INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

COMPARING VONOPRAZAN TO HIGH-DOSE PROTON PUMP INHIBITORS FOR REFRACTORY GASTROESOPHAGEAL REFLUX DISEASE.

Original Research

Muhammad Azhar Sherkheli[1]*, Muhammad Waqas Irshad[2], Durr-e-Shahwar Malik[3], Kainat Balach[4]

[1] Associate Professor Pharmacy, Abbottabad University of Science and Technology

[2]Worcestershire Royal Hospital, Worcester, United Kingdom.

[3]Clinical Pharmacist, A.O Clinic

[4]Peoples University of Medical and Health Sciences for Women Shaheed Benazirabad, Nawab Shah

Corresponding Author: Muhammad Azhar Sherkheli, Associate Professor Pharmacy,Abbottabad University of Science and Technology Abbottabad, azhar.sherkheli@gmail.com

Acknowledgement: The authors sincerely acknowledge the patients and clinical staff of participating gastroenterology centers in the Islamabad–Rawalpindi region for their cooperation and support during this study.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is a common chronic gastrointestinal disorder that significantly affects quality of life. Although proton pump inhibitors (PPIs) remain the primary pharmacological therapy, a considerable proportion of patients continue to experience persistent symptoms despite optimized or high-dose treatment, resulting in refractory GERD. Potassium-competitive acid blockers, particularly vonoprazan, have recently emerged as an alternative therapeutic option capable of producing rapid and sustained gastric acid suppression.

Objective: To compare the effectiveness of vonoprazan with high-dose proton pump inhibitors in achieving sustained symptomatic remission among patients with refractory gastroesophageal reflux disease.

Methods: A prospective randomized comparative study was conducted over four months in gastroenterology clinics in the Islamabad–Rawalpindi region. Adult patients with persistent reflux symptoms despite twice-daily high-dose PPI therapy were enrolled and randomly assigned to receive either vonoprazan (20 mg once daily) or continued high-dose PPI therapy. Symptom severity and disease-related quality of life were assessed using validated instruments including the Reflux Disease Questionnaire (RDQ) and the Gastroesophageal Reflux Disease–Health-Related Quality of Life (GERD-HRQL) questionnaire at baseline and during follow-up. Sustained symptomatic remission and time to remission were evaluated. Data were analyzed using parametric statistical tests with a significance level of $p < 0.05$.

Results: A total of 72 participants completed the study. Sustained symptomatic remission was achieved in 69.4% of patients receiving vonoprazan compared with 41.7% in the high-dose PPI group ($p = 0.017$). The mean time to remission was significantly shorter with vonoprazan (3.1 ± 1.2 weeks) compared with high-dose PPI therapy (5.4 ± 1.6 weeks; $p < 0.001$). Greater improvements were also observed in symptom severity and quality-of-life scores, with RDQ scores decreasing from 21.6 to 7.4 in the vonoprazan group versus 21.2 to 12.8 in the PPI group.

Conclusion: Vonoprazan demonstrated superior efficacy compared with high-dose proton pump inhibitors in achieving sustained symptomatic remission and improving quality of life in patients with refractory GERD. These findings support the potential role of vonoprazan as an effective therapeutic alternative for patients with persistent reflux symptoms despite conventional treatment.

Keywords: Esophagitis; Gastroesophageal Reflux; Gastroesophageal Reflux Disease; Proton Pump Inhibitors; Quality of Life; Randomized Controlled Trial; Vonoprazan

