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Original article

Vonoprazan causes symptomatic improvement in non-erosive gastroesophageal reflux disease: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy and safety of vonoprazan therapy as compared to conventional proton pump inhibitors (PPIs) or no vonoprazan for non-erosive esophagitis.
Methods: A thorough search was conducted across databases. The primary outcome was to determine the mean variance in the gastroesophageal reflux disease (GERD) score after vonoprazan treatment. Secondary outcomes comprised alterations in the scores for epigastric pain and post-prandial distress, the proportion of patients displaying improvement, and the occurrence of adverse events. Pooled mean differences and relative risks were determined utilizing random effects models.
Results: A total of 1,944 articles were screened and nine of them were included. As compared to PPI or no vonoprazan therapy, vonoprazan treatment led to a significant reduction in the GERD score [mean difference: -3.88 (95 % CI: -5.48, -2.28), $p < 0.01$, i^2=95 %]. As compared to PPI or no vonoprazan therapy, vonoprazan treatment led to a significant reduction in the epigastric pain score [mean difference: -3.02 (95 % CI: -5.41, -0.63), $p = 0.01$, i^2=75 %] and post-prandial distress score [mean difference: -2.82 (95 % CI: -3.51, -2.12), $p < 0.01$, i^2=0 %] (all moderate GRADE evidence). Vonoprazan therapy was found to be safe.
Conclusion: Treatment with vonoprazan could significantly improve symptoms in patients with non-erosive esophagitis or non-erosive GERD.

Introduction

Nonerosive reflux disease (NERD) is prevalent in both Western and Asian nations, imposing a substantial impact on the quality of life for affected individuals and placing a notable burden on healthcare systems [1,2]. The clinically pertinent objective in treating NERD is to alleviate symptoms associated with acid reflux, such as heartburn. The primary approach for initial treatment is the use of proton pump inhibitors (PPIs) [3]. Although PPIs are widely recognized for their documented clinical effectiveness and safety, they have certain limitations. Notably, only around 50−60 % of patients with NERD experience symptom resolution within the first 4 weeks of PPI treatment [4,5]. Hence, there exists a demand for innovative medications to enhance outcomes for individuals with NERD. Those with NERD have reported a lower quality of life compared to individuals with erosive esophagitis or Barrett's esophagus, potentially stemming from a restricted response to anti-reflux treatments. The pain and discomfort resulting from episodes of heartburn may curtail involvement in physical and social engagements, adversely affecting sleep quality and contributing to fatigue, further constraining participation in daily activities [6,7]. Furthermore, some patients (12–35 %) with GERD may have functional dyspepsia. There is evidence that PPIs are effective for treating functional dyspepsia; however they are not always effective [8].

In contrast to traditional PPIs, vonoprazan fumarate competitively hinders H+, K+ -ATPase by attaching to the potassium ion binding site, and it does not necessitate activation by gastric acid. Vonoprazan has gained approval in certain countries for addressing gastric and duodenal ulcers, promoting the healing of reflux esophagitis and preventing relapse, as well as for the secondary prevention of gastric mucosal damage induced by low-dose aspirin or nonsteroidal anti-inflammatory

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drugs. Additionally, it is approved as both the first- and second-line therapy for eradicating *Helicobacter pylori* [9]. In the context of NERD, a prior randomized controlled study involving Japanese participants did not establish the superiority of vonoprazan 10 mg over a placebo. Various explanations have been suggested for this outcome, including concerns related to the heartburn symptom scale utilized for assessment in the study and the potential inclusion of individuals with heartburn not linked to acid reflux, such as those with functional dyspepsia or functional heartburn, in the patient selection process [10]. Several studies have been conducted to evaluate the efficacy and safety of vonoprazan as compared to conventional PPIs for non-erosive esophagitis. Hence, this systematic review and meta-analysis was conducted to summarize the evidence qualitatively and quantitatively.

