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Systematic Review and Meta-analysis

Treatment Response With Potassium-competitive Acid Blockers Based on Clinical Phenotypes of Gastroesophageal Reflux Disease: A Systematic Literature Review and Meta-analysis

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Background/Aims
Gastroesophageal reflux disease (GERD) is typically managed based on the clinical phenotype. We evaluated the efficacy and safety of potassium-competitive acid blockers (PCABs) in patients with various clinical GERD phenotypes.

Methods
Core databases were searched for studies comparing PCABs and proton pump inhibitors (PPIs) in clinical GERD phenotypes of erosive reflux disease (ERD), non-erosive reflux disease (NERD), PPI-resistant GERD and night-time heartburn. Additional analysis was performed based on disease severity and drug dosage, and pooled efficacy was calculated.

Results
In 9 randomized controlled trials (RCTs) evaluating the initial treatment of ERD, the risk ratio for healing with PCABs versus PPIs was 1.09 (95% CI, 1.04-1.13) at 2 weeks and 1.03 (95% CI, 1.00-1.07) at 8 weeks, respectively. PCABs exhibited a significant increase in both initial and sustained healing of ERD compared to PPIs in RCTs, driven particularly in severe ERD (Los Angeles grade C/D). In 3 NERD RCTs, PCAB was superior to placebo in proportion of days without heartburn. Observational studies on PPI-resistant symptomatic GERD reported symptom frequency improvement in 86.3% of patients, while 90.7% showed improvement in PPI-resistant ERD across 5 observational studies. Two RCTs for night-time heartburn had different endpoints, limiting meta-analysis. Pronounced hypergastrinemia was observed in patients treated with PCABs.

Conclusions
Compared to PPIs, PCABs have superior efficacy and faster therapeutic effect in the initial and maintenance therapy of ERD, particularly severe ERD. While PCABs may be an alternative treatment option in NERD and PPI-resistant GERD, findings were inconclusive in patients with night-time heartburn.
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Key Words
Gastroesophageal reflux; Meta-analysis; Potassium-competitive acid blocker; Proton pump inhibitors

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Introduction

Gastroesophageal reflux disease (GERD) is a chronic condition characterized by the reflux of stomach contents into the esophagus. The severity of esophageal inflammation varies depending on the degree of dysfunction of the lower esophageal sphincter and disruption of the esophagogastric junction. GERD has various clinical phenotypes. Erosive reflux disease (ERD) and Barrett's esophagus are characterized by high reflux burden, whereas non-erosive reflux disease (NERD) is characterized by symptoms in the absence of visible mucosal damage on endoscopy.[1] In clinical practice, NERD can be confirmed as "true NERD" when pathologic acid reflux is demonstrated on ambulatory reflux monitoring.[2] When esophageal acid exposure times are within normal range, symptoms may associate with physiologic reflux events, termed reflux hypersensitivity.[2,3] Distinguishing GERD from reflux hypersensitivity and functional heartburn, which are associated with abnormal peripheral and/or central sensory processing without pathologic acid reflux, requires esophageal physiological tests. These various clinical phenotypes need to be taken into consideration along with pathophysiologic features in managing GERD. In other words, GERD requires a personalized patient-tailored approach which balances the use of acid-suppressing agents to control inflammation caused by acid reflux and down-regulates enhanced esophageal sensitivity.

Proton pump inhibitors (PPIs) are the mainstay of GERD management because of their anti-secretory effects in healing ERD, controlling GERD symptoms, and preventing complications such as esophageal ulcers, peptic strictures, and cancer progression in Barrett's esophagus. Despite this, PPIs provide only 50-60% relief from heartburn after 4 weeks of treatment in NERD patients, which is lower than in ERD.[4,5] Moreover, as many as 40% of patients with heartburn have either partial response or complete lack of response to once-daily PPI therapy.[6] This incomplete response might be related to the short-half-lives of PPIs and irreversible binding to H^+/K^+-ATPase, which in turn may result in night-time acid breakthrough, causing night-time heartburn, affecting sleep quality and contributing to daytime dysfunction.[7]

Potassium-competitive acid blockers (PCABs) such as vonoprazoan, fexuprazan, tegoprazan, and keverprazan, known for their potent acid suppression, have emerged as effective alternatives to PPIs. PCABs reversibly inhibit H^+/K^+-ATPase by competitively binding to the K^+-binding domain. Unlike PPIs, PCABs do not require activation and rapidly suppress gastric acid secretion. While PPIs irreversibly bind to proton pumps and lose efficacy against newly generated pumps, PCABs can reversibly block newly synthesised pumps, leading to sustained duration of action.

This systematic review and meta-analysis aim to compare the efficacy and safety of PCABs and PPIs in various clinical GERD phenotypes, including ERD, NERD, PPI-resistant GERD, and night-time heartburn. Subgroup analysis based on disease severity, duration of drug use and dosage was performed. Additionally, the pooled efficacy of each treatment was calculated, and adverse drug events were evaluated.

Materials and Methods

Literature Search and Study Selection

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We searched electronic databases including Ovid MEDLINE, Ovid EMBASE, SCOPUS, and Cochrane Library for English-language articles published between January 1, 1946 and Oct 29, 2023. The search was conducted on Oct 29, 2023. We specifically searched for randomized controlled trials (RCTs) that evaluated the efficacy of PCABs and PPIs in various GERD phenotypes, including ERD, NERD, and night-time heartburn. However, considering the lack of RCTs on PPI-resistant GERD, we searched for single-arm cohort studies using PCABs in this phenotype. The PCABs investigated in the included studies consisted of vonoprazan, fexuprazan, tegoprazan, and keverprazan. The following search terms were included: PCAB, GERD or acid related disease (Supplementary Material). Additional literature was included through manual searching, incorporating further research, relevant systematic reviews, or meta-analyses.

Initially, we reviewed the titles and abstracts of papers retrieved through keyword searches and excluded irrelevant as well as duplicate reports. Subsequently, the full texts of the selected articles were reviewed. The first author extracted data elements from all selected studies into a Microsoft Excel spreadsheet. These elements included author names, publication year, study populations based on GERD phenotypes, types of studies, names of medications used, drug dosages, duration of use, and outcomes. The data were crosschecked and confirmed by a second reviewer. Based on these processes, inclusion eligibility and data consistency were re-assessed, and disagreements were resolved by discussion with a third author. Institutional review board approval was waived because all data analyzed was obtained from published literature.