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common chronic gastrointestinal disorders worldwide and represents a major source of healthcare utilization and patient morbidity. The condition results from the retrograde movement of gastric contents into the esophagus, leading to symptoms such as heartburn, regurgitation, and chest discomfort, and in some cases to complications including erosive esophagitis, strictures, and Barrett's esophagus. Beyond its physical manifestations, GERD significantly affects daily functioning and quality of life, contributing to sleep disturbance, impaired work productivity, and psychological distress. Due to its chronic and relapsing nature, many patients require long-term pharmacologic therapy aimed at suppressing gastric acid secretion and preventing mucosal injury (1, 2). For several decades, proton pump inhibitors (PPIs) have been regarded as the cornerstone of medical management for GERD. These agents suppress gastric acid secretion through irreversible inhibition of the gastric H^+/K^+-ATPase proton pump, thereby reducing esophageal acid exposure and promoting mucosal healing. Their introduction revolutionized the treatment of acid-related disorders and remains the standard first-line pharmacological approach. However, despite their widespread use and clinical effectiveness, accumulating evidence indicates that a considerable proportion of patients continue to experience persistent symptoms even when treated with optimized or high-dose PPI therapy. Approximately one-third of patients fail to achieve adequate symptomatic relief with conventional PPI regimens, a clinical scenario commonly described as refractory GERD (1). This therapeutic limitation highlights an important unmet need in GERD management(3, 4).

Several mechanisms have been proposed to explain the incomplete response to PPIs. These include variations in drug metabolism, particularly involving the CYP2C19 enzyme system, incomplete acid suppression during nocturnal periods, delayed onset of pharmacologic action, and the requirement for meal-dependent drug activation. These pharmacokinetic and pharmacodynamic limitations may result in insufficient or inconsistent acid inhibition in some individuals, ultimately contributing to ongoing reflux symptoms and reduced treatment satisfaction (5). Consequently, patients with refractory GERD often undergo treatment escalation with higher PPI doses, combination therapy, or additional diagnostic evaluation, yet symptom control frequently remains suboptimal(6). In response to these challenges, new pharmacologic strategies have emerged with the aim of providing more potent and reliable suppression of gastric acid secretion. Among these, potassium-competitive acid blockers (PCABs) represent a novel class of acid-suppressing agents that inhibit the gastric proton pump through a mechanism distinct from that of traditional PPIs. Unlike PPIs, which require activation in an acidic environment and irreversibly bind to active proton pumps, PCABs competitively block the potassium-binding site of the H^+/K^+-ATPase enzyme. This mechanism allows for rapid, reversible, and sustained inhibition of acid secretion, independent of meal timing or pump activation state (7, 8).

Vonoprazan, the first widely studied PCAB, has gained increasing attention as a promising alternative to conventional PPI therapy. Pharmacological studies demonstrate that vonoprazan produces faster onset of action, stronger acid suppression, and more stable intragastric pH control compared with PPIs. Additionally, its acid inhibitory effect appears less influenced by genetic polymorphisms affecting drug metabolism, potentially resulting in more consistent therapeutic responses among diverse patient populations (9). Clinical investigations have further shown that vonoprazan can effectively improve symptoms and maintain mucosal healing in patients with GERD, including those who previously failed to respond adequately to PPI therapy (10). Recent systematic reviews and meta-analyses comparing PCABs with conventional PPIs suggest that these newer agents may offer superior healing rates in erosive esophagitis and comparable or improved symptomatic relief while maintaining similar safety profiles (11, 12). These findings suggest that more consistent acid suppression may translate into better clinical outcomes for patients whose symptoms persist despite high-dose PPI therapy. Nevertheless, despite growing interest in PCAB therapy, comparative evidence focusing specifically on patients with refractory GERD remains relatively limited, and further clinical evaluation is required to determine the extent to which vonoprazan can overcome the therapeutic limitations of traditional PPI regimens(13).

Given the rising prevalence of GERD and the substantial proportion of patients who remain symptomatic despite optimized acid-suppressive therapy, identifying more effective treatment strategies is of considerable clinical importance. Understanding whether novel agents such as vonoprazan can provide superior symptomatic control compared with high-dose PPIs may help refine treatment algorithms and improve long-term outcomes for patients with refractory disease(14, 15). Therefore, the present study aims to evaluate whether vonoprazan demonstrates superior efficacy compared with high-dose proton pump inhibitor therapy in achieving sustained symptomatic remission among patients with refractory gastroesophageal reflux disease. By directly comparing these therapeutic strategies, the study seeks to clarify the potential role of vonoprazan as an alternative or next-line treatment in patients who fail to respond adequately to conventional acid-suppressive therapy.