Methods

Search strategy and selection criteria

In this study, an exhaustive search was executed using databases including PubMed, Embase, Scopus, Cochrane CENTRAL, and ClinicalTrials.gov. The objective was to pinpoint pertinent studies published in English up to January 31, 2024. Inclusion criteria involved randomized controlled trials (RCTs), non-randomized interventional studies, and observational studies exploring the effects of oral vonoprazan compared to PPIs in a head-to-head comparison or without a comparator in adult patients (≥18 years old, any gender) with NERD. Studies involving patients with erosive esophagitis or erosive gastroesophageal reflux disease (GERD) were excluded. The search strategy employed specific terms adapted to the requirements of each database. Two independent authors assessed titles and abstracts of identified studies, with no language restrictions. They then obtained abstracts and, if needed, full texts of articles to evaluate their eligibility for inclusion using the Rayyan software (https://www.rayyan.ai/). Corresponding authors of relevant articles were contacted via email for any missing information. Articles that had full text were considered here. Other materials, such as, conference papers, review articles, commentaries etc. were excluded from this analysis. The literature search strategy is detailed in Table S1

The primary outcome of this study was to evaluate the mean difference in GERD scores at the conclusion of the treatment period as the primary outcome measure. Secondary outcomes encompassed alterations in epigastric pain scores, post-prandial distress scores, the percentage of patients exhibiting improvement, and the occurrence of adverse events. The study obtained an "exemption from review" from the relevant Institutional Ethics Committee, and the study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42024507172).

Data analysis

In the course of abstract review and data extraction, three authors autonomously carried out these tasks utilizing a pre-formatted data extraction spreadsheet. The process maintained a commitment to accuracy and reliability by avoiding assumptions or simplifications. The included studies underwent a risk of bias assessment using the revised Cochrane risk-of-bias 2 tool [11] for RCTs, ROBINS-I tool [12] for non-randomized studies of interventions, and Newcastle-Ottawa scale [13] for observational studies. The analysis employed summary estimates, and meta-analysis was conducted when adequate data were accessible for the predetermined primary and secondary outcomes. Statistical analysis was executed using RevMan version 5.3 software. To enhance the model's robustness across diverse populations and address potential outliers, a random-effects model was utilized. The treatment effects for efficacy outcomes were estimated using the mean difference with a corresponding 95 % confidence interval (CI). Similarly, the mean difference with a corresponding 95 % CI was employed to estimate the treatment effects for safety outcomes.

When data were inadequate, descriptive statistics were employed. The analysis also considered attrition rates, encompassing dropouts, loss to follow-up, and withdrawals. The examination included a critical appraisal of missing data issues and the methods used for imputation [14]. Heterogeneity was analyzed in the following approach: χ^2 test conducted on n-1 degrees of freedom, 5 % α error for statistical significance, and i^2 test [15]. The i^2 values were categorised as low: 25 %, medium : 50 %, and high: 75 %. Funnel plots were generated to evaluate the potential effect of small study effects and publication bias [14,16]. The GRADE approach, which stands for Grading of Recommendations Assessment, Development, and Evaluation, was utilized in this study to assess the quality of the generated evidence [17,18]. This meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results

Out of a total of 1944 articles screened, nine [19-27] met the inclusion criteria and were included in the final analysis (refer to Fig. 1). Among these, there was one randomized controlled trial, one single-arm interventional study, and the remaining seven were observational studies. Study characteristics are tabulated in Table 1. With the exception of the randomized controlled trial, all other studies were conducted in Japan. The sample sizes ranged from 22 to 457 participants. Across various studies, the dose of vonoprazan ranged from 10 to 40 mg, administered for durations spanning 1 to 12 months. The randomized controlled trial and the single-arm interventional study exhibited low risk of bias, while the observational studies demonstrated low to moderate risk (refer to Figure s1).

As compared to PPI or no vonoprazan therapy, vonoprazan treatment led to a significant reduction in the GERD score [mean difference: −3.88 (95 % CI: −5.48, −2.28), $p < 0.01$, i^2=95 %] (moderate GRADE evidence) (Fig. 2). As compared to PPI or no vonoprazan therapy, vonoprazan treatment led to a significant reduction in the epigastric pain score [mean difference: −3.02 (95 % CI: −5.41, −0.63), $p = 0.01$, i^2=75 %] (moderate GRADE evidence) (Figure s3) and post-prandial distress score [mean difference: −2.82 (95 % CI: −3.51, −2.12), $p < 0.01$, i^2=0 %] (moderate GRADE evidence) (Figure s4). No publication bias was reported for the primary outcome (Figure s2). Vonoprazan therapy was found to be safe in all studies without any significant serious adverse events.