Inclusion and Exclusion Criteria

Studies fulfilling the following inclusion criteria were selected: (1) Study type: RCTs within ERD, NERD, and night-time heartburn, except for PPI-resistant GERD, where observational studies were selected due to the absence of RCTs. (2) Study population: adult men and women presenting with typical symptoms were selected as the focus of the study. For ERD research, the study targeted patients with observed endoscopic esophagitis. In NERD studies, emphasis was placed on subjects without endoscopic esophagitis who had experienced heartburn or regurgitation in the week prior to randomization. (3) PPI-resistant GERD was categorized into 2 clinical phenotypes, and due to the absence of RCTs, observational studies were chosen. Firstly, observational studies were selected for meta-analysis, targeting patients with PPI-resistant symptomatic GERD who had not experienced symptom improvement despite at least 8 weeks of standard or double-dose PPI administration, and showed improvement with PCAB administration based on similar symptom assessments. Secondly, for PPI-resistant ERD, patients who did not show improvement on endoscopy despite standard-dose PPI usage were included in the meta-analysis based on interim results from another study.[8,9] (4) For night-time heartburn, studies of patients with GERD-related sleep disturbances or those experiencing night-time heartburn were selected. (5) RCTs comparing PCABs to PPIs, however, in NERD studies, we included papers that compared PCABs to a placebo. (6) Outcome measures were selected based on suitability for clinical phenotypes, and detailed definitions were provided separately.

Exclusion criteria consisted of studies that did not meet criteria described above for the type of study, participants, and intervention, studies with outcomes that prevented conducting a meta-analysis, animal studies, narrative reviews, and conference abstracts. Studies conducted on PPI-resistant GERD that included groups using PPIs at doses below standard levels were excluded.[10] Additionally, studies with differing methods of patient evaluation at interim assessments were excluded as they precluded meta-analysis.[11,12]

Data Extraction for Outcome Measurement

The primary ERD outcome evaluated was the endoscopic healing rate 8 weeks after the initiation of treatment with standard dose of PCAB.[13-19] The secondary ERD end points included the proportion of patients with endoscopic healing at 2 weeks[13-16] and 4 weeks,[13-15,17-19] as well as proportions of patients with baseline Los Angeles (LA) grade C/D esophagitis with healing at 2 weeks,[13-16] 4 weeks,[13-15,17] and 8 weeks.[13-17] The primary endpoint in maintenance therapy for ERD was the proportion of patients who remained healing upon endoscopic confirmation after 24 weeks of therapy with maintenance dose (half dosage of standard dose) of PCAB.[16,20,21] Subgroup analysis based on treatment duration (12 weeks vs 24 weeks) and drug dosage (maintenance dose vs standard dose) was also performed. The primary NERD outcome was the proportion of symptom-free days during the treatment period.[22-24] Studies on PPI-resistant GERD with consistent outcomes and confirmed patient improvement were analysed using frequency scale for the symptoms of GERD (FSSG) scores as an indicator.[8,25,26] Furthermore, an analysis was conducted on patients with PPI-resistant GERD who used standard-dose PCABs for more than 4 weeks to assess improvement in ERD.[8,9,27-29] The outcome for night-time heartburn aimed to analyze the improvement rate of night-time symptoms, and although 2 studies were identified, the differing study designs limited a meta-analysis.[30,31] The secondary outcome was the treatment-emergent adverse events (TEAEs), where we calculated the risk ratios (RRs) from the available data. Because the dosages and treatment durations of PCABs varied across studies, meta-analyses were conducted for each phenotype. For hypergastrinemia, meta-analyses were performed based on clinical judgment, considering dosages and treatment durations.

Risk of Bias Assessment

All RCTs were evaluated for bias using the Cochrane risk-of-bias tool.[32] This evaluation encompassed various biases, including selective outcome data (reporting bias), incomplete outcome data (attrition bias), blinding of outcome assessment (detection bias), blinding of participants and personnel (performance bias), allocation concealment (selection bias), and random sequence generation (selection bias). In the case of PPI-resistant GERD, where there was no control group and only an intervention group in observational studies, we utilized the Quality Assessment for Before-After (Pre-Post) Studies with No Control Group to assess the quality of the studies.[33] Two authors assessed the quality of the included studies.

Data Analysis

Data synthesis and statistical analyses were performed using R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) to generate a meta-analysis, except for night-time heartburn, which did not align with the other outcomes.[30,31] To summarize the pooled effect size, continuous outcomes were expressed as mean with standard deviation, and binary outcomes were expressed as number of subject with cases and total sub-

jects. To determine heterogeneity of included studies, we used the Cochrane Q and I^2: $I^2 > 75\%$, considerable heterogeneity; $I^2 =$ 50-90%, substantial heterogeneity; and $I^2 <$ 30-60%, moderate heterogeneity.[34] If heterogeneity was evident, a random-effect model was used to generate pooled effect size. Pooled proportion for the binary outcomes in each group was estimated using the metaprop function from the meta package in R. Pooled RRs were also calculated using the Mantel–Haenszel model with a 95% CI of healing rate and TEAEs. For the meta-analysis of NERD, we converted values presented as median ± quartile into mean ± standard deviation in 2 vonoprazan studies according to formulas in the Cochrane Handbook.[22,23,35] In PPI-resistant GERD, pooled prevalence rates were analyzed only for studies with consistent outcomes. In the analysis of TEAEs, serum gastrin levels were presented graphically on a continuous scale. We extracted data from graphs published with eligible studies when required data was not available in the text or tables and the original authors could not provide the data.[36] For some data, the authors were contacted directly to obtain raw data.[19,21] Continuous outcomes measured on different instruments across studies were pooled using the standardized mean difference method.[13,14,16,19-23,36]

Funnel plots and Egger's tests for publication bias were appropriate for more than 10 studies, but did not meet this condition and were therefore not assessed.[37] All statistical analyses were two-tailed and considered significant with $P < 0.05$, except for the Cochrane Q heterogeneity significance level, which was set to $P < 0.1$.

Results

Characteristics of Included Studies

Of the 1155 studies retrieved from the electronic databases, 684 studies remained after eliminating duplicates and non-English language publications. Screening of titles and abstracts led to the exclusion of 651 articles. Upon reviewing the 33 remaining studies, we identified RCTs that utilized PPIs as a control, and observational studies evaluating PPI-resistant GERD. Eventually, 21 were included in the final analysis (Fig. 1): 9 studies on ERD,[13-21] 3 on NERD,[22-24] 7 on PPI-resistant GERD,[8,9,25-29] and 2 on night-time heartburn.[30,31] All RCTs showed a low bias in their risk-of-bias assessments (Supplementary Fig. 1). Furthermore, all observational studies also demonstrated a tendency of fair or higher quality in the quality assessment (Supplementary Fig. 2).