METHODS

A prospective, randomized comparative study was conducted over a four-month period in the Islamabad–Rawalpindi region to evaluate the therapeutic effectiveness of vonoprazan compared with continued high-dose proton pump inhibitor therapy in patients with refractory gastroesophageal reflux disease. The study was carried out in collaboration with gastroenterology clinics affiliated with tertiary care hospitals and specialized outpatient centers in the region. The prospective design allowed systematic follow-up of enrolled participants and standardized assessment of clinical outcomes during the study period(10). Adult patients presenting with persistent symptoms suggestive of gastroesophageal reflux disease despite optimized pharmacological therapy were screened for eligibility. Patients were

considered to have refractory GERD when they continued to experience troublesome reflux symptoms, such as heartburn or regurgitation, despite receiving twice-daily high-dose proton pump inhibitor therapy for at least eight consecutive weeks. Individuals aged between 18 and 70 years who met these criteria and were willing to participate were considered eligible for inclusion. Patients were excluded if they had a history of upper gastrointestinal malignancy, prior anti-reflux surgery, severe hepatic or renal impairment, pregnancy or lactation, or known hypersensitivity to potassium-competitive acid blockers or proton pump inhibitors. Individuals with significant comorbid gastrointestinal conditions such as inflammatory bowel disease, peptic ulcer complications, or esophageal motility disorders were also excluded to minimize confounding factors that could influence symptom reporting or treatment response(16).

Eligible participants who satisfied the inclusion criteria were enrolled consecutively after providing written informed consent. Following enrollment, participants were randomly assigned to one of two treatment groups using a computer-generated randomization sequence to ensure allocation concealment and reduce selection bias. The intervention group received vonoprazan at a standard therapeutic dose of 20 mg once daily, whereas the control group continued their existing regimen of high-dose proton pump inhibitors administered twice daily. Both groups received treatment for a duration of eight weeks, and participants were advised to maintain their usual dietary and lifestyle practices throughout the study period to minimize behavioral influences on symptom severity(17). Baseline demographic and clinical characteristics were recorded for all participants at the time of enrollment. Information collected included age, sex, body mass index, duration of reflux symptoms, prior medication use, smoking status, and the presence of associated comorbidities. A detailed clinical assessment was performed to document symptom severity and frequency before initiation of the study treatment. To ensure standardized measurement of patient-reported outcomes, validated questionnaires were used to quantify symptom burden and quality of life(18).

Symptom severity and disease-related quality of life were assessed using two widely accepted instruments: the Gastroesophageal Reflux Disease–Health-Related Quality of Life (GERD-HRQL) questionnaire and the Reflux Disease Questionnaire (RDQ). The GERD-HRQL questionnaire evaluates the impact of reflux symptoms on daily functioning and overall well-being, whereas the RDQ focuses on the frequency and severity of core symptoms including heartburn, regurgitation, and dyspeptic discomfort. Both questionnaires were administered at baseline and during follow-up visits at four and eight weeks after initiation of therapy. Participants completed the questionnaires under the supervision of trained research personnel to ensure accuracy and completeness of responses(19). The primary outcome of interest was sustained symptomatic remission, defined as a clinically significant reduction in reflux symptom scores maintained for the duration of the treatment period. Secondary outcomes included the time to symptomatic remission and improvement in quality-of-life scores as measured by the GERD-HRQL questionnaire. Symptomatic remission was considered achieved when participants reported minimal or absent reflux symptoms with a marked reduction in RDQ and GERD-HRQL scores compared with baseline measurements. Time to remission was calculated from the initiation of treatment until the first documented assessment demonstrating sustained symptom improvement.

