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SYSTEMATIC REVIEW

A systematic review with meta-analysis: Efficacy and safety of potassium-competitive acid blocker compared with proton pump inhibitor in the maintenance of healed erosive esophagitis

Daniel M Simadibrata,*,† Elvira Lesmana,* Muhammad I A Pratama,* Adrianus J Sugiharta,* Afiah S Winarizal,* Yeong Y Lee‡,§ and Ari F Syam¶

*Faculty of Medicine Universitas Indonesia, ¶Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia—Ciptomangkunkusumo General Hospital, Jakarta, Indonesia, †Nuffield Department of Population Health, University of Oxford, Oxford, UK, ‡School of Medical Sciences, Universiti Sains Malaysia and §GI Function and Motility Unit, Hospital USM, Kota Bharu, Malaysia

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Correspondence
Prof Ari F Syam, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia—Ciptomangunkusumo General Hospital, Jakarta, Indonesia. Email: ari_syam@hotmail.com

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Abstract

Introduction: Proton pump inhibitor (PPI) is the mainstay therapy for the maintenance of healed erosive esophagitis (EE). It is unknown whether potassium-competitive acid blockers (PCABs) are more efficacious and safer than PPIs.
Methods: Only randomized controlled trials (RCTs) comparing PCABs to PPIs in the maintenance of healing rates of endoscopically proven healed EE and indexed in MEDLINE, EMBASE, and CENTRAL until 3 February 2024, were included. A fixed-effects model meta-analysis was performed to pool primary efficacy outcome (maintenance of healing rates at week 24) and safety data (any treatment-emergent adverse event or TEAE). The risk of bias was assessed using Cochrane's Risk of Bias 2 (RoB2) tool.
Results: Four RCTs with a total of 2554 patients were eligible for inclusion. All trials were of low risk of bias. Compared to lansoprazole 15 mg, the maintenance rates of healed EE at week 24 were significantly higher with vonoprazan 10 mg (RR 1.13; 95% CI 1.07–1.19) and vonoprazan 20 mg (RR 1.15; 95% CI 1.10–1.21). Likewise, compared to lansoprazole 15 mg, any TEAEs were significantly greater with vonoprazan 20 mg (RR 1.10; 95% CI 1.01–1.20) but not vonoprazan 10 mg.
Conclusion: Vonoprazan 10 and 20 mg were superior to lansoprazole 15 mg in the maintenance of the healing of EE. Any TEAEs were greater with vonoprazan 20 mg.

Introduction

After the healing (initial) phase of erosive esophagitis (EE), it is recommended to continue treatment during the maintenance phase, which will prevent the recurrence or relapse of EE in the longer term.[1] The current mainstay treatment for healing and maintenance of healing of EE is proton pump inhibitor (PPI).[1,2] Despite being efficacious, recent studies have highlighted the potential risks associated with PPI use, such as kidney disease, dementia, bone fracture, and infections (pneumonia and *C. difficile*).[3–5] Moreover, up to 40% of patients remain unresponsive or show minimal improvement after PPI.[6]

Potassium-competitive acid blocker (PCAB) is a novel acid-suppressive drug with differential pharmacological characteristics from PPI, making this new compound more potent. PPI works by irreversibly blocking the H^+/K^+-ATPase and requiring an acidic environment to work effectively. PCAB works by competitively inhibiting the proton pumps reversibly and does not require gastric acid activation.[7,8] Previous meta-analyses have shown that PCAB was superior to PPI in healing EE[9–12]; however, it is unknown whether the same was true for the maintenance of healed EE.

Thus, the current systematic review and meta-analysis aimed to determine the efficacy and safety of PCABs over PPIs in the maintenance rates of healed EE.

Methods

A protocol was created *a priori* and registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42023413656). The current review was written in accordance with the 2020 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Checklist (Table S1).

Eligibility criteria. Eligibility criteria included adults (≥18 years old), a previous diagnosis of erosive esophagitis (irrespective of baseline severity), and a successful initial treatment evidenced by complete endoscopic healing. In addition, only randomized controlled trials (RCTs) that compared PCABs to PPIs, regardless of types or doses, were considered for study inclusion.