The characteristics of the selected studies are summarized in Table 1. A total of 5633 patients with GERD were included. Except for 6 observational studies on PPI-resistant GERD,[8,9,25,26,28,29] all remaining studies were RCTs. Of the 21 included papers, only 1 was conducted in a Western country (United States [US]),[16] whereas all the others were conducted in Asian countries. The initial treatment duration for ERD was 2-8 weeks, whereas maintenance therapy lasted for 12 and 24 weeks. The US study by Laine et al[16] provided results for the 2- and 8-week initial treatment periods and the 24-week maintenance period. The outcome measured for NERD was the proportion of days without heartburn or the pro-

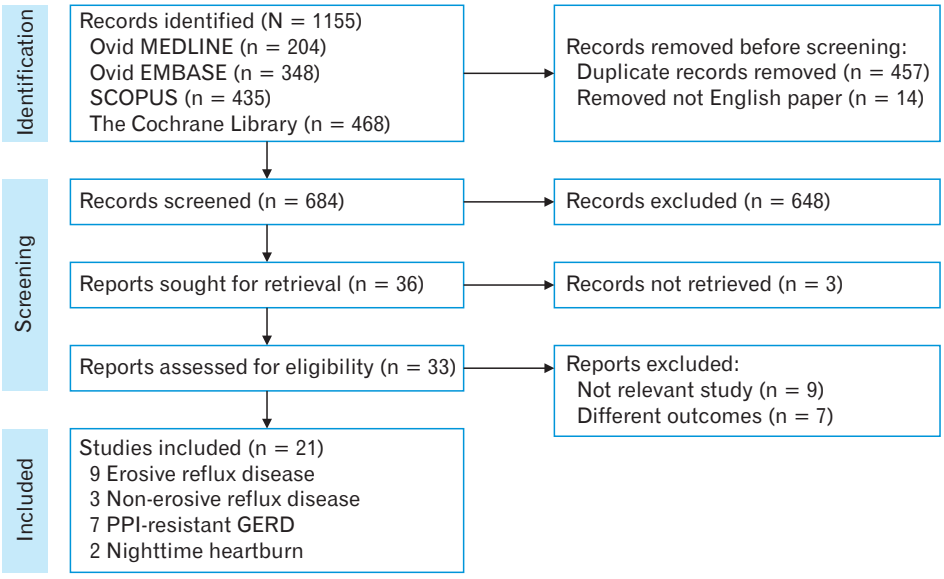

Figure 1. Chart of the research selection process. GERD, gastroesophageal reflux disease.

Table 1. Characteristics of Studies Included in the Meta-analysis

First author	Year of publication	Country	Study design	Participants	PCAB No.	Types and dosage	Controls No.	Types and dosage	Duration in weeks
Ashida[13]	2015	Japan	RCT	ERD	144	20 mg vonoprazan	132	30 mg lansoprazole	2, 4, 8
Ashida[14]	2016	Japan	RCT	ERD	204	20 mg vonoprazan	199	30 mg lansoprazole	2
					205				4, 8
Lee[18]	2019	Korea	RCT	ERD	99	50 mg tegoprazan	99	40 mg esomeprazole	4, 8
Xiao[15]	2020	China Korea Taiwan Malaysia	RCT	ERD	238	20 mg vonoprazan	230	30 mg lansoprazole	2, 4, 8
Chen[17]	2022	China	RCT	ERD	119	20 mg keverprazan	119	30 mg lansoprazole	4, 8
Lee[19]	2022	Korea	RCT	ERD	116	40 mg fexuprazan	115	40 mg esomeprazole	4, 8
Laine[16]	2023	US	RCT	ERD	514	20 mg vonoprazan	510	30 mg lansoprazole	2, 8
					293[a]	10 mg vonoprazan	294[a]	15 mg lansoprazole	24
					291[a]	20 mg vonoprazan			24
Cho[21]	2023	Korea	RCT	ERD	154	25 mg tegoprazan	151	15 mg lansoprazole	12, 24
Ashida[20]	2018	Japan	RCT	ERD	202	10 mg vonoprazan	201	15 mg lansoprazole	12, 24
					204	20 mg vonoprazan			12, 24
Kinoshita[23]	2016	Japan	RCT	NERD	278	10 mg vonoprazan	278	Placebo	4
					271	20 mg vonoprazan			4
Kinoshita[22]	2019	Japan	RCT	NERD	238	10 mg vonoprazan	245	Placebo	4
Kim[24]	2021	Korea	RCT	NERD	106	50 mg tegoprazan	99	Placebo	4
					99	100 mg tegoprazan			4
Hoshino[8]	2017	Japan	Single arm cohort, prospective study	PPI-resistant GERD	24	20 mg vonoprazan		No	4
Iwakiri[27]	2017	Japan	RCT	PPI-resistant GERD	5	20 mg vonoprazan			8
Yamashita[28]	2017	Japan	Single arm cohort, prospective study	PPI-resistant GERD	8	20 mg vonoprazan			8
Akiyama[29]	2020	Japan	Single arm cohort, retrospective study	PPI-resistant GERD	13	20 mg vonoprazan			8
Takenouchi[9]	2020	Japan	Single arm cohort, prospective study	PPI-resistant GERD	26	20 mg vonoprazan			4
Gotoh[26]	2020	Japan	Single arm cohort, prospective study	PPI-resistant GERD	104	20 mg vonoprazan		No	4
Abe[25]	2021	Japan	Single arm cohort, retrospective study	PPI-resistant GERD	10	20 mg vonoprazan		No	At least 4
Kim[30]	2023	Korea	RCT	Night-time heartburn	22	50 mg tegoprazan	24	40 mg esomeprazole	2
Oshima[31]	2019	Japan	RCT	Night-time heartburn	16	20 mg vonoprazan	16	30 mg lansoprazole	2

[a]The number of patients in the maintenance dose.
PCAB, potassium-competitive acid blocker; RCT, randomised controlled trial; ERD, erosive reflux disease; GERD, gastroesophageal reflux disease; NERD, non-erosive reflux gastritis; PPI, proton pump inhibitor.