All collected data were entered into a secure electronic database and verified for completeness prior to analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 26. Continuous variables were summarized using means and standard deviations, while categorical variables were presented as frequencies and percentages. The distribution of quantitative variables was assessed for normality using the Shapiro–Wilk test. Since the data demonstrated normal distribution, parametric statistical tests were applied. Independent sample t-tests were used to compare continuous variables between treatment groups, whereas paired t-tests were applied to assess changes in symptom scores within groups over time. Categorical variables were compared using the chi-square test. A p-value of less than 0.05 was considered statistically significant(7). Ethical approval for the study was obtained from the Institutional Review Board of the participating medical institution prior to commencement of the research. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. All participants received detailed information regarding the objectives, procedures, and potential risks of the study, and written informed consent was obtained from each participant before enrollment. Confidentiality of patient information was strictly maintained throughout the study, and all data were anonymized prior to statistical analysis to ensure privacy and data protection.

RESULTS

A total of 78 patients were initially screened for eligibility during the study period. Six individuals were excluded due to not meeting inclusion criteria or declining participation. The remaining 72 participants were enrolled and randomized equally into two treatment groups: 36 participants received vonoprazan therapy, while 36 continued high-dose proton pump inhibitor therapy. All enrolled participants completed the follow-up period and were included in the final analysis. The baseline demographic and clinical characteristics of the participants were comparable between the two groups. The mean age of participants in the vonoprazan group was 44.8 ± 10.7 years, while the high-dose proton pump inhibitor group had a mean age of 45.6 ± 11.3 years. Male participants constituted 55.6% of the vonoprazan group and 52.8% of the high-dose PPI group. The mean body mass index was 26.2 ± 3.9 kg/m² in the vonoprazan group and 26.6 ± 4.1 kg/m² in the PPI group. The average duration of reflux symptoms prior to enrollment was 3.4 ± 1.6 years in the vonoprazan group and 3.6 ± 1.7 years in the PPI group. Baseline symptom severity assessed using the Reflux Disease Questionnaire (RDQ) and GERD-Health Related Quality of Life (GERD-HRQL) questionnaire did not differ significantly between groups ($p > 0.05$), indicating similar disease burden at study entry (Table 1).

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Table 1. Baseline Characteristics of Study Participants

Variable	Vonoprazan (n=36)	High-Dose PPI (n=36)	p-value
Mean age (years)	44.8 ± 10.7	45.6 ± 11.3	0.74
Male sex, n (%)	20 (55.6%)	19 (52.8%)	0.81
BMI (kg/m²)	26.2 ± 3.9	26.6 ± 4.1	0.68
Duration of GERD symptoms (years)	3.4 ± 1.6	3.6 ± 1.7	0.62
Baseline RDQ score	21.6 ± 4.2	21.2 ± 4.5	0.73
Baseline GERD-HRQL score	27.3 ± 5.1	26.9 ± 5.4	0.79

Both treatment groups demonstrated measurable improvement in symptom severity over the study period. However, the magnitude of improvement was significantly greater in the vonoprazan group. At the end of eight weeks, the mean RDQ score decreased from 21.6 ± 4.2 to 7.4 ± 3.1 in participants receiving vonoprazan, representing a mean reduction of 14.2 points ($p < 0.001$). In comparison, the high-dose PPI group showed a reduction from 21.2 ± 4.5 to 12.8 ± 4.0, corresponding to a mean improvement of 8.4 points ($p < 0.001$). Between-group comparison demonstrated a statistically significant greater reduction in RDQ scores in the vonoprazan group ($p = 0.003$). Quality-of-life outcomes followed a similar pattern. The GERD-HRQL score improved substantially in both groups; however, participants receiving vonoprazan experienced greater improvement. Mean GERD-HRQL scores declined from 27.3 ± 5.1 at baseline to 8.6 ± 3.8 at week eight in the vonoprazan group, compared with a reduction from 26.9 ± 5.4 to 14.7 ± 4.5 in the high-dose PPI group. The difference in improvement between the two groups was statistically significant ($p = 0.002$) (Table 2).