Search strategy and study selection. Peer-reviewed papers and conference/abstract proceedings published from the beginning to 3 February 2024, were sought from the following electronic databases: MEDLINE (Ovid interface), EMBASE (Ovid interface), and CENTRAL (the Cochrane Library). Clinical trials registered in ClinicalTrials.Gov, EU Clinical Trials Registers, and WHO International Clinical Trials Registry Platform were manually hand-searched for additional relevant RCTs. References and citations of published papers were also inspected for potential additional studies. There were no restrictions on the language of publications. Search strategies were formulated using the following keywords, their synonyms, abbreviations, and MeSH terms: "Proton Pump Inhibitor," "Potassium-Competitive Acid Blocker," and "Erosive Esophagitis" (Table S2). Additionally, search filters endorsed by the Cochrane Collaboration and in consultation with a librarian were used to best identify relevant RCTs. All retrieved papers were first imported into Endnote 20, where an initial deduplication of the studies was performed. Two investigators (DMS and EL) screened titles and abstracts, followed by a full-text review (and its Supplementary Files) according to the abovementioned eligibility criteria.

Outcome. The primary outcome was the maintenance rate of healed EE at week 24. Secondary outcomes were (1) the maintenance rate of healed EE at week 12, (2) 24-h heartburn-free days at week 24, (3) any treatment-emergent adverse event (TEAE), (4) serious or severe TEAE, and (5) TEAE leading to treatment discontinuation at week 24. Only data presented using the intention-to-treat (ITT) principle were extracted for the efficacy outcomes. Meanwhile, only data presented using the safety analysis set (SAS) defined by each study were extracted for the safety outcomes.

Data extraction and risk of bias assessment. Data extraction and risk of bias assessment were performed by at least two independent reviewers (AJS, ASW, or MAIP). Before data extraction, a standardized Excel form was created to capture the following information: study identifier including author, year of publication, and trial registration number; study design; study location; types and dosages of PCAB/PPI; treatment duration; baseline characteristics including sample size, mean age, proportion of males, mean BMI, smokers, alcohol drinkers, *Helicobacter pylori* infection, severity (LA grade); and outcomes as defined above.

The risk of bias assessment was evaluated using Cochrane's Risk of Bias 2 (RoB2) tool and graded as "low risk," "some concerns," or "high risk" of bias. The RoB2 tool assessed for risk of bias in the following components: (i) randomization process, (ii) any deviation from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, (v) selection of the reported result, and (vi) overall RoB. When there were discrepancies between two reviewers, a third reviewer would perform independent data extraction and risk of bias assessment and arbitrate the dispute.

Statistical analysis. Meta-analysis was performed using the R program (Vienna, Austria) with the "meta" package. The crude maintenance and TEAE rates were manually calculated. The inverse variance-weighted fixed-effect meta-analysis of risk ratio (RR) was performed to calculate the pooled maintenance rates. The inverse variance-weighted fixed-effect meta-analysis of RR for safety outcomes was also performed. The random-effects model was also conducted for sensitivity analysis. The fixed-effects model assumed a "true effect size" across all studies. In contrast, the random-effects model assumed that the "true effect size" varies between studies due to the underlying heterogeneity, leading to a 95% CI that is much wider than that of the fixed-effects model.[13] A two-tailed *P*-value of less than 0.05 was considered statistically significant. Between-study heterogeneity was calculated using the I^2 statistics, and an I^2 value of >50% was considered substantially heterogeneous.[14] Pooling of studies was performed only for individual studies using the same type and dose of PCAB. Subgroup analysis was conducted to investigate differences between the overall maintenance rate at 24 weeks based on the baseline severity measured by the LA grade (LA grade A/B *vs* LA grade C/D) with *P*-value <0.05 considered statistically significant. The LA grading is a classification system used to grade the severity of EE, where LA grade A/B is considered mild, while LA grade C/D is considered severe EE.[15] Publication bias was not formally assessed due to the number of studies <10.[16]

Results

The online database search and manual hand searching yielded a total of 270 studies, of which four RCTs were included in the final analysis[17–20] (Fig. 1). The reasons for the exclusion of other papers are detailed in Table S3. The four studies randomized a