In the randomized controlled trial conducted by Fass et al. [19], the primary outcome revealed that all doses of vonoprazan (10–40 mg/day) demonstrated significant superiority over the placebo, with percentages of success as follows: 10 mg (56 %), 20 mg (60.6 %), and 40 mg (70 %) compared to placebo (27.3 %). This superiority was consistent when considering criteria within 2 h and sustained, and even within 1.5 h and sustained. Despite these results, there was no discernible difference between the groups regarding the median percentage of heartburn-free days, with values of 81 %, 79 %, and 81 % for different vonoprazan doses versus 80 % for the placebo group. In the study by Shinozaki et al. 2021 [20], GERD symptoms in NERD patients markedly improved from baseline and sustained this improvement after 1 year of vonoprazan therapy. Additionally, vonoprazan exhibited positive effects on epigastric pain and postprandial distress symptoms in NERD patients, and the therapy for one year did not exacerbate constipation or diarrhea.

Abe et al. [21] observed a decrease in the GERD score, an increase in the pH value of the refluxate, and a reduction in the percentage of times with intragastric pH <4 or <5 after switching from PPI to vonoprazan compared to findings before the switch. In the study by Hamada et al. [22], a significant decrease in the proportion of NERD cases was noted in the vonoprazan group compared to the conventional PPI group. Notably, no cases of acid-related GERD were found in the group taking vonoprazan. In the study by Hoshikawa et al. [23], comparing patient satisfaction levels before and after therapy, no significant differences

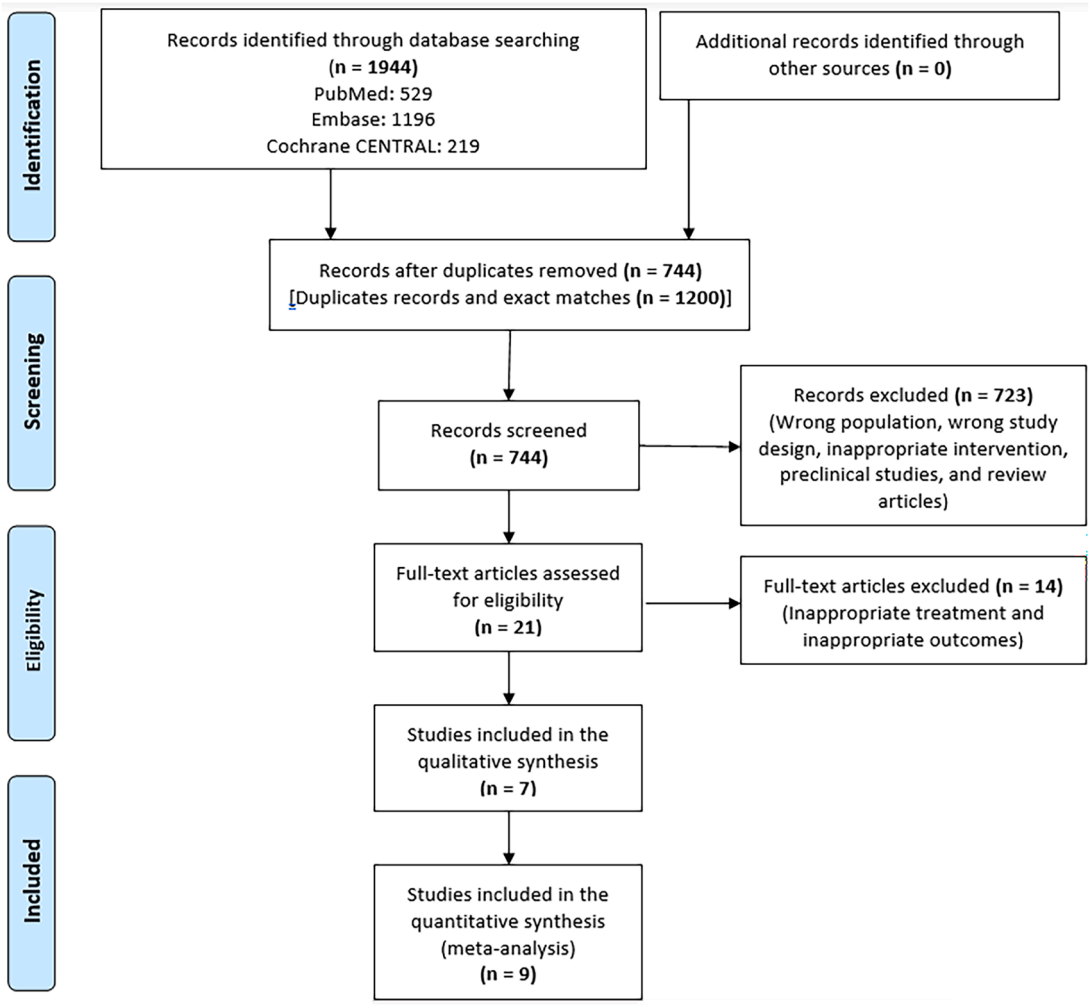

Fig. 1. Study flow chart.