portion of patients with symptom relief. We confirmed these results based on the most prevalent outcome (ie, proportion of days without heartburn) in the included studies. For PPI-resistant GERD, we investigated studies with consistent outcomes of symptom improvement using FSSG scores[8,25,26] and the rate of endoscopic healing of ERD.[8,9,27-29] For the 2 studies on night-time heartburn, the outcomes reported did not align; therefore, a meta-analysis was not conducted for this specific outcome.[30,31]

Erosive Reflux Disease

Initial treatment for erosive reflux disease

Seven RCTs compared the efficacy of PCABs vs PPIs in the initial treatment of ERD. Each study reported healing rates at weeks 2, 4, and 8. The PCABs used in these studies were 20 mg vonoprazan, 40 mg fexuprazan, 20 mg keverprazan, and 50 mg tegoprazan. In the initial treatment of ERD, the RR for healing with the use of a standard dose of PCABs compared to PPIs was 1.03 (95% CI, 1.00-1.07) at week 8, and the pooled proportion of healed patients were 95.2% and 92.5% in the PCAB and PPI groups, respectively. The RRs for PCABs vs PPIs in the initial treatment of ERD were 1.09 (95% CI, 1.04-1.13) and 1.03 (95% CI, 0.99-1.06) at weeks 2 and 4, respectively (Fig. 2). PCABs consistently demonstrated higher healing rates than PPIs at all time points, and statistical significance was observed at the 2-week marks. The pooled healing rate of PCABs was significantly higher than that of PPIs at week 2 (85.1% vs 77.3%), however, there was no difference at week 4 (89.3% vs 87.2%).

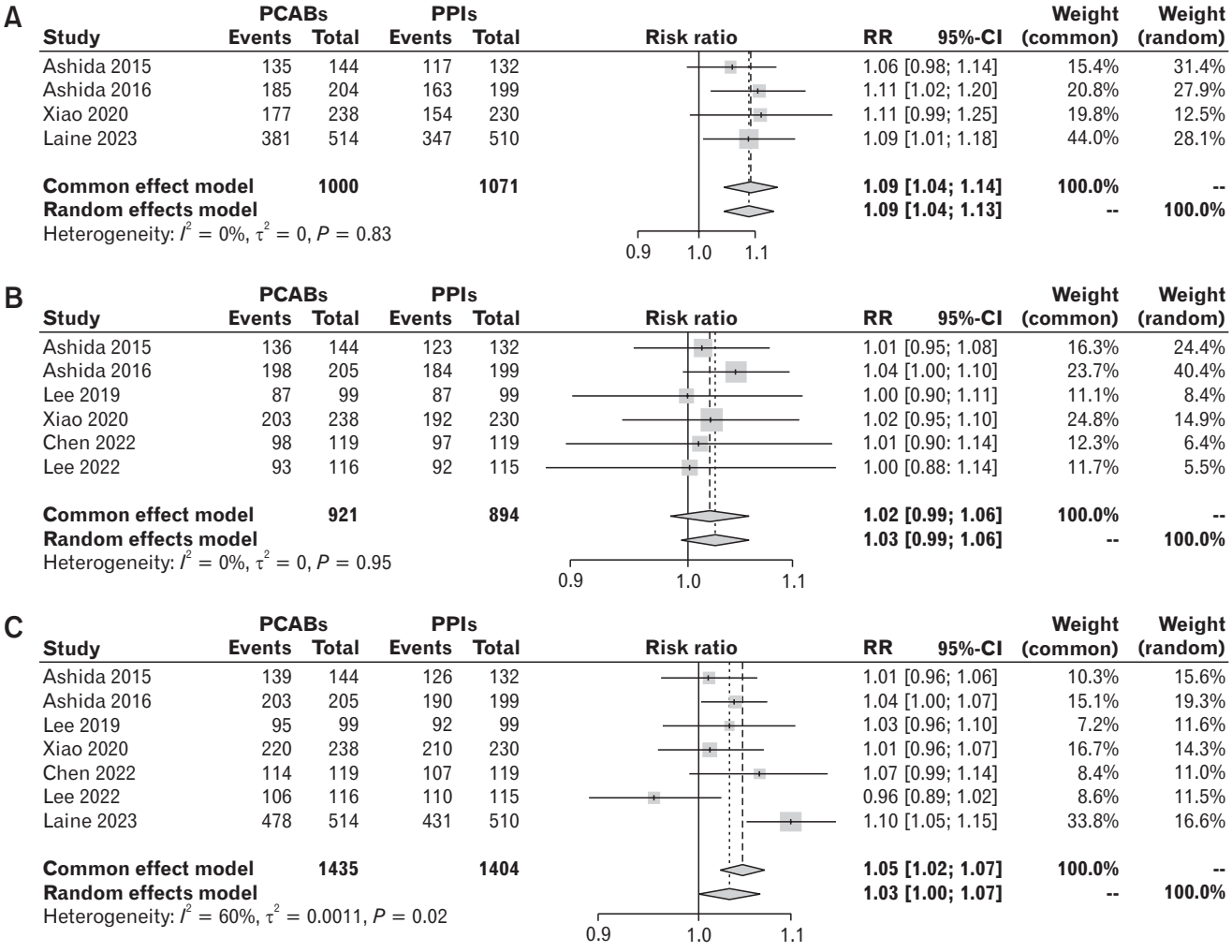

Figure 2. Forest plot depicting the relative efficacies of potassium-competitive acid blockers (PCABs) and proton pump inhibitors (PPIs) in the initial treatment of erosive reflux disease, showing the healing rates at weeks 2 (A), 4 (B), and 8 (C). RR, risk ratio.

Maintenance therapy for healing in erosive reflux disease

Three RCTs reported healing rates after 12 weeks and 24 weeks of maintenance therapy for ERD. The results included the use of vonoprazan 10 mg, vonoprazan 20 mg, and tegoprazan 25 mg. In the maintenance therapy of ERD, the RR for maintenance dose PCABs vs PPIs was 1.04 (95% CI, 0.90-1.19) and 1.09 (95% CI, 1.03-1.16) at week 12 week 24, respectively (Fig. 3). PCABs showed higher healing rates than PPIs at weeks 12 and 24, but the difference was statistically significant only at week 24. When both maintenance and standard doses were used, the RR were 1.04 (95% CI, 0.90-1.19) and 1.09 (95% CI, 1.03-1.16) at weeks 12 and 24, respectively with statistical significance observed only at 24 weeks. The RR for 10 mg vonoprazan vs 20 mg vonoprazan at week 24 was 0.97 (95% CI, 0.93-1.01), indicating that there was no difference between 20 mg vonoprazan and 10 mg vonoprazan at weeks 24. The pooled proportion for 10 mg vonoprazan and 25 mg tegoprazan at week 24 was 86.7%, whereas that for 20 mg vonoprazan was 90.3%.

