differences in CYP2C19 metabolism, drug responses, and demographic characteristics, further studies in Western populations are required. Third, this study included only RCTs, resulting in a limited number of studies. In particular, a lack of studies on new drugs such as fexuprazan, keverprazan, and zastaprazan limited the interpretation of NMA results for these drugs. The wide CIs and imprecision for these agents should be explicitly acknowledged, and the apparently favorable rankings should not be overinterpreted; larger, adequately powered RCTs are needed to confirm these findings. Although vonoprazan appeared superior to other PCABs in terms of clinical outcomes, this observation may largely reflect the relatively greater volume of evidence available, as vonoprazan was introduced earlier and has been more extensively studied. Nevertheless, structural heterogeneity among PCABs may translate into differences in efficacy and safety. These molecular considerations highlight the need for future head-to-head trials to determine whether such variations result in clinically meaningful differences. Furthermore, most vonoprazan trials used lansoprazole as the comparator, whereas studies of other PCABs more often used esomeprazole. This imbalance in comparator choice may also have contributed to the apparently greater relative effect of vonoprazan. Accordingly, the current findings should not be overinterpreted as confirming inherent pharmacological superiority. Future research with direct comparative trials and balanced evidence across PCABs is warranted. Fourth, although heterogeneity between studies was low to moderate in most analyses, substantial heterogeneity (I^2 > 60%) was observed in some comparisons, particularly recurrence and 24-week TEAEs, which reduces confidence in these pooled estimates and warrants cautious interpretation. Therefore, this study applied a random-effects model to account for the heterogeneity between the studies in the meta-analysis. This approach contributed to the adjustment for clinical and methodological differences between studies and enabled a more reliable interpretation of the results. Additionally, the relatively small number of patients with severe EE, especially in Asian studies, contributed to wide confidence intervals and instability in treatment ranking. Therefore, the interpretation of P-scores in this subgroup should be approached with caution. Fifth, reliable data on long-term safety beyond 6 months also remains limited. While our pooled analysis suggests comparable tolerability between P-CABs and PPIs in the short to intermediate term, the durability of safety outcomes over prolonged use could not be determined. Given that EE often requires long-term therapy, further long-term and real-world studies are essential to establish the extended safety profile of P-CABs. Finally, some outcomes, particularly symptom improvement, have been inconsistently reported across studies owing to variations in measurement instruments (eg, different symptom questionnaires), limiting the ability to perform uniform subgroup analyses. This heterogeneity weakens the interpretability of the pooled analysis, and therefore these results should be viewed with caution. In future trials, standardized, validated outcome measures and reporting practices should be adopted to enhance comparability. Despite these limitations, our study offers a comprehensive synthesis of the available RCT evidence and provides clinically meaningful guidance for the individualized use of P-CABs in the management of EE across disease severity and treatment phases.

In conclusion, this NMA demonstrated that P-CABs, particularly vonoprazan, offer superior efficacy compared to PPIs for both healing and maintaining remission of EE, with enhanced efficacy in severe EE and CYP2C19 EM. The safety profiles of P-CABs were comparable to those of PPIs. These findings support the preferential use of P-CABs, especially vonoprazan, as a potent and reliable option for personalized management of EE. However, further research is warranted to address current evidence gaps. In particular, long-term studies are needed to es-

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tablish the safety profile of P-CABs, evaluate their durability in long-term therapy, and clarify their role across diverse patient populations beyond Asia.

SUPPLEMENTARY MATERIALS

Note: To access the supplementary methods, tables, and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm25161.

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