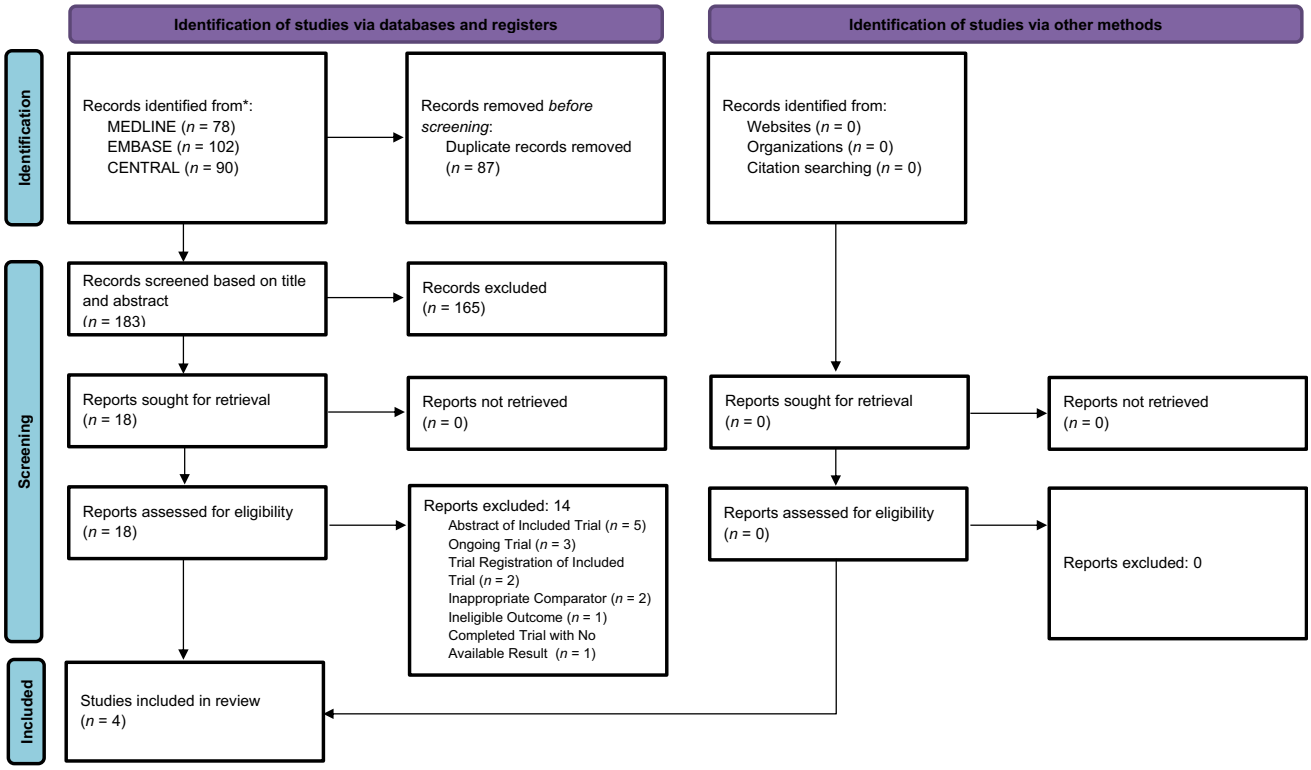

Figure 1 PRISMA flow diagram (2020 version).

total of 2554 adult patients with healed erosive esophagitis to either PCAB or PPI. Three studies randomized patients to either vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg.[17,19,20] One study randomized healed EE patients to either tegoprazan 25 mg or lansoprazole 15 mg (Tables 1 and S4).[18] The studies recruited patients from Japan, Korea, the USA, Europe, China, Malaysia, and Taiwan. All the studies had a treatment duration of 24 weeks (6 months). The randomized patients had a mean age between 51 and 58 years, more than half were men (1605/2493; 64.4%), and more than two-thirds had a baseline LA grade of A/B (~80%). Other baseline characteristics are described in Table 1. Overall, the risk of bias in all included studies was low (Fig. 2).