Non-erosive Reflux Esophagitis

In 3 RCTs with consistent outcomes, the number of symptom-free days during a 4-week period was compared between PCABs (10 mg vonoprazan, 20 mg vonoprazan, 50 mg tegoprazan, and 100 mg tegoprazan) and placebo. The mean difference for PCABs vs placebo in NERD was 7.94 (95% CI, 3.80-12.08) (Fig. 4). In sensitivity analyses conducted by combining different drug types and dosages in 3 NERD studies, PCAB consistently demonstrated a statistically significant effect compared to a placebo with no heterogeneity (Supplementary Fig. 3).

The tegoprazan study, which analyzed the percentage of patients experiencing complete relief from heartburn and reflux symptoms as the primary endpoint, showed that PCAB had a significantly higher symptom relief rate compared to placebo (tegopra-

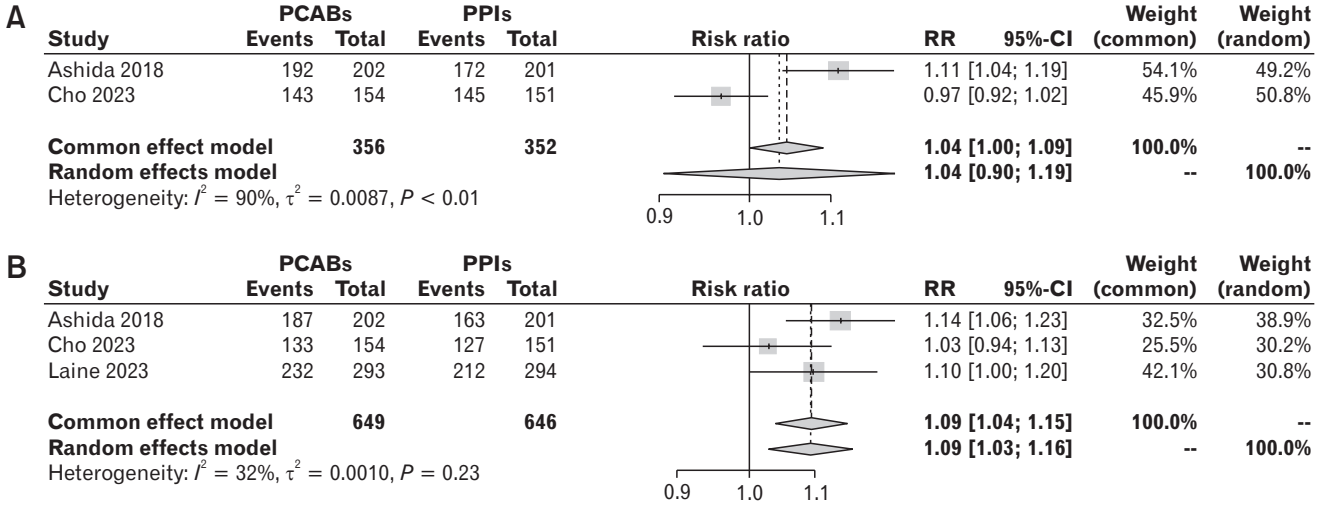

Figure 3. Forest plot depicting the relative efficacies of potassium-competitive acid blockers and proton pump inhibitors in the maintenance therapy of healing erosive oesophagitis, showing the healing rates at weeks 12 (A) and 24 (B). RR, risk ratio.

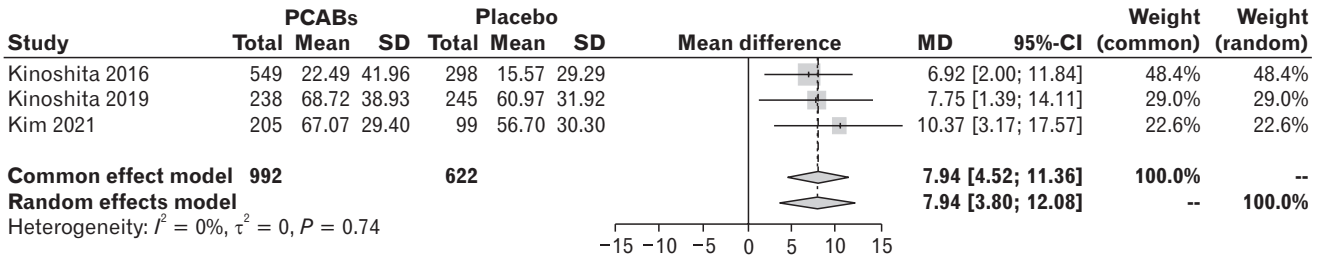

Figure 4. Forest plot depicting the proportion of symptom-free days during the treatment period between potassium-competitive acid blockers (PCABs) and placebo in patients with non-erosive reflux disease. PPIs, proton pump inhibitors; RR, risk ratio; MD, mean difference.

zan 50 mg vs placebo, 42.5% vs 24.2%, $P = 0.0058$; tegoprazan 100 mg vs placebo, 48.9% vs 24.2%, $P = 0.0004$).[24]

Proton Pump Inhibitor-resistant Gastroesophageal Reflux Disease

In the absence of RCTs, 3 observational studies on PPI-resistant GERD, all of which examined symptom improvement using FSSG scores, had consistent outcomes.[8,25,26] All 3 studies utilised vonoprazan 20 mg, with 2 studies reported use for 4 weeks 8, 26 and 1 study investigated patients who used this agent for at least 4 weeks.[25] Defining the effects of PCABs when FSSG scores were less than 8 points and decreased by at least 2 points compared with the baseline, the pooled proportion of patients with an effective response was 86.3% (95% CI, 0.46-0.98). This finding indicated that PCABs were effective in patients with PPI-resistant GERD. Additionally, in cases where standard or higher doses of PPI were used but ERD was observed via endoscopy, a study found that when patients were switched to vonoprazan 20 mg for 4 weeks or more, endoscopic improvement was observed in 90.7% (95% CI, 0.82-0.96) (Supplementary Fig. 4).

