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COMPARING POTASSIUM-COMPETITIVE ACID BLOCKER AND PROTON PUMP INHIBITOR FOR GASTROESHOPAGEAL REFLUX DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract:

Clinical management is typically used to treat gastroesophageal reflux disease (GERD). Assessed individuals with a range of clinical symptoms of gastroesophageal reflux disease (GERD) to determine the safety and effectiveness of potassium-competitive acid blockers (PCABs). By examining core databases, studies comparing PCABs and proton pump inhibitors (PPIs) in clinical gastroesophageal reflux disease (GERD) and PPI-resistant GERD were identified. In nine randomized controlled trials (RCTs) evaluating the first care of GERD, 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) after 8 weeks, respectively. While 86.3% of PPI-resistant GERD patients reported an improvement in symptom frequency, 90.7% of patients showed improvement in five observational trials. When it comes to the initial and ongoing treatment of GERD, especially severe GERD, PCABs are more effective and have a quicker therapeutic effect than PPIs. However, PCABs might be a different kind of treatment for GERD and GERD that is resistant to PPIs.

Keywords: *gerd, inhibitor pompa proton, kompetitif kalium, meta-analisis, penghambat asam, refluks gastroesofagus*

Introduction

Gastroesophageal reflux disease (GERD), a medical condition in which stomach contents reflux into the esophagus, affects the esophagus, pharynx, larynx, and airways (Durazzo et al., 2020; Maret-Ouda et al., 2020). However, strictures, Barrett's esophagus, and even esophageal and cardiac cancer have been documented to result from reflux of stomach contents into the esophagus. The use of PPIs (proton pump inhibitors) has been widespread in the management of gastric diseases, especially those related to gastric reflux. However, many PPI drugs have recently become resistant in patients with gastroesophageal reflux disease (GERD). PCAB (Potassium Competitive Acid Blocker) competitively inhibits H+/K+ ATPase ions and is more potent, faster, and can survive the

inhibitory effects of acids, making it a choice over PPIs. Venoprazan is the first member of the potassium-competitive acid blockers (PCABs) family, and like PPIs, it is an acid-independent activator. A study found that Venoprazan inhibited stomach acid secretion faster than PPIs from the first day of dosing. There have also been other reports of PCAB's effectiveness in improving the clinical symptoms of GERD and functional dyspepsia (Simadibrata et al., 2022; Kothadia & Howden, 2024).

A systematic review is a methodical examination of a specific issue, focusing on a single question that has been thoroughly investigated, evaluated, selected, and concluded based on established criteria derived from high-quality research data pertinent to the research question (Booth, 2016; Johnston et al., 2019). The aim of this research, employing a systematic review approach, is to investigate the efficacy of PCAB compared to PPI in alleviating symptoms in patients with gastroesophageal reflux disease (GERD).

This research provides valuable insights into the potential of Potassium Competitive Acid Blockers (PCABs) as an alternative and more effective treatment for patients with gastroesophageal reflux disease (GERD), particularly those who are resistant to Proton Pump Inhibitors (PPIs). The findings could significantly contribute to the development of more efficient treatment options, improving the quality of life for GERD patients who do not respond well to PPI therapy. Additionally, this study enhances the understanding of the mechanisms behind acid suppression by PCABs, which may lead to better clinical decision-making and more tailored treatment approaches. The results also have the potential to influence healthcare policies, guiding the development of clinical guidelines that offer safer and more effective treatments for GERD. Furthermore, this research addresses the needs of patients with PPI-resistant GERD, providing an important solution for a previously underserved group.

Method

This systematic review follows the publication protocol and guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). These PRISMA guidelines provide standards to ensure that systematic reviews are structured with transparency and proper methodologies. The protocol also guarantees that every step in the research, from the search for the study to the analysis of the results, is carried out systematically and organised.