Maintenance rate of healed EE at week 24. The crude maintenance rates of healed EE at week 24 were 84.76% for vonoprazan 10 mg, 86.54% for vonoprazan 20 mg, and 75.00% for lansoprazole 15 mg (Table 2). Compared to lansoprazole 15 mg, significantly greater maintenance rates at 24 weeks were seen for vonoprazan 10 mg (RR 1.13; 95% CI 1.07–1.19) and vonoprazan 20 mg (RR 1.15; 95% CI 1.10–1.21) (Fig. 3). Sensitivity analysis by pooling outcomes with a random-effects model did not change the conclusion of the finding (Table S5). In two studies comparing lansoprazole 15 mg vs. vonoprazan 10 mg, there was no difference in maintenance rate at week 24 between the two LA subgroups (p-interaction = 0.06) (Fig. S1B).[17,19] However, vonoprazan 20 mg was found to be more superior to lansoprazole 15 mg in maintenance rates at week 24 with baseline LA grade of C/D vs. A/B (RR 1.35; 95% CI 1.16–1.58 vs. RR 1.09; 95% CI 1.02–1.16; p-interaction = 0.01) (Fig. S1C).

In the only study that compared tegoprazan 25 mg versus lansoprazole 15 mg, both compounds expressed similar crude maintenance rates at week 24, that is, 76.44% and 71.75%, respectively (RR 1.07; 95% CI 0.94–1.21).[18] However, in those with baseline LA grade C/D, there was a significant decrease in maintenance rates of healed EE in the lansoprazole 15 mg group but not in the tegoprazan 25 mg group.

Maintenance rate of healed EE at week 12. In two studies, the crude maintenance rates at week 12 for vonoprazan 10 mg, vonoprazan 20 mg, and lansoprazole 15 mg were 82.84%, 93.49%, and 74.27%, respectively (Table 2).[17,20] Vonoprazan 10 mg and vonoprazan 20 mg were significantly superior to lansoprazole 15 mg (RR 1.11; 95% CI 1.04–1.19; and RR 1.25; 95% CI 1.18–1.33, respectively) (Fig. S1A). In contrast, tegoprazan 25 mg was similar to lansoprazole 15 mg in maintenance rates at week 12 (RR 1.00; 95% CI 0.91–1.11).[18]

24-h heartburn-free days at week 24. In the only study, the overall 24-h heartburn-free days at week 24 for vonoprazan 10 mg, vonoprazan 20 mg, and lansoprazole 15 mg were 80.9 (SD 28.6), 80.6 (30), and 78.6 (27.5), respectively (Table 2).[19] While not superior (irrespective of dose), the authors were able to conclude the non-inferiority of vonoprazan to lansoprazole with a margin of 15%.

Table 1 Study characteristics of included studies

Author (year)	Ashida (2018)			Cho (2023)		Laine (2023)			Unpublished study		
ClinicalTrials.Gov ID	NCT01459367			NCT04022096		NCT04124926			NCT02388737		
Study design	Randomized, double-blind, multicenter, parallel-group clinical trial			Randomized, double-blind, multicenter, active-controlled clinical trial		Randomized, double-blind, multicenter, parallel-group clinical trial			Randomized, double-blind, multicenter, parallel-group clinical trial		
Study location	Japan			South Korea		The USA, Bulgaria, Czechia, Hungary, Poland, and the UK			China, Malaysia, South Korea, and Taiwan		
Type of PCAB/PPI	VPZ 10 mg	VPZ 20 mg	LPZ 15 mg	TPZ 25 mg	LPZ 15 mg	VPZ 10 mg	VPZ 20 mg	LPZ 15 mg	VPZ 10 mg	VPZ 20 mg	LPZ 15 mg
Treatment duration	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks
Sample size	202	204	201	154	151	293	291	294	235	226	242
Mean age (SD)	55.5 (13.8)	56.8 (13.6)	57.8 (12.9)	55.4 (12.1)	56.0 (13.4)	52.3 (13.8)	51.0 (14.5)	51.0 (13.0)	51.7 (11.8)	52.8 (13.0)	54.0 (12.8)
Male *N* (%)	160 (79)	160 (78)	140 (70)	114 (74)	110 (73)	134 (46)	145 (50)	123 (42)	176 (75)	165 (73)	178 (74)
Mean BMI (SD)	NR	NR	NR	NR	NR	31.6 (6.8)	31.0 (6.7)	31.1 (6.1)	25.1 (3.4)	24.6 (3.1)	24.8 (3.5)
Smoking, *N* (%)											
Never smoker	54 (27)[†]	60 (30)[†]	76 (39)[†]	123 (80)	121 (80)	254 (87)	253 (87)	252 (86)	157 (67)	135 (60)	147 (61)
Ex-smoker	82 (42)	84 (42)	80 (41)						28 (12)	44 (19)	40 (17)
Current smoker	61 (31)	57 (28)	40 (20)	31 (20)	30 (20)	39 (13)	38 (13)	42 (14)	50 (21)	47 (21)	55 (23)
Alcohol, *N* (%)											
Any drinker	NR	NR	NR	58 (38)	62 (41)	183 (62)	187 (64)	180 (61)	92 (39)	79 (35)	86 (36)
Never drinker				96 (62)	89 (59)	110 (38)	104 (36)	114 (39)	143 (61)	147 (65)	156 (64)
H. pylori (+) N (%)	37 (18)	23 (11)	29 (14)	33 (21)	38 (25)	NR	NR	NR	NR	NR	NR
Baseline severity (LA grade), *N* (%)											
A	162 (80)	161 (79)	160 (80)	88 (57)	86 (57)	110 (38)	106 (36)	101 (34)	91 (39)	96 (42)	93 (38)
B				58 (38)	55 (36)	88 (30)	93 (32)	97 (33)	94 (40)	84 (37)	100 (41)
C	40 (20)	43 (21)	41 (20)	8 (5)	9 (6)	86 (29)	81 (28)	92 (31)	42 (18)	39 (17)	38 (16)
D				0 (0)	1 (1)	9 (3)	11 (4)	4 (1)	8 (3)	7 (3)	11 (5)