Night-time Heartburn

Two RCTs were identified. In the first study, time duration till the first day without night-time heartburn was investigated over a 2-week period using 50 mg tegoprazan.[30] The PCAB group had a time duration of 1.5 days, whereas the PPI group had a duration of 3.0 days, indicating that the PCAB group showed a faster onset of the effect compared to the PPI group, although the difference was not statistically significant. In the second study, the proportions of patients with no night-time heartburn on the first day, and on 7 consecutive days after taking vonoprazan 20 mg or PPIs for 2 weeks were compared.[31] In patients with night-time heartburn at the start

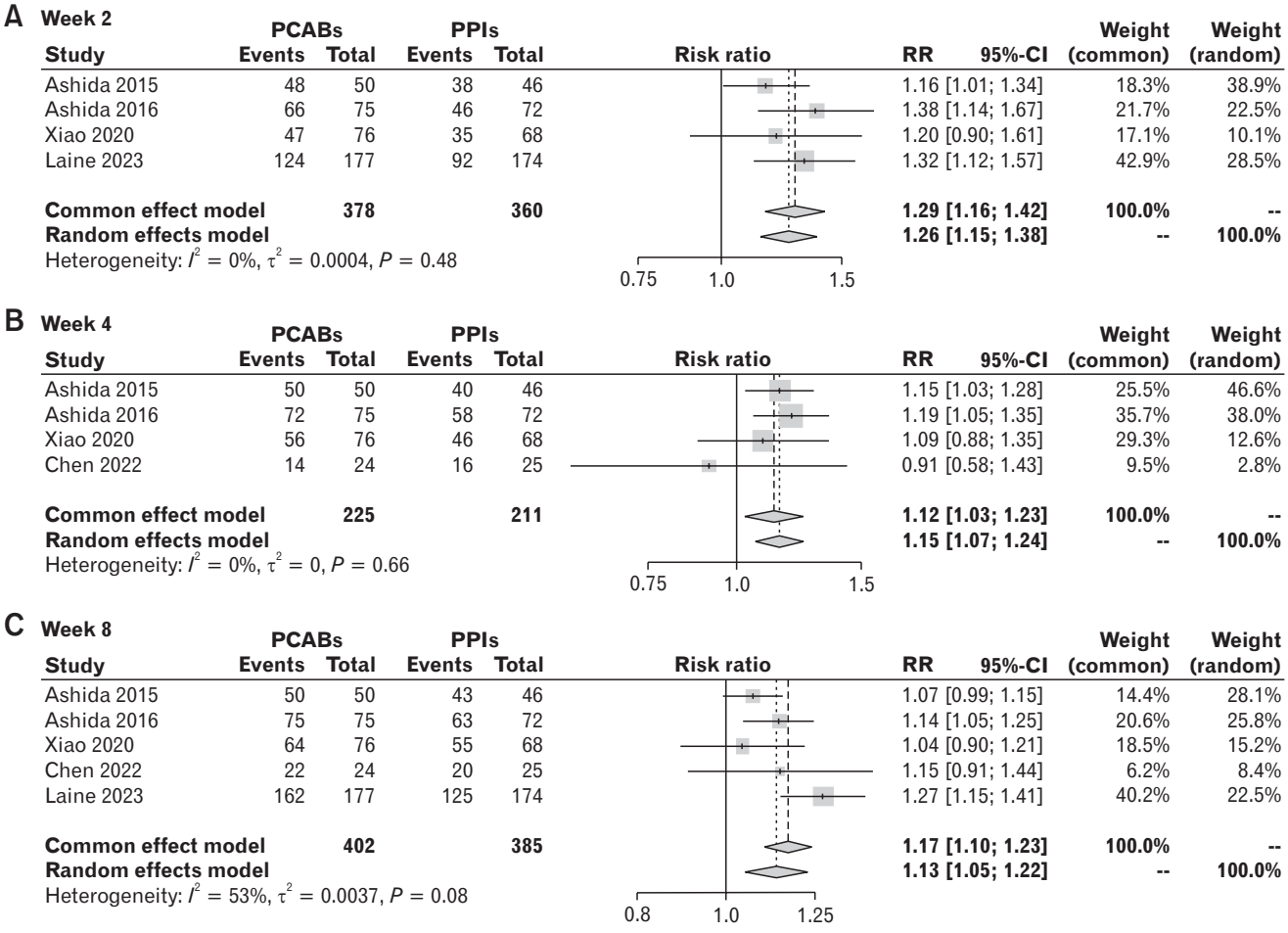

Figure 5. Forest plot depicting the comparison of potassium-competitive acid blockers (PCABs) and proton pump inhibitors (PPIs) in the improvement rate of erosive reflux disease of Los Angeles grade C/D based on severity at weeks 2 (A), 4 (B), and 8 (C). RR, risk ratio.

of the study, vonoprazan showed a significantly higher complete relief of night-time heartburn than lansoprazole during days 1-7 of treatment (hazard ratio, 6.22; 95% CI, 1.72-22.52; $P < 0.01$).

Healing Rate Using Potassium-competitive Acid Blockers vs Proton Pump Inhibitors Based on Erosive Reflux Disease Severity

The secondary outcome examined was the healing rates using PCABs and PPIs based on ERD severity (Fig. 5). In the initial treatment, the RR for PCABs vs PPIs in LA grade A/B was 1.02 (95% CI, 0.97-1.07) at week 2, 0.98 (95% CI, 0.95-1.01) at week 4, and 1.00 (95% CI, 0.98-1.02) at week 8, indicating that PCABs did not show a distinct advantage over PPIs. The pooled ratios for LA-A/B grades at weeks 2, 4, and 8 were 89.1%, 92.3%, and 96.1%, respectively. However, in LA grade C/D, the RR was 1.26 (95% CI, 1.15-1.38) at week 2, 1.15 (95% CI, 1.07-1.24) at week 4, and 1.13 (95% CI, 1.05-1.22) at week 8, demonstrating the superiority of PCABs at all time-points. The pooled ratios for PCABs in the LA grade C/D group were 82.2%, 91.5%, and 96.7% at weeks 2, 4, and 8, respectively. These results are consistent with maintenance therapy for erosive esophagitis. In LA grade C/D, the RR was 1.32 (95% CI, 1.13-1.55) at weeks 24, indicating the greater effectiveness of PCABs than PPIs. Assuming equivalent dosages of 10 mg vonoprazan and 25 mg tegoprazan, the RR for these maintenance dosages alone was 1.28 (95% CI, 1.10-1.50) at weeks 24.