Additionally, this study was conducted under the approach outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The guidelines from the Cochrane Handbook provide widely accepted methodological guidelines for conducting systematic reviews and meta-analyses, with a focus on clinical interventions. This approach enables the systematic and objective identification, assessment, and synthesis of evidence from various relevant studies.

The following four databases were searched: PubMed, Google Scholar, Cochrane Library, and EMBASE. Gastroesophageal reflux disease, PCAB, PPI, and clinical trials are among the search phrases that are displayed in Figure 1. By manually reviewing the reference lists of included research and pertinent systematic reviews, additional studies were also identified.

Duplicate articles were eliminated once all retrieved articles were put into Microsoft Excel. After that, the titles and abstracts were reviewed, the full texts were

examined, data extraction was performed, and the risk of bias was assessed. The study identifier, year of publication, study design, types of diseases associated with gastric acid, treatment plan, outcome measurement, and treatment outcome were all extracted. The Cochrane risk of bias (RoB) technique was used to assess the risk of bias in the included studies. The instruments evaluated five main areas: (i) the procedure of randomization; (ii) differences from intended interventions; (iii) incomplete outcome data; (iv) outcome assessment; and (v) the selection of the reported result.

The remission rate of heartburn symptoms on day 1 and day 7 was the main result. Heartburn with a "non" rating on a scale of one to four points (none, mild, moderate, and severe) was considered to have resolved its symptoms.

Findings were reported in tables, and data were presented narratively. Due to the limited number of studies and the diversity in the improvement of GI symptoms in GERD patients, we did not conduct a meta-analysis for that particular outcome of interest. R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for data synthesis and statistical analysis to produce a meta-analysis. To evaluate the heterogeneity of the included studies, we employed the Cochrane Q and I2 statistics. I2 values greater than 75% denote significant heterogeneity, 50-90% denote substantial heterogeneity, and values between 30-60% define moderate heterogeneity. A random-effect model was employed to produce the pooled effect size in cases where heterogeneity was apparent. The pooled proportion for the binary outcomes in each group was estimated using the metaprop function from the R meta package. Pooled RRs were also calculated using the Mantel–Haenszel model, along with a 95% CI for the healing rate and TEAEs. Using methods from the Cochrane Handbook, we transformed values from two vonoprazan studies, which were presented as median ± quartile, into mean ± standard deviation for the NERD meta-analysis. Only studies with consistent results were included in the analysis of pooled prevalence rates in PPI-resistant GERD. For the TEAE investigation, serum gastrin levels were graphically represented on a continuous scale. We used data from graphs published with pertinent research when the original authors were unable to provide the data, and it was not included in the text or tables. For specific data, raw data was obtained by contacting the authors directly. The standardized mean difference approach was used to combine continuous outcomes from multiple studies, which were measured using various instruments. Egger's tests for publication bias and funnel plots did not meet this condition and were not evaluated, despite being suitable for more than ten studies. Except for the Cochrane Q heterogeneity significance level, which was set at $P < 0.1$, all statistical analyses were two-tailed and deemed significant when $P < 0.05$.

Results and Discussion

After removing duplicates and non-English papers, 654 studies remained from the 1,125 articles originally in the computerized database. Six hundred nineteen articles were excluded after screening titles and abstracts. After going over the remaining 35 studies, we found observational studies assessing PPI-resistant GERD and Randomized Clinical Trials that used PPI as a control. The final analysis ultimately comprised five papers on PPI-resistant GERD and twenty studies on GERD (Figure 1). The risk-of-bias

evaluations for all randomized clinical trials revealed minimal bias (Figure 1). Furthermore, in the quality assessment, all observational studies showed a tendency toward fair or higher quality (Figure 2).

A summary of the attributes of the chosen studies is provided in Table 1. There were a total of 3,000 GERD patients. For gastroesophageal reflux disease, the initial treatment course lasted 2–8 weeks, followed by a maintenance course of 12 weeks. Nobuhiro et al.'s study from Japan shows results for 2, 4, and 8 weeks. Using FSSG ratings and the rate of endoscopic healing of ERD, we examined studies that consistently demonstrated symptom relief in PPI-resistant GERD.