[†]Total number in VPZ 10 mg: 197; VPZ 20 mg: 201; LPZ 15 mg: 196.

BMI, Body mass index; LA, Los Angeles grading; LPZ, lansoprazole; *N*, number of subject; NR, not reported; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; SD, standard deviation; TPZ, tegoprazan; UK, the United Kingdom; USA, the United States of America; VPZ, vonoprazan; wks: weeks.

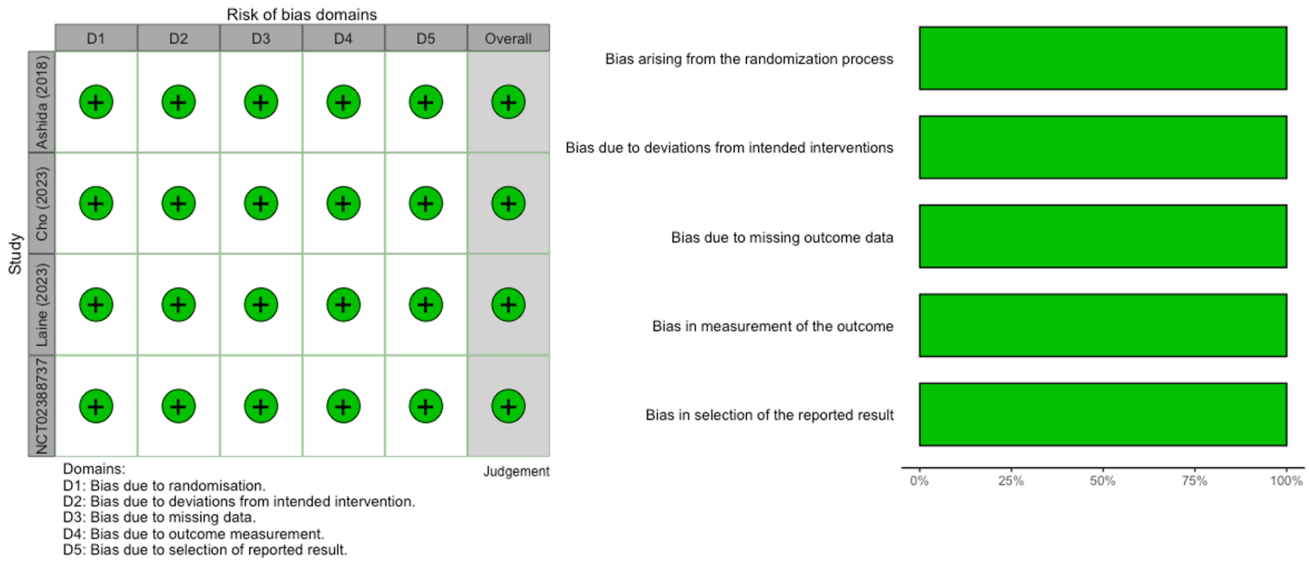

Figure 2 Risk of bias assessment using the Cochrane RoB2 Tool. +, low; ■, low risk of bias.