Safety and Tolerability

TEAEs were reported in 13 studies of patients receiving PCABs (Table 2). The RRs of TEAEs between the ERD patients in the PCAB and PPI groups were 1.06 (95% CI, 0.96-1.17) and 1.07 (95% CI, 0.99-1.16) in the initial treatment and maintenance therapy, respectively, showing no statistically significant difference between the 2 groups. In the NERD group, the RR of TEAEs compared with the placebo group was 0.91 (95% CI, 0.78-1.05).

Table 2. Relative Ratio of Adverse Events Associated With Potassium-competitive Acid Blockers and Proton Pump Inhibitors

Variables	Dosage of PCAB	Control	Phenotypes of GERD	Duration in weeks	Event No. (total No.) in PCAB	Event No. (total No.) in control	Risk ratio (95% CI)
Adverse events	20 mg vonoprazan 20 mg keverprazan 40 mg fexuprazan 50/100 mg tegoprazan	30 mg lansoprazole 40 mg esomeprazole	ERD	8	519 (1570)	487 (1534)	1.06 (0.96-1.17)
	10/20 mg vonoprazan 25 mg tegoprazan	15 mg lansoprazole	ERD	24	605 (1171)	572 (1170)	1.07 (0.99-1.16)
	10/20 mg vonoprazan 50/100 mg tegoprazan	Placebo	NERD	4	254 (1003)	283 (1015)	0.91 (0.78-1.05)
	50 mg tegoprazan	40 mg esomeprazole	Night-time heartburn	2	1 (22)	1 (24)	1.09 (0.07-16.41)
Severe adverse events	20 mg vonoprazan	30 mg lansoprazole	ERD	8	5 (877)	8 (864)	0.67 (0.22-2.10)
	10/20 mg vonoprazan	15 mg lansoprazole	ERD	24	25 (592)	16 (594)	1.53 (0.73-3.18)
Serious adverse events	20 mg vonoprazan 40 mg fexuprazan 50/100 mg tegoprazan	30 mg lansoprazole 40 mg esomeprazole	ERD	8	10 (1207)	9 (1180)	1.22 (0.46-3.22)
	10/20 mg vonoprazan 25 mg tegoprazan	15 mg lansoprazole	ERD	24	35 (1171)	32 (1170)	1.09 (0.56-2.12)
	10/20 mg vonoprazan 50/100 mg tegoprazan	Placebo	NERD	4	5 (1003)	3 (1015)	1.24 (0.32-4.85)
Hepatotoxicity	20 mg vonoprazan 20 mg keverprazan 40 mg fexuprazan	30 mg lansoprazole 40 mg esomeprazole	ERD	8	8 (1369)	4 (1336)	1.25 (0.21-7.56)
	10 mg vonoprazan 25 mg tegoprazan 20 mg vonoprazan	15 mg lansoprazole	ERD	24	11 (1171)	16 (1170)	0.72 (0.27-1.95)

PCAB, potassium-competitive acid blocker; GERD, gastroesophageal reflux disease; ERD, erosive reflux disease; NERD, non-erosive reflux gastritis.

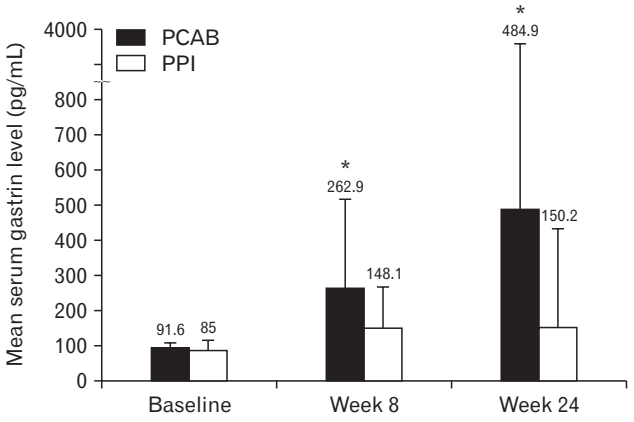

Figure 6. Comparison of changes in serum gastrin levels between potassium-competitive acid blockers (PCABs) and proton pump inhibitors (PPIs) based on drug use duration. Graph shows statistically significant differences in the mean $*P < 0.01$.

In the initial treatment of ERD, the comparison of elevated liver function test (LFT) results between the PCAB and PPI groups showed an RR of 1.25 (95% CI, 0.21-7.56), indicating no statistically significant difference. Similarly, no significant differences in LFT abnormalities were found among patients undergoing maintenance therapy for ERD.

As shown in Figure 6, serum gastrin levels were higher in the PCAB group than those in the PPI group, and the increase in serum gastrin levels was proportional to the dosage and duration. The standardized mean difference for serum gastrin levels between the PCAB and PPI groups was 0.61 (95% CI, 0.10-1.13) at week 8 when the standard dose was administered and 0.95 (95% CI, 0.06-1.83) at week 24. Thus, PCABs significantly increased serum gastrin levels compared to PPIs. The studies using vonoprazan in Japan showed a dose- and duration-dependent increase in serum gastrin levels,[13,20,22,23] whereas the study conducted in the US exhibited a comparatively smaller increase in serum gastrin levels.[16] Additionally, studies on fexuprazan and tegoprazan reported only marginal increases in serum gastrin levels.[19,21]

Discussion

In this meta-analysis, we demonstrate that PCAB effects vary across different GERD phenotypes. PCABs showed a faster effect in the initial treatment of ERD than PPIs, but the initial and maintenance therapies for mild ERD showed no significant difference in efficacy. However, PCABs exhibited significantly higher healing rates in LA-C/D than in LA-A/B esophagitis. Additionally, PCABs demonstrated potential effectiveness in PPI-resistant GERD and NERD, whereas inconclusive results were found in patients with night-time heartburn because of limited studies. While occurrence of hypergastrinemia significantly increased after 24 weeks of PCAB treatment, there were no significant difference in overall TEAEs, including hepatotoxicity, between PCABs and PPIs.

The Seoul consensus on GERD in 2020 concluded that PCABs and PPIs exert similar therapeutic efficacies and thus both have been recommended as first-line GERD treatment.[3] However, Japanese guidelines based on domestic data suggested that PCABs are more effective than PPIs, prompting the recommendation to reduce the initial treatment duration from 8 weeks to 4 weeks.[38] In the present study, all investigated PCABs demonstrated significant healing of ERD at 2 weeks after initiation of treatment. However, 4 weeks of PCAB therapy results in a healing rate of 89.9% on initial therapy, which is more effective than PPIs but still not sufficient. When extended to 8 weeks, PCABs exhibited a high healing rate of 95.2%. Particularly in LA C/D esophagitis, PCABs were statistically more effective than PPIs. Our meta-analysis thus demonstrates that PCABs significantly improve the success rate of the initial ERD treatment, even in cases of severe ERD, but do not necessarily shorten the duration of initial therapy.