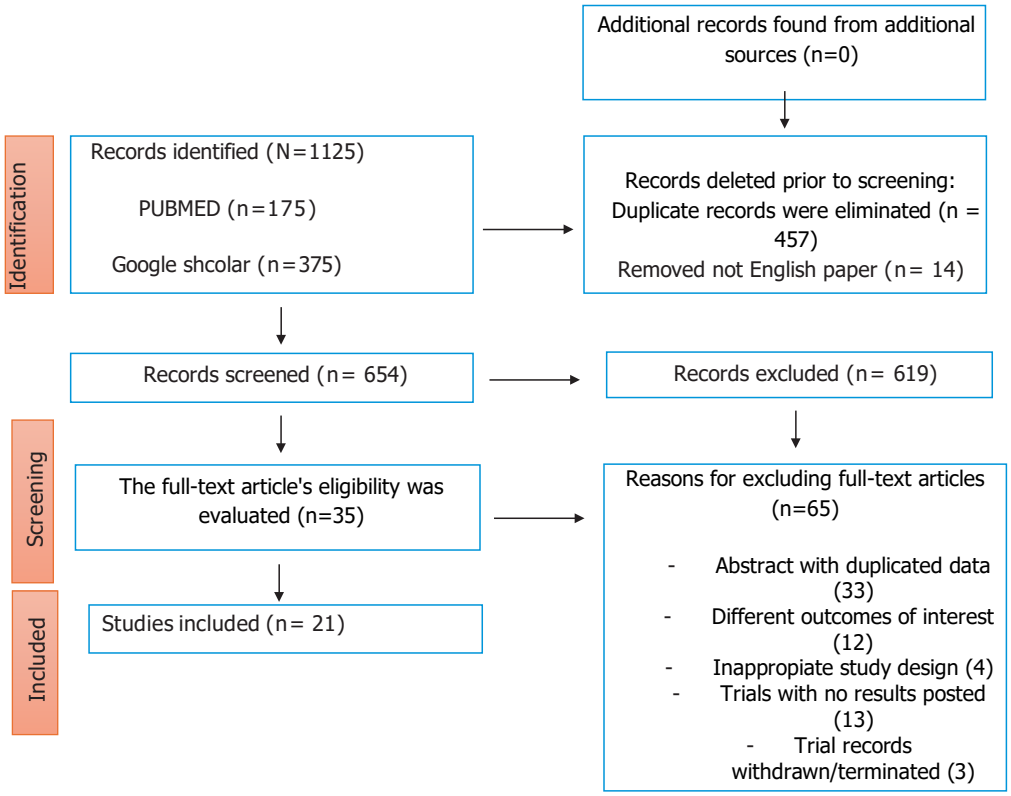

Figure 1. Summary of study search and study selection process

1. Gastroesophageal Reflux Disease

The effectiveness of PCABs and PPIs in the initial treatment of ERD was examined in seven randomized controlled trials (RCTs). The PCABs utilized in these investigations were 50 mg tegoprazan, 20 mg keverprazan, 40 mg fexuprazan, and 20 mg vonoprazan. Healing rates were recorded at weeks 2, 4, and 8 of each research. At week eight of the first ERD treatment, the PCAB group's pooled proportion of healed patients was 95.2%, compared to 92.5% for the PPI group. When compared to PPIs, the RR for healing with a typical dose of PCABs was 1.03 (95% CI, 1.00-1.07). At weeks two and

four, respectively, the RRs for PCABs versus PPIs in the initial therapy of ERD were 1.03 (95% CI, 0.99-1.06) and 1.09 (95% CI, 1.04-1.13) (Fig. 2). At all time points, PCABs continuously showed more excellent healing rates than PPIs; at the 2-week mark, statistical significance was noted. At week two, the pooled healing rate of PCABs was significantly greater than that of PPIs (85.1% vs. 77.3%); however, by week four, there was no difference (89.3% vs. 87.2%).