Table 2. Changes in Symptom Severity and Quality of Life

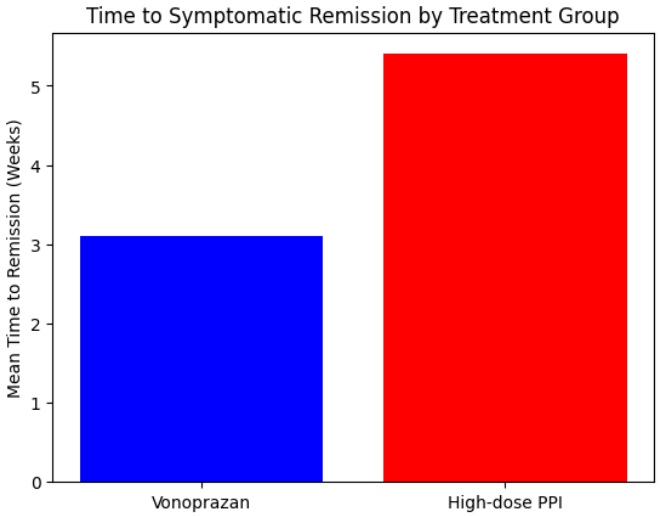
Outcome Measure	Vonoprazan (n=36) Baseline	Vonoprazan Week 8	High-Dose PPI (n=36) Baseline	High-Dose PPI Week 8	p-value
RDQ score	21.6 ± 4.2	7.4 ± 3.1	21.2 ± 4.5	12.8 ± 4.0	0.003
GERD-HRQL score	27.3 ± 5.1	8.6 ± 3.8	26.9 ± 5.4	14.7 ± 4.5	0.002

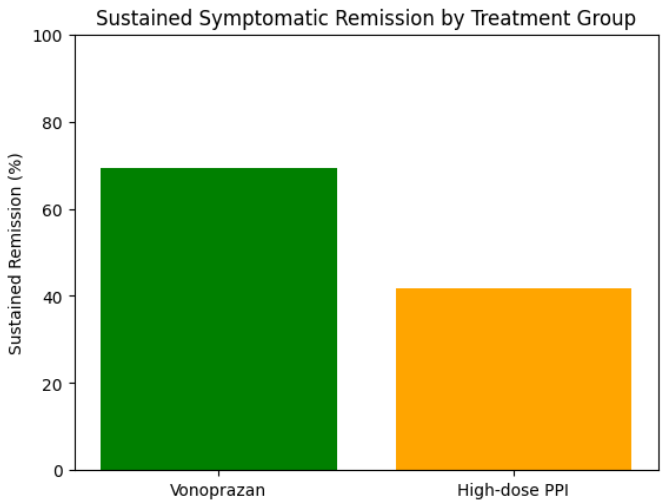
Sustained symptomatic remission was achieved in 25 participants (69.4%) in the vonoprazan group compared with 15 participants (41.7%) in the high-dose PPI group. The difference between the two groups was statistically significant ($\chi^2 = 5.64$, $p = 0.017$). Furthermore, the time required to achieve remission differed notably between treatment groups. The mean time to remission was 3.1 ± 1.2 weeks among participants treated with vonoprazan, whereas the high-dose PPI group required an average of 5.4 ± 1.6 weeks to achieve comparable symptom control ($p < 0.001$).

Table 3. Treatment Outcomes

Outcome	Vonoprazan (n=36)	High-Dose PPI (n=36)	p-value
Sustained symptomatic remission, n (%)	25 (69.4%)	15 (41.7%)	0.017
Mean time to remission (weeks)	3.1 ± 1.2	5.4 ± 1.6	<0.001
Mean RDQ reduction	14.2 ± 4.0	8.4 ± 3.8	0.003
Mean GERD-HRQL reduction	18.7 ± 5.2	12.2 ± 5.6	0.002

The graphical representation of sustained remission rates demonstrated a markedly higher proportion of patients achieving remission in the vonoprazan group compared with those receiving high-dose PPIs. Similarly, the chart illustrating time to remission indicated that symptom control occurred earlier among patients treated with vonoprazan. Overall, improvements in symptom burden and quality-of-life measures were consistently greater in the vonoprazan group across all outcome assessments during the study period.





INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

DISCUSSION

The present study evaluated the comparative effectiveness of vonoprazan and high-dose proton pump inhibitor therapy in patients with refractory gastroesophageal reflux disease within a clinical population in the Islamabad–Rawalpindi region. The findings demonstrated that both treatment strategies resulted in measurable clinical improvement; however, vonoprazan therapy produced substantially greater reductions in symptom burden and higher rates of sustained symptomatic remission. In the current cohort, sustained remission was achieved in 69.4% of patients treated with vonoprazan compared with 41.7% among those who continued high-dose proton pump inhibitors. In addition, the mean time required to achieve remission was notably shorter with vonoprazan therapy (3.1 ± 1.2 weeks) than with conventional therapy (5.4 ± 1.6 weeks). Improvements in disease-related quality of life also favored vonoprazan, with GERD-HRQL scores declining from 27.3 to 8.6 in the intervention group compared with a reduction from 26.9 to 14.7 in the control group.

These observations were consistent with the evolving understanding of acid suppression pharmacology. Conventional proton pump inhibitors inhibit active proton pumps irreversibly but require activation in an acidic environment and are influenced by meal timing and metabolic variability. Such characteristics may lead to incomplete or inconsistent acid suppression in certain individuals, particularly during nocturnal periods or among rapid metabolizers. In contrast, potassium-competitive acid blockers inhibit the proton pump through reversible blockade of the potassium-binding site, enabling rapid and sustained acid suppression regardless of pump activation status. This pharmacodynamic difference likely contributed to the more rapid symptom resolution observed in the vonoprazan group in the present study(20, 21).

Comparable trends have been reported in previous clinical investigations evaluating the efficacy of potassium-competitive acid blockers in GERD management. Several randomized trials and pooled analyses have demonstrated higher healing rates of erosive esophagitis with potassium-competitive acid blockers compared with conventional proton pump inhibitors, with healing rates frequently exceeding 80–90% after eight weeks of therapy. Symptom remission rates in those studies have generally ranged from approximately 65% to 75% among patients receiving vonoprazan, while comparable proton pump inhibitor regimens achieved remission in roughly 40–60% of cases. The remission rate of 69.4% observed in the present study therefore aligned closely with previously reported clinical outcomes, supporting the reproducibility of these therapeutic benefits across different patient populations(22, 23). The improvement in quality-of-life measures observed in the current study further reinforced the clinical relevance of enhanced acid suppression. GERD is well recognized for its substantial impact on daily functioning, sleep quality, and overall well-being. The substantial decline in GERD-HRQL scores in the vonoprazan group indicated that more effective symptom control translated into tangible improvements in patient-reported outcomes. Such findings were particularly meaningful in the context of refractory GERD, a condition in which persistent symptoms frequently impair work productivity and psychosocial health(24, 25).

The study also contributed region-specific clinical data from a South Asian population, an area where evidence regarding newer acid-suppressive therapies remains limited. Differences in dietary patterns, healthcare access, and genetic factors influencing drug metabolism may affect treatment outcomes in this region. The observation that vonoprazan demonstrated favorable efficacy within this cohort suggested that the therapeutic advantages reported in other geographic settings may also be applicable within the Pakistani population(9, 26). Several methodological strengths enhanced the reliability of the present findings. The prospective randomized design minimized selection bias and allowed systematic follow-up of treatment outcomes. The use of validated symptom and quality-of-life instruments, including the Reflux Disease Questionnaire and the GERD-HRQL scale, ensured standardized assessment of patient-reported outcomes. In addition, the complete follow-up of all enrolled participants reduced the likelihood of attrition bias and strengthened the internal validity of the results(5, 27).