Table 1
Characteristics of the included studies.

Author, year, country	Type of study	Patients	Age (years)	Total n	Male: female	Vonoprazon dosing (per day)	Comparator medicine(s)	Vonoprazan treatment duration
Fass, et al., 2023, United States of America	Randomized controlled trial	Patients with NERD	52 ±14.4	457	161: 296	10, 20, and 40 mg	–	6 weeks
Shinozaki et al. 2021, Japan	Observational study	Patients with PPI resistant non-erosive GERD	69±3	22	6:16	10 or 20 mg	–	12 months
Abe et al. 2021, Japan	Observational study	Patients with PPI- refractory NERD	58.6 ± 14.9	29	–	20 mg	–	4 weeks
Hamada et al. 2021, Japan	Observational study	Patients with refractory non-erosive GERD on treatment for ≥8 weeks	60±5.7	39	18: 21	20 mg	PPIs	8 weeks
Hoshikawa, et al., 2019	Single-arm interventional study	Patients with NERD	67.8	30	11: 19	20 mg	PPIs	8 weeks
Shinozaki, et al., 2018, Japan	Observational study	Patients with non-erosive GERD	59.9 ± 13.6	55	28: 27	10–20 mg	–	1 month
Nikura, et al., 2018, Japan	Observational study	Patients with severe GERD	67.5 ± 12.2	26	7: 19	10–20 mg	PPIs	12 weeks
Shinozaki, et al., 2017, Japan	Observational study	Patients with non-erosive GERD	55.9 ± 16.0	88	40: 48	10 mg	–	1 month
Asaoka, et al., 2016, Japan	Observational study	Patients with reflux esophagitis, NERD, and functional dyspepsia	60.2 ± 14.7	88	30: 58	20 mg	–	4 weeks

GERD, gastroesophageal reflux disease; NERD, non-erosive reflux disease; PPI, proton pump inhibitors.

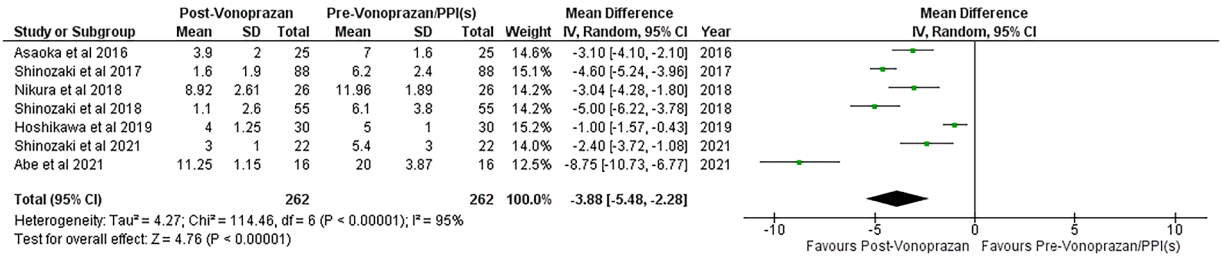

Fig. 2. Effect of vonoprazan on gastrointestinal reflux disease score.

were found in the number of patients who reported being very satisfied or satisfied with the treatment. Moreover, there were no significant variations in symptom scores or gastrin levels before and after therapy. Shinozaki et al. 2018 [24] demonstrated that one-month therapy with vonoprazan (10 mg) improved GERD symptoms in 89 % of patients, and this improvement was maintained at one year in 82 % without additional treatment. Maintaining the therapy for one completed year resulted in alleviation of GERD symptoms in 47 % of the patients. Both time points of one month and one year showed significant improvement for all of the following symptoms: diarrhoea, epigastric pain, distress after food, and constipation.