2. Maintenance therapy for healing in Gastroesophageal Reflux Disease

Following 12 and 24 weeks of GERD maintenance therapy, three RCTs observed healing rates. Tegoprazan 25 mg, vonoprazan 20 mg, and vonoprazan 10 mg were used in the results. At weeks 12 and 24, respectively, the RR for maintenance dose PCABs vs. PPIs in the ERD maintenance therapy was 1.04 (95% CI, 0.90-1.19) and 1.09 (95% CI, 1.03-1.16) (Fig. 3). In terms of healing rates, PCABs performed better than PPIs at weeks 12 and 24, but the difference was only statistically significant at week 24. The RR was 1.04 (95% CI, 0.90-1.19) at week 12 and 1.09 (95% CI, 1.03-1.16) at week 24 when both maintenance and regular dosages were employed. Only at week 24 was statistical significance noted. At week 24, the relative risk (RR) for 20 mg vonoprazan versus 10 mg vonoprazan was 0.97 (95% CI, 0.93-1.01), indicating no difference between the two doses. At week 24, the combined percentage for 25 mg tegoprazan and 10 mg vonoprazan was 86.7%, whereas the percentage for 20 mg vonoprazan was 90.3%.

3. Proton Pump Inhibitor-resistant Gastroesophageal Reflux Disease

Three observational studies on PPI-resistant GERD that looked at symptom improvement using FSSG ratings produced consistent results in the absence of RCTs.[8,25,26] Vonoprazan 20 mg was used in all three trials; two of these studies documented use for at least four weeks,[8,26] and one study looked into individuals who had been using the medication for at least four weeks.[25] FSSG values that were fewer than 8 points and had dropped by at least 2 points from the baseline were considered to be the effects of PCABs; 86.3% of patients had a good response, which is 95% CI, 0.46–0.98.

According to this research, PCABs helped individuals with PPI-resistant GERD. Additionally, a study found that endoscopic improvement occurred in 90.7% (95% CI, 0.82-0.96) of instances when traditional or greater doses of PPI were administered but endoscopy revealed ERD in patients who were switched to vonoprazan 20 mg for 4 weeks or more.

4. Healing Rate Using Potassium-competitive Acid Blockers vs Proton Pump Inhibitors Based on Gastroesophageal Reflux Disease

The healing rates with PCABs and PPIs according to the severity of ERD were the secondary result that was investigated. PCABs did not significantly outperform PPIs in the first therapy, as evidenced by the RR for PCABs vs. PPIs in LA grade A/B, which 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. At weeks two, four, and eight, the pooled ratios for LA-A/B grades were 89.1%, 92.3%, and 96.1%, respectively. At weeks two, four, and eight, the RR in LA grade C/D was 1.26 (95% CI, 1.15-1.38), 1.15 (95% CI, 1.07-1.24), and 1.13 (95% CI, 1.05-1.22). For erosive esophagitis, these results are consistent with

maintenance therapy; at week 24, the RR for LA grade C/D was 1.32 (95% CI, 1.13-1.55), suggesting that PCABs are more effective than PPIs, and the RR for these maintenance dosages alone was 1.28 (95% CI, 1.10-1.50) at week 24, assuming equivalent dosages of 10 mg vonoprazan and 25 mg tegoprazan. These pooled ratios for PCABs in the LA grade C/D group were 82.2%, 91.5%, and 96.7%, respectively, at weeks 2, 4, and 8.