Table 2 Primary and secondary outcome comparing vonoprazan 10 and 20 mg to lansoprazole 15 mg (fixed-effects model)

VPZ 10 mg *versus* LPZ 15 mg					VPZ 20 mg *versus* LPZ 15 mg				
Study (*n*)	I^2 (%)	Crude maintenance rate/TEAE rate		Risk ratio (95% CI)	Study (*n*)	I^2 (%)	Crude maintenance rate/TEAE rate		Risk ratio (95% CI)
		VPZ 10 mg	LPZ 15 mg				VPZ 20 mg	LPZ 15 mg	
Primary outcome (maintenance rate at 24 weeks)									
LA grade A/B									
2	0	315/357 (88.24)	288/353 (81.59)	1.08 (1.02–1.15)†	2	0	317/357 (88.80)	288/353 (81.59)	1.09 (1.02–1.16)*
LA grade C/D									
2	0	104/133 (78.20)	84/137 (61.31)	1.28 (1.09–1.50)†	2	45	112/135 (82.96)	84/137 (61.31)	1.35 (1.16–1.58)*
Overall									
3	0	623/735 (84.76)	555/740 (75.00)	1.13 (1.07–1.19)	3	0	630/728 (86.54)	555/740 (75.00)	1.15 (1.10–1.21)
Secondary outcome									
Maintenance rate at 12 weeks									
2	0	362/437 (82.84)	329/443 (74.27)	1.11 (1.04–1.19)	2	90	402/430 (93.49)	329/443 (74.27)	1.25 (1.18–1.33)
24-h Heartburn-free days at 24 weeks (days)									
1	-	80.9 (28.6)	78.6 (27.5)	N/A	1	-	80.6 (30)	78.6 (27.5)	N/A
Any TEAE									
3	0	426/733 (58.12)	411/740 (55.54)	1.05 (0.96–1.14)	3	0	443/726 (61.02)	411/740 (55.54)	1.10 (1.01–1.20)
Serious TEAE									
2	21	15/498 (3.01)	15/498 (3.01)	1.00 (0.49–2.02)	2	12	22/500 (4.40)	15/498 (3.01)	1.46 (0.77–2.78)
TEAE leading to treatment discontinuation									
2	0	7/498 (1.41)	6/497 (1.21)	1.16 (0.39–3.43)	2	44	12/500 (2.40)	6/497 (1.21)	1.99 (0.75–5.24)

*Statistically significant test for subgroup differences ($P < 0.05$).

†No significant in test for subgroup difference ($P \geq 0.05$).

Categorical outcomes presented in n/n (%); continuous outcomes presented in mean (SD).

CI, confidence interval; LA, Los Angeles grade; LPZ, lansoprazole; N/A, not applicable; TEAE, treatment-emergent adverse event; VPZ, vonoprazan.