In the maintenance therapy of ERD for 12 and 24 weeks, PCABs showed a higher healing rate than PPIs, but the difference was statistically significant only at week 24. PCABs demonstrated greater effectiveness in patients with ERD after 24 weeks of maintenance therapy, showing that a lower dosage can be used for maintenance. Similar to initial treatment, subgroup analysis based on disease severity showed that PCABs were more effective in LA-C/D esophagitis, but not in LA-A/B esophagitis during the maintenance phase. At 24 weeks, low-dosage vonoprazan (10 mg) and tegoprazan (25 mg) alone proved to be more effective than PPIs. Thus, PCABs are recommended for maintenance therapy of patients with severe ERD (LA-C/D), and low dosages are adequate for maintenance therapy.

In patients with NERD, the effects of PCABs were significantly higher compared to placebo. However, the limited number of studies, and heterogenous data-reporting requiring data conversion for meta-analysis, necessitates caution in interpreting our results. Appropriate conversion or estimation can increase accuracy and reduce the risk of bias from incomplete reporting.[35] Conversely, skewed results may bias estimates, and observed differences may be further influenced by expansion of the size of the intervention group and when standard deviation is underestimated during conversion, potentially affecting the outcomes. To overcome this, sensitivity

analysis was conducted with combinations of drug types and all doses, and the same results were obtained, with a heterogeneity of 0%, indicating low inter-study variability. Further accumulation of research results and thorough data analysis in the future are warranted to better understand and validate these findings.

According to Mermelstein et al,[39] approximately 40% of patients with NERD do not achieve symptom control with standard PPI therapy. Similarly, approximately 10-15% of patients with ERD fail to achieve complete resolution of symptoms even after 8 weeks of PPI treatment. Proven GERD patients with persistent symptoms despite PPI therapy, accounting for approximately 30% of patients with GERD, are classified as having refractory GERD.[40,41] PPIs suppress gastric acid secretion, which may result in more frequent weakly acidic or weakly alkaline reflux events rather than persisting acid reflux. Reflux events with a pH of 4-5 are major triggers of GERD symptoms.[42] According to impedance-pH monitoring studies, acidic reflux is associated with 7-28% of persistent symptoms, whereas weakly acidic reflux is associated with 30-40% of symptoms.[40] In the study by Abe et al,[25] the proportion of pH < 5 was 25.7% in the group, where vonoprazan showed effectiveness, while it was 50.9% in the group where vonoprazan did not show effectiveness. In the present study, PCAB treatment for GERD patients who did not respond to PPI therapy demonstrated a therapeutic response rate of 86.3% for symptom improvement based on FSSG scores and 90.7% for improvement in ERD confirmed by endoscopy. These findings suggest that PCABs may serve as a new alternative to PPIs in refractory GERD; however, RCTs are needed to firmly establish this.

The period until the first day without night-time heartburn was shorter in the PCAB group than that in the PPI group, indicating that PCABs may provide early symptom relief in patients with night-time heartburn. Furthermore, the proportion of patients who remained symptom-free for at least 7 days was higher in the PCAB group than that in the PPI group. This result suggests that PCABs may be more effective than PPIs in achieving sustained symptom relief, although this difference was not statistically significant. In patients with night-time heartburn, PCABs could potentially be considered a treatment option.

In terms of overall safety, PCABs did not show any significant differences compared with PPIs, including severe TEAEs and LFT abnormalities, across all clinical phenotypes of GERD. PPIs are metabolized in the liver by $CYP2_C19$, and $CYP2_C19$ polymorphism is one of the factors that can influence the efficacy of PPIs. However, PCABs are less affected by $CYP2_C19$ genotypes since they are primarily metabolised by $CYP3_A4$, along with $CYP2_B6$, $CYP2_C19$, and $CYP2_D6$.[43] GERD is a common condition, and many patients with this disease require long-term maintenance of acid-suppressive medications. Hypergastrinemia is a consequence of acid suppression but long-term consequences remain unclear. Moderate gastrin elevations (approximately 200-400 pg/mL) have been observed with the long-term use of PPIs, and no association with serious pathology has been reported.[44] In the present study, serum gastrin levels increased proportionally to the dosage and duration of PCAB administration. Overall, the PCAB group had higher serum gastrin levels than the PPI group. However, clinically significant symptoms associated with this increase have not yet been reported. In the 24-week maintenance therapy for GERD using PCABs, no clinically relevant impact on the gastric mucosa was observed despite the increase in serum gastrin levels. Nevertheless, certain studies conducted with vonoprazan in Japan have indicated elevated gastrin levels of 500 pg/mL or more, suggesting the potential occurrence of hypergastrinemia in some individuals.[13,20] Recently, in a 3-year long-term study of vonoprazan, hypergastrinemia was observed, but clinically significant neoplastic changes were not found. Additional long-term follow-up observations are necessary.[45]

This meta-analysis has some limitations. First, of the 17 available studies, only 1 was conducted in a Western country, whereas the rest were conducted in Asia. Thus, geographical and genetic differences inherent in GERD may have influenced our results. Second, most studies have focused on vonoprazan, and evidence regarding the effects of other PCABs is limited. Third, only a few studies have specifically evaluated the outcomes of PPI-resistant GERD, NERD, and night-time heartburn. Fourth, a consensus among study designs was lacking in the night-time heartburn group, resulting in a reduced accuracy of the results. Finally, in cases where obtaining raw data for serum gastrin levels was challenging, values were estimated and calculated from the graphs provided in the paper, and this includes conducting data transformation for meta-analysis in NERD. However, this meta-analysis was applied within an appropriate context based on the evidence.[34,35]

In conclusion, PCABs may serve as therapeutic alternatives to PPIs in patients with ERD, NERD and PPI-resistant GERD. PCABs demonstrated superior efficacy to PPIs in the initial treatment and maintenance therapy for ERD, especially for severe ERD (LA-C/D subgroup). They can also be considered a therapeutic option for patients with night-time heartburn. Moreover, PCABs had comparable safety to PPIs. However, long-term follow-up is required to understand the potential consequences of hypergastrinemia in patients. Additionally, accumulation and analysis of further high quality data is essential as novel PCABs beyond vonoprazan

continue to be developed.

Supplementary Materials

Note: To access the supplementary material 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/jnm24024.

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