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 (weeks)
Daniel MS	2023	Indonesia	RCT	ERD	99	50 mg **xxxxx**	99	40 mg esomeprazole	4, 8
Nakasu	2017	Japan	RCT	ERD	238	20 mg **xxxxx**	230	30 mg lansoprazole	2, 4, 8
Shuo	2024	China	RCT	ERD	119	20 mg **xxxxx**	119	30 mg lansoprazole	4, 8
Jiten	2023	USA	RCT	ERD	116	40 mg **xxxxx**	115	45 mg esomeprazole	4, 8
Xuyan	2024	China	RCT	ERD	514	20 mg **xxxxx**	510	30 mg lansoprazole	2, 8
Tadayuki	2018	Japan	RCT	ERD	154	25 mg **xxxxx**	151	15 mg lansoprazole	12, 24
Dousa	2024	China	RCT	ERD	202	10 mg **xxxxx**	201	15 mg lansoprazole	12, 24
Carol	2023	USA	RCT	NERD	278	20 mg **xxxxx**	278	Placebo	4
-	-	-	RCT	NERD	271	20 mg **xxxxx**	271	Placebo	4
Prashanth	2021	Korea	RCT	NERD	106	50 mg **xxxxx**	99	Placebo	4
Hoshino	2017	Japan	Single-arm cohort	PPI-resistant GERD	24	20 mg **xxxxx**	No	-	4
Iwaki	2017	Japan	RCT	PPI-resistant GERD	5	20 mg **xxxxx**	-	-	8

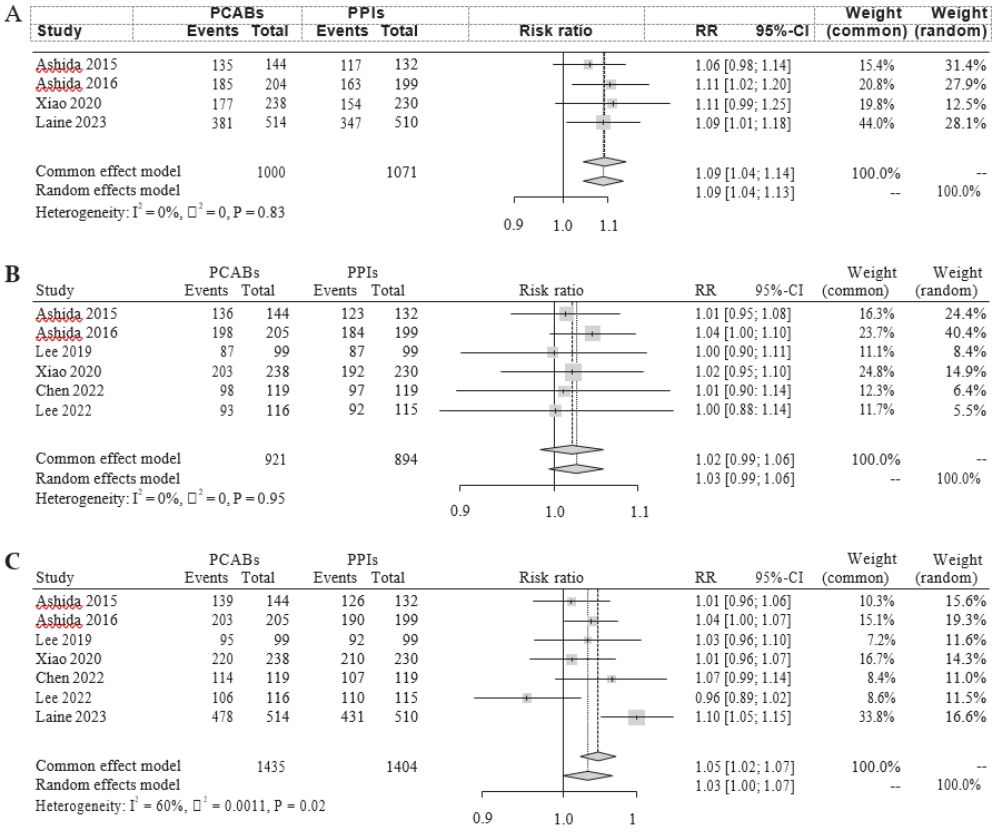

Figure 1. Forest plot depicting the relative efficacies of potassium competitive acid blockers (PCAB) and Proton Pump Inhibitor (PPI) in the initial treatment of Gastroesophageal Reflux disease, showing healing rates at weeks 2 (A), weeks 4 (B) and Weeks 8 (C).