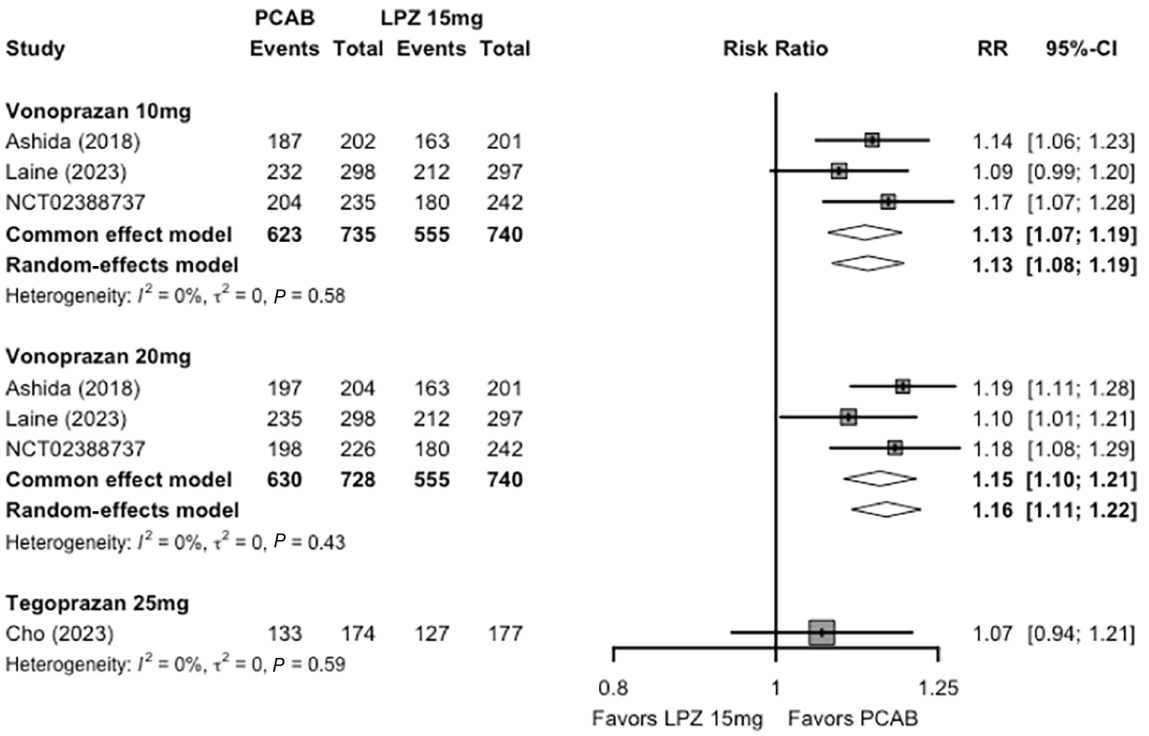

Figure 3 Forest plot of primary outcome—maintenance rate at 24 weeks for vonoprazan 10 mg, vonoprazan 20 mg, and tegoprazan 25 mg *versus* lansoprazole 15 mg (fixed- and random-effects model).

Any TEAE, severe TEAE, serious TEAE, and TEAE leading to treatment discontinuation. From the three RCTs, the crude rates of any TEAE were 58.12% for vonoprazan 10 mg group, 61.02% for vonoprazan 20 mg, and 55.54% for lansoprazole 15 mg. Any TEAE was significantly more with vonoprazan 20 mg vs. lansoprazole 15 mg (RR 1.10; 95% 1.01–1.20) but not different between vonoprazan 10 mg and lansoprazole 15 mg (RR 1.05; 95% CI 0.96–1.14) (Fig. S2A). The rates of severe TEAE (data not shown),[19] serious TEAE, and TEAE leading to treatment discontinuation were low across all groups (Table 2, Fig. S2B,C).

Discussion

The following is a summary of the main findings from the current review and meta-analysis. First, vonoprazan was superior to lansoprazole 15 mg in maintenance rates of healed EE irrespective of doses (10 and 20 mg) and duration (weeks 12 and 24). Second, vonoprazan 20 mg showed greater efficacy than lansoprazole 15 mg in the maintenance rates at week 24 if the initial baseline EE was of greater severity (LA grade C/D). Third, no difference was observed in the maintenance of healing with tegoprazan 25 mg vs. lansoprazole 15 mg at week 12 or 24, likely due to the lack of studies available. Fourth, a significantly greater number of any TEAEs were observed with vonoprazan 20 mg but not 10 mg when compared to lansoprazole 15 mg.

The better efficacy of vonoprazan vs. lansoprazole could be attributed to the unique pharmacological characteristics of PCABs in achieving better acid suppression.[21,22] Several advantages of PCABs include the stability of the prodrug under acidic conditions, higher affinity towards gastric parietal cells, and its ability to remain pharmacologically active even under neutral conditions. In contrast, PPI such as lansoprazole 15 mg requires an acidic condition to achieve its pharmacologically active state and is also notably less acid-stable, which could significantly reduce its duration of efficacy. However, not all PPIs have the same efficacy at equivalent potency. For example, a previous study by Devault et al.[23] demonstrated that esomeprazole 20 mg was superior to lansoprazole 15 mg in the maintenance of healed EE at week 24 (84.8% *vs* 75.9%, respectively). Furthermore, our study showed that vonoprazan 10 or 20 mg could potentially show better efficacy than tegoprazan 25 mg in maintaining healed EE despite needing more data to make a robust claim. Previous phase I study has shown that single-dose of tegoprazan 50 mg yielded a faster time to reach intragastric pH ≥ 4 and an overall more rapid, potent, and well-sustained night-time gastric acid suppression compared to vonoprazan 20 mg (1 h *vs* 4 h).[24] Although we acknowledge that data for tegoprazan 25 mg were unavailable, it is interesting to note that this pharmacological characteristic tested in healthy subjects may not fully translate to the observed clinical outcomes. Until more data are available for tegoprazan, these findings will remain speculative.