Despite these strengths, certain limitations should be acknowledged when interpreting the findings. The study was conducted over a relatively short observation period of eight weeks, which limited evaluation of long-term therapeutic durability and safety. Acid-suppressive therapies are often required for extended durations in patients with chronic reflux disease, and long-term outcomes may differ from those observed during short-term treatment. The sample size was modest and confined to a specific geographic region, which may restrict the generalizability of the findings to broader populations. Furthermore, endoscopic evaluation was not performed systematically during follow-up, preventing direct assessment of mucosal healing and limiting analysis primarily to symptom-based outcomes(7). Additional research may therefore help clarify several unresolved aspects of potassium-competitive acid blocker therapy in refractory GERD. Larger multicenter randomized trials with longer follow-up periods would provide more robust evidence regarding sustained remission, relapse rates, and long-term safety. Future studies incorporating objective measures such as pH monitoring or endoscopic assessment could further elucidate the relationship between acid suppression and mucosal healing. Investigations evaluating cost-effectiveness, patient adherence, and combination treatment strategies may also assist clinicians in optimizing therapeutic algorithms for refractory reflux disease(26).

Overall, the present findings contributed to the growing body of evidence suggesting that more potent and rapid acid suppression may improve clinical outcomes in patients who fail to respond adequately to conventional therapy. The higher remission rate, shorter time to symptom control, and greater improvements in quality of life observed with vonoprazan therapy supported its potential role as an effective alternative in the management of refractory gastroesophageal reflux disease.

CONCLUSION

The findings of this study indicated that vonoprazan provided significantly greater symptomatic improvement and higher sustained remission rates compared with high-dose proton pump inhibitor therapy in patients with refractory gastroesophageal reflux disease. Faster symptom resolution and greater quality-of-life improvement were also observed with vonoprazan treatment. These results suggested that vonoprazan may represent a valuable therapeutic option for patients who remain symptomatic despite optimized conventional therapy, particularly in clinical settings where refractory GERD remains a persistent management challenge.

AUTHOR CONTRIBUTION

Author	Contribution
Muhammad Azhar Sherkheli	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Muhammad Waqas Irshad	Methodology, Investigation, Data Curation, Writing - Review & Editing
Durr-e-Shahwar Malik	Investigation, Data Curation, Formal Analysis, Software
Kainat Balach	Software, Validation, Writing - Original Draft

REFERENCES

1. Hsu P, Kim N, Goh K, Wu D-C. Diagnosis and Management of Gastroesophageal Reflux Disease. Gastroenterology Research and Practice. 2013;2013.

2. Zou S, Ouyang M, Cheng Q, Shi X, Sun M. Acid-suppressive drugs: A systematic review and network meta-analysis of their nocturnal acid-inhibitory effect. Pharmacotherapy. 2024;44(2):171-83.

3. Patel A, Laine L, Moayyedi P, Wu J. AGA Clinical Practice Update on Integrating Potassium-Competitive Acid Blockers Into Clinical Practice: Expert Review. Gastroenterology. 2024;167(6):1228-38.

4. Zhuang Q, Chen S, Zhou X, Jia X, Zhang M, Tan N, et al. Comparative Efficacy of P-CAB vs Proton Pump Inhibitors for Grade C/D Esophagitis: A Systematic Review and Network Meta-analysis. Am J Gastroenterol. 2024;119(5):803-13.

5. Scott D, Marcus E, Sachs G. Vonoprazan: MarKed Competition for PPIs? Digestive Diseases and Sciences. 2016;61:1783-4.

6. Kang N, Kang MG, Lee SE, Kang SY, Jo EJ, Lee JH, et al. Efficacy and Safety of Fexuprazan Versus Esomeprazole for Gastroesophageal Reflux Disease-Related Chronic Cough: A Randomized, Double-Blind, Active-Controlled Exploratory Trial. Lung. 2025;203(1):59.