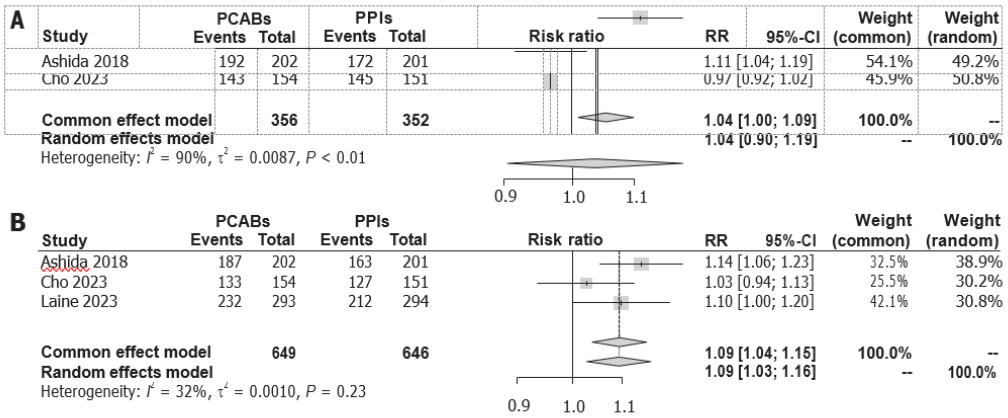

Figure 3. Forest plot depicting the relative efficacies of potassium-competitive acid blockers and proton pump inhibitors in the maintenance thera- py of healing erosive oesophagitis, showing the healing rates at weeks 12 (A) and 24 (B). RR, risk ratio.

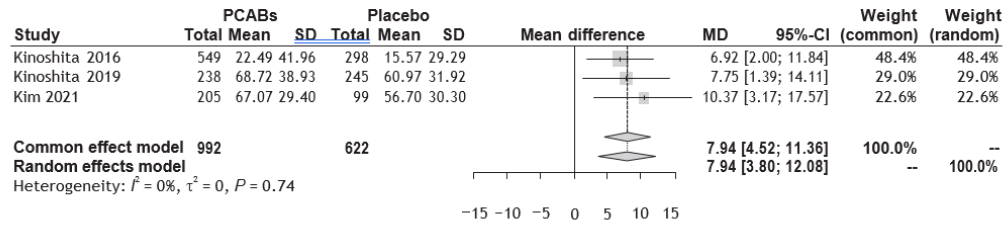

Figure 2. Forest plot illustrating the proportion of symptom-free days during the treatment period for potassium-competitive acid blockers (PCABs) compared to placebo in patients with non-erosive reflux disease. PPIs, proton pump inhibitors; RR, risk ratio; MD, mean difference.

According to this meta-analysis, the effects of PCAB differ depending on the kind of GERD. Although PCABs had a quicker effect than PPIs when treating ERD initially, there was no discernible difference in the effectiveness of initial and maintenance therapy for mild ERD. In contrast to LA-A/B esophagitis, PCABs showed noticeably more excellent healing rates in LA-C/D esophagitis. Furthermore, PCABs showed promise in treating PPI-resistant GERD and NERD, but limited research on individuals with nighttime heartburn produced conflicting findings. After 24 weeks of PCAB treatment, the incidence of hypergastrinemia rose noticeably, although there was no discernible difference between PCABs and PPIs in terms of overall TEAEs, including hepatotoxicity.