Nikura et al. [25] reported that after switching from a PPI to vonoprazan, 69 % of patients experienced improvement. This also reflected in improved self-reported symptoms. In the study by Shinozaki et al. 2017 [26], vonoprazan therapy led to the improvement and resolution of GERD symptoms in 86 % and 57 % of patients, respectively. Advanced age, obesity, and erosive esophagitis were identified as positive predictors of resolution of GERD symptoms, while alcohol use and a history of Helicobacter pylori eradication were identified as negative predictors. With vonoprazan, 73 % of the GERD patients experienced improved epigastric pain, 60 % experienced improved after-food distress, 58 % had less constipation, and 52 % had less diarrhoea. Asaoka et al. [27] found that following vonoprazan therapy, the rates of symptomatic improvement in patients with reflux esophagitis, NERD, and functional dyspepsia were 75 %, 60 %, and 49 %, respectively. For patients resistant to 8 weeks of PPI therapy, reflux esophagaitis patients had symptomatic improvement rate of 55.6 %, NERD 53.8 %, and functional dyspepsia 42.3 %.

Discussion

In this comprehensive systematic review and meta-analysis, the findings indicate that vonoprazan treatment can yield significant benefits for patients with NERD, particularly in terms of symptomatic improvement. Moreover, the therapy was identified as generally safe. NERD represents the predominant phenotype of gastroesophageal reflux disease, characterized by typical reflux symptoms without visible esophageal mucosal injury. Patients with NERD may exhibit esophageal hypersensitivity or functional heartburn based on symptom-reflux correlation. The progression of NERD to severe disease (erosive esophagitis or even Barrett's oesophagus) is uncommon over time [28,29]. The primary goal of therapy is to alleviate or reduce symptoms and enhance quality of life. While PPIs stand as the most effective agents for treating NERD, their efficacy in providing symptom relief is comparatively less than in patients with erosive esophagitis. These symptoms may be of concern in patients with co-morbidities, e.g. hyperkalemia [30]. Consequently, early intervention is crucial to address these patients before the condition progresses to more severe diseases [31].

PPIs function as prodrugs, requiring activation by acid, and subsequently, they form a covalent bond with the gastric $H+/K+$ ATPase through a disulfide bond. The metabolic inactivation of PPIs primarily occurs through cytochrome P450 (CYP) enzymes, with CYP2C19 and CYP3A4 playing key roles in this process [32]. While PPIs have demonstrated effectiveness, they come with certain limitations. These include a delayed onset of action (typically 3–5 days), low bioavailability, potential for nocturnal acid breakthrough, susceptibility to drug interactions, and the requirement for proper timing in relation to meals for optimal efficacy [33]. Additionally, PPIs are influenced by significant inter-individual variability in pharmacodynamics and clinical activity, attributed to the presence of cytochrome polymorphisms. Moreover, there is a growing concern regarding the rising prevalence of antibiotic resistance linked to treatment regimens that involve PPIs for the eradication of H. pylori infection [32]. Finally, recently, few safety concerns have been emphasized in different studies [33].

The factors mentioned above have spurred the development of new drugs, aiming to address the limitations associated with PPIs and fulfil unmet clinical needs [33]. Potassium-competitive acid blockers (P-CABs) represent a novel and diverse class of drugs that competitively obstruct the potassium binding site of the gastric $H+/K+$ ATPase. Once absorbed into the systemic circulation, P-CABs accumulate in the canalicular membrane of parietal cells, where they undergo protonation in a highly acidic environment. Notably, P-CABs differ from PPIs as they are acid-stable and do not necessitate enteric-coated formulations. Additionally, P-CABs exhibit a faster onset of acid inhibition and intragastric pH elevation compared to PPIs. This is attributed to their rapid achievement of peak plasma levels following oral administration, enabling them to block $H+/K+$ ATPase without the need for proton-pump activation [33]. P-CABs, exemplified by vonoprazan, have the distinctive ability to achieve a complete antisecretory effect from the first dose and provide a more consistent control of gastric pH compared to PPIs. Vonoprazan stands out as the sole potassium-competitive acid blocker currently available for clinical use. Its development was specifically geared towards addressing the limitations associated with PPIs, including their short half-life, inadequate acid suppression, delayed onset of action, and susceptibility to metabolic variability [32,33].