The superiority of vonoprazan compared with lansoprazole in maintaining EE healing was more pronounced in those with more severe (LA C/D) disease at baseline. Previous meta-analysis has demonstrated that vonoprazan was superior to lansoprazole in healing severe EE but was similar in efficacy for

mild EE.[12] Notably, patients with LA grade C/D at baseline tended to be older.[25] Older adults are known to exhibit characteristic histological changes, such as a decreased number of mucus cells that are important in protecting the gastric lining from stomach acidity.[26] Since PPI is less acid-stable compared to PCAB, this means that PCAB may stay pharmacologically active for an extended period in older adults, conferring better efficacy.

Vonoprazan 20 mg resulted in a slightly higher but statistically significant frequency of any TEAEs compared to lansoprazole 15 mg. Based on Laine et al.,[19], the vonoprazan group experienced a greater number of patients with an increase in serum gastrin level > 500 pg./mL. A possible explanation for this finding could be found in the VISION trial, which evaluated the long-term safety of vonoprazan.[27] At the four-year interim result, they found a higher proportion of G-cell hyperplasia with vonoprazan despite an absence of neoplastic changes. In addition, Saito et al. (2021)[28] reported a case of a 51-year-old man with no family history of gastric cancer and current *H. pylori* infection who developed a foveolar-type gastric adenocarcinoma 156 weeks after starting maintenance therapy with vonoprazan 10 mg. Whether vonoprazan is the cause of hyperplastic or neoplastic changes in the gastric mucosa will require further studies.

This meta-analysis adds to the gap in the literature regarding the efficacy of PCAB over PPI in the maintenance of healed EE, building on prior non-inferiority studies.[17–20] The four RCTs reviewed were of low risk of bias, and, when combined, statistically yielding a higher event count from a greater sample size, further strengthened the validity of our results. Adding to that, each RCT was of moderate size and included both Western and Asian populations.

There are limitations to this meta-analysis. First, the number of studies was limited (only four were included) because of our study design, which included only RCTs. Furthermore, only one study provided a comparison between tegoprazan and lansoprazole. Due to the limited number of studies available with a limited number of events and sample size, it was not feasible to conclude the overall superiority of PCAB over PPI except for differences between vonoprazan or tegoprazan and lansoprazole. Third, the reported adverse events were relatively short term (up to 24 weeks).

Conclusion

Vonoprazan 10 or 20 mg is superior to lansoprazole 15 mg in maintaining healed EE at both weeks 12 and 24. There are safety concerns with a higher dose of vonoprazan 20 mg. Vonoprazan may be a suitable alternative to lansoprazole in maintaining healed EE.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. PRISMA Checklist (2020 version)
Table S2. Search strategy for electronic databases
Table S3. Excluded studies with reasons
Table S4. Inclusion and exclusion criteria of the subjects randomized in the studies
Table S5. Primary and secondary outcome comparing vonoprazan 10 and 20 mg to lansoprazole 15 mg (random-effects model)
Figure S1. Forest plot of secondary efficacy outcomes—maintenance rate for (A) vonoprazan 10 mg and vonoprazan 20 mg *vs* lansoprazole 15 mg at 12 weeks and subgroup analysis based on baseline la grade for (B) vonoprazan 10 mg and (C) vonoprazan 20 mg *vs* lansoprazole 15 mg at 24 weeks (fixed- and random-effects model).
Figure S2. Forest plot of secondary safety outcomes—any treatment-emergent adverse event (TEAE) for (A) vonoprazan 10 mg and (B) vonoprazan 20 mg *versus* lansoprazole 15 mg, serious TEAE for (C) vonoprazan 10 mg and (D) vonoprazan 20 mg *versus* lansoprazole 15 mg, and TEAE leading to treatment discontinuation for (E) vonoprazan 10 mg and (F) vonoprazan 20 mg *versus* lansoprazole 15 mg (fixed- and random-effects model).