Reducing the initial treatment length from 8 weeks to 4 weeks was recommended by Japanese recommendations based on domestic data, which indicated that PCABs are more successful than PPIs. 38 At two weeks following the start of treatment, all examined PCABs in this study showed a notable improvement in ERD. Nonetheless, 89.9% of patients heal after 4 weeks of PCAB therapy, which is more successful than PPIs but still insufficient. When PCABs were used for eight weeks, the recovery rate was an impressive 95.2%. Particularly for LA C/D esophagitis, PCABs were statistically more effective than PPIs. Consequently, our meta-analysis demonstrates that PCABs

significantly improve the success rate of initial ERD treatment, particularly in patients with severe ERD; however, they do not necessarily reduce the duration of initial therapy.

PCABs demonstrated a greater healing rate than PPIs in the maintenance therapy of ERD for 12 and 24 weeks; however, the difference was only statistically significant at week 24. During 24 weeks of maintenance therapy, PCABs demonstrated increased efficacy in ERD patients, suggesting that a lower dosage can be used for maintenance. Subgroup analysis based on the level of discomfort revealed that PCABs were more beneficial in the maintenance phase for LA-C/D esophagitis than for LA-A/B esophagitis, consistent with the initial treatment. At 24 weeks, it was discovered that low-dose vonoprazan (10 mg) and tegoprazan (25 mg) alone were more effective than PPIs. Therefore, PCABs are recommended for maintenance therapy in patients with severe ERD (LA-C/D); low dosages are adequate for this purpose.

In NERD patients, the effects of PCABs were noticeably more potent than those of a placebo (Seo et al., 2024; Chapelle et al., 2021). However, due to the limited number of studies and the varied data reporting that necessitates data translation for meta-analysis, caution must be exercised when interpreting our findings. Accuracy can be increased, and bias resulting from inadequate reporting can be reduced through proper conversion or estimation. Increasing the size of the intervention group and underestimating the standard deviation during conversion could skew the results and further impact observed differences (Higgins et al., 2019; Kent et al., 2016). To address this, a sensitivity analysis was conducted using all doses and combinations of medication types. The same outcomes were achieved, showing little inter-study variability with a heterogeneity of 0%. To better comprehend and validate these findings, more study findings and in-depth data analysis are anticipated in the future.

PCABs may offer patients with nighttime heartburn early symptom relief, as indicated by the shorter interval between the first day without nighttime heartburn in the PCAB group compared to the PPI group (Seo et al., 2024)(Antequera et al., 2024). Additionally, a more significant percentage of patients in the PCAB group than in the PPI group were symptom-free for at least seven days. Although the difference was not statistically significant, this outcome suggests that PCABs may be superior to PPIs in providing long-lasting symptom alleviation. PCABs may be a viable therapy option for patients with heartburn that occurs at night.

Across all clinical GERD phenotypes, PCABs did not differ significantly from PPIs in terms of overall safety, including severe treatment-emergent adverse events (TEAEs) and liver function test (LFT) abnormalities. CYP2C19 metabolizes PPIs in the liver, and one of the variables that may affect PPI effectiveness is CYP2C19 polymorphism. Since PCABs are mainly metabolized by CYP3A4, along with CYP2B6, CYP2C19, and CYP2D6, they are less impacted by CYP2C19 genotypes. GERD is a prevalent disorder, and many patients with this illness need to take acid-suppressive drugs for the duration of their lives. Although acid suppression causes hypergastrinemia, the long-term effects are still unknown. Long-term PPI usage has been linked to moderate gastrin increases (around 200–400 pg/mL), although no significant pathology has been linked to this use.

In conclusion, patients with GERD and PPI-resistant GERD may benefit from PCABs as a therapeutic substitute for PPIs (Simadibrata et al., 2022)(Rettura et al., 2021).

Particularly for severe GERD, PCABs were shown to be more effective than PPIs in both initial and ongoing treatment. PCABs and PPIs were equally safe. Additionally, as other PCABs beyond venoprazan are developed, the collection and analysis of additional high-quality data is crucial.