The absence of a universally agreed-upon definition for a standardized endpoint in symptomatic GERD has led to the utilization of different endpoints in various studies. Effectively managing PPI-resistant non-erosive GERD proves to be more challenging than treating erosive GERD. In individuals with newly symptomatic GERD, erosive GERD is generally more manageable compared to non-erosive GERD [34]. Several factors (e.g., visceral hypersensitivity, reduced intestinal motility coordination, gastric accommodation disorders, and psychiatric issues) significantly affect the symptoms in individuals with non-erosive GERD, in contrast to symptomatic erosive GERD. Acid reflux has a lesser modulatory role in expressing symptoms in patients with non-erosive GERD than in erosive GERD. Addressing PPI-resistant non-erosive GERD may require additional therapies such as prokinetics, dietary modifications, and psychiatric medications [35].

The effectiveness of PPIs in alleviating dyspepsia symptoms has been well-established. PPIs exhibit a slightly superior efficacy compared to prokinetics in addressing dyspeptic symptoms [36]. A feeling of heaviness, bloating, and belching, indicating dyspeptic symptoms, can occur after direct introduction of hydrochloric acid into the stomach and inducing dysmotility [37]. The suppression of gastric acid by vonoprazan by inhibiting the H+/K+-ATPase enzyme system in gastric parietal cells could represent a promising avenue for alleviating dyspepsia symptoms. However, the individualized nature of dyspepsia warrants a

comprehensive evaluation by healthcare professionals to determine the underlying cause and tailor an appropriate treatment strategy for optimal patient outcomes [38]. Further large-scale randomized controlled trials are required to evaluate the role of vonoprazan in alleviating dyspepsia symptoms.

It is firmly established that vonoprazan exhibits a greater acid-suppressing effect compared to PPIs, and this heightened potency in acid suppression contributes to its efficacy in the treatment of patients with PPI-resistant GERD [39]. Reflux esophagitis that is refractory to PPIs, may have a greater chance of developing in patients with an excessive metabolism of the CYP2C19 genotype than those with poor metabolism. Importantly, the acid suppression effect of vonoprazan is not influenced by the CYP2C19 genotype, indicating a consistent efficacy across different metabolic profiles [39]. In an open-label crossover study, significantly superior acid suppression was demonstrated with vonoprazan compared to rabeprazole. Specifically, the pH4 holding time ratios were 88.4 % in vonoprazan and 53.8 % in rabeprazole. This indicates a more robust and sustained acid-suppressing effect with vonoprazan [40]. Twenty mg/ day Vonoprazan improved acid clearance time and the number of reflux events, a Japanese study found. This suggests that vonoprazan effectively contributes to the reduction of acid clearance time and reflux events, indicating its potential in managing acid-related conditions [41]. The nocturnal acid suppression effect of vonoprazan has been demonstrated to be superior to that of PPIs [42]. Switching from PPI therapy to vonoprazan improved GERD symptoms within days. This underscores the effectiveness of vonoprazan, particularly in addressing nocturnal acid-related symptoms and providing rapid relief in GERD patients [43]. Vonoprazan induced improvement in PPI-resistant GERD patients is characterized by a quick onset, longer duration and stronger acid suppression effects.

The studies included in the analysis exhibit several limitations. Firstly, the low number of studies and small sample sizes may impact the robustness of the findings, and the results could potentially change with the availability of more extensive studies. Additionally, the absence of evaluation of endoscopic or histological parameters is a limitation, as it could provide a more accurate assessment of NERD or GERD. During the review process, some outcomes of interest had limited data availability, leading to their exclusion or inability to be included in the meta-analysis. Substantial heterogeneity in most outcomes is another limitation, and this heterogeneity can be attributed to variations in the study population, the duration and severity of NERD or GERD in participants, the use of different concurrent medications across the studies, and variations in the disease and duration of vonoprazan therapy. The overall quality of evidence, as assessed by the GRADE, was moderate for some outcomes, suggesting the need for further research with larger sample sizes and a more comprehensive evaluation of histological parameters to enhance the reliability and generalizability of the findings.

Conclusion

This is the first systematic review and meta-analysis to show that treatment with vonoprazan could significantly improve symptoms in patients with non-erosive esophagitis or non-erosive GERD. The results should be confirmed by future large-sized clinical trials.

Data sharing

The original contributions presented in the study are included in the main article/supplementary material. Further inquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Sanjay Bandyopadhyay: Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Pooja Verma:** Writing – original draft, Methodology, Investigation. **Shambo Samrat Samajdar:** Resources, Methodology, Investigation. **Saibal Das:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

There are no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinre.2024.102373.

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