According to this meta-analysis, the effects of PCAB differ depending on the kind of GERD. Although PCABs had a quicker effect than PPIs when treating ERD initially, there was no discernible difference in the effectiveness of initial and maintenance therapy for mild ERD. In contrast to LA-A/B esophagitis, PCABs showed noticeably better healing rates in LA-C/D esophagitis. Furthermore, PCABs showed promise in treating PPI-resistant GERD and NERD, but limited research on individuals with nighttime heartburn produced conflicting findings. After 24 weeks of PCAB treatment, the incidence of hypergastrinemia rose noticeably, although there was no discernible difference between PCABs and PPIs in terms of overall TEAEs, including hepatotoxicity.

Japanese recommendations suggested reducing the first treatment length from 8 weeks to 4 weeks, based on domestic data indicating that PCABs were more successful than PPIs (Yaghoobi & Armstrong, 2022; Foret et al., 2023). 38 At two weeks following the start of treatment, all examined PCABs in this study showed a notable improvement in ERD. Nonetheless, 89.9% of patients heal after 4 weeks of PCAB therapy, which is more successful than PPIs but still insufficient. PCABs showed a remarkable healing rate of 95.2% when extended to 8 weeks. PCABs were statistically more successful than PPIs, especially in LA C/D esophagitis. Therefore, our meta-analysis demonstrates that PCABs do not always shorten the length of initial therapy; however, they do considerably increase the success rate of the initial ERD treatment, especially in cases of severe ERD.

PCABs demonstrated a greater healing rate than PPIs in the maintenance therapy of ERD for 12 and 24 weeks. However, the difference was only statistically significant at week 24 (Seo et al., 2024)(Herdiana, 2023). After 24 weeks of maintenance medication, PCABs demonstrated increased efficacy in ERD patients, suggesting that a lower dosage can be used for maintenance. As with initial treatment, PCABs were more beneficial in the maintenance phase for LA-C/D esophagitis but not for LA-A/B esophagitis, according to subgroup analysis based on disease severity. At 24 weeks, tegoprazan (25 mg) and low-dose vonoprazan (10 mg) by themselves outperformed PPIs. For patients with severe ERD (LA-C/D), PCABs are therefore advised for maintenance therapy; low dosages are sufficient for this purpose.

The effects of PCABs were much more significant than those of a placebo in NERD patients. The small number of studies and inconsistent data reporting, however, necessitate careful interpretation of our results to support a meta-analysis. Accurate estimating or conversion can improve accuracy and lessen the possibility of bias caused by inadequate reporting. The results could be skewed by increasing the size of the intervention group and underestimating the standard deviation during conversion, which would further alter apparent differences. To address this, a sensitivity analysis was conducted using all doses and combinations of medication types. The same outcomes were achieved, showing little inter-study variability with a heterogeneity of 0%. To better comprehend and validate these findings, more study findings and in-depth data analysis are anticipated in the future.

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In conclusion, patients with GERD and PPI-resistant GERD may benefit from PCABs as a therapeutic substitute for PPIs. When it comes to the initial and ongoing treatment of GERD, particularly severe GERD, PCABs have proven to be more effective than PPIs. PCABs and PPIs were equally safe. Additionally, as new PCABs beyond venoprazan are developed, the collection and analysis of additional high-quality data is crucial.

Conclusion

Vonoprazan is equally as effective as PPIs in treating GERD symptoms, erosive esophagitis, and gastric and duodenal ulcers. Vonoprazan, however, performs better than PPI in terms of the rate of H. pylori infection eradication with first-line treatment. Compared to PPI, vonoprazan is also very safe; however, only short-term effects have been assessed. To support the conclusions that PCAB is a quicker and more effective acid suppressant and a substitute for PPIs in PPI-refractory circumstances, more RCTs with bigger samples, in more demographics, and with more varied PCAB use (apart from Vonoprazan) are required.

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