7. Jain S, Agrawal A, Gupta A. Potassium-competitive acid blockers (PCABs): A novel era in gastric acid suppression. International Journal of Pharmaceutical Chemistry and Analysis. 2025.

8. Li F, Tan J, Qin L. Efficacy, safety and cost-effectiveness of potassium-competitive acid blockers versus proton pump inhibitors in gastroesophageal reflux disease. Scand J Gastroenterol. 2026;61(2):241-56.

9. Sugano K. Vonoprazan fumarate, a novel potassium-competitive acid blocker, in the management of gastroesophageal reflux disease: safety and clinical evidence to date. Therapeutic Advances in Gastroenterology. 2018;11.

10. Shinozaki S, Osawa H, Hayashi Y, Miura Y, Lefor A, Yamamoto H. Long-term vonoprazan therapy is effective for controlling symptomatic proton pump inhibitor-resistant gastroesophageal reflux disease. Biomedical reports. 2021;14 3:32.

11. Agago D, Hanif N, Kumar ASA, Arsalan M, Dhanjal MK, Hanif L, et al. Comparison of Potassium-Competitive Acid Blockers and Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Cureus. 2024;16.

12. Simadibrata D, Syam A, Lee Y. A comparison of efficacy and safety of potassium-competitive acid blocker and proton pump inhibitor in gastric acid-related diseases: A systematic review and meta-analysis. Journal of Gastroenterology and Hepatology. 2022;37:2217-28.

13. Jankovic K, Gralnek IM, Awadie H. Emerging Long-Term Risks of the Use of Proton Pump Inhibitors and Potassium-Competitive Acid Blockers. Annu Rev Med. 2025;76(1):143-53.

14. Marabotto E, Calabrese F, Pasta A, Visaggi P, de Bortoli N, Mari A, et al. Evaluating Vonoprazan for the treatment of erosive GERD and heartburn associated with GERD in adults. Expert Opin Pharmacother. 2024;25(17):2319-25.

15. Savarino EV, Barberio B, Scarpignato C, Savarino V, Barbara G, Bertin L, et al. Italian guidelines for the diagnosis and management of gastro-esophageal reflux disease: Joint consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), and General Medicine (SIMG). Dig Liver Dis. 2025;57(8):1550-77.

16. Wang Y, Dai X, Zhang X. Network Meta-Analysis of Comparing Different Dosages of Potassium-Competitive Acid Blocker With Proton-Pump Inhibitor in Acid-Related Disorders. Clin Transl Gastroenterol. 2024;15(11):e00776.

17. Shang H, Mao H, Wang J, Tian X, Zheng K, Wang J. Optimizing acid-related disease management: insights into potassium-competitive acid blockers and proton pump inhibitors. Eur J Clin Pharmacol. 2025;81(12):1773-86.

18. Visaggi P, Bertin L, Pasta A, Calabrese F, Ghisa M, Marabotto E, et al. Pharmacological management of gastro-esophageal reflux disease: state of the art in 2024. Expert Opin Pharmacother. 2024;25(15):2077-88.

19. Davis TA, Gyawali CP. Potassium-competitive acid blockers. Curr Opin Gastroenterol. 2025;41(6):389-98.

20. Huang KZ, Weber HC. Potassium-competitive acid blockers and acid-related disorders. Curr Opin Endocrinol Diabetes Obes. 2024;31(3):107-14.

21. Leowattana W, Leowattana T. Potassium-competitive acid blockers and gastroesophageal reflux disease. World J Gastroenterol. 2022;28(28):3608-19.

22. Scarpignato C, Hunt RH. Potassium-competitive Acid Blockers: Current Clinical Use and Future Developments. Curr Gastroenterol Rep. 2024;26(11):273-93.

23. Antequera CM, Orleck K, Jacob R, Kenneally A, Wright WL. Potassium-competitive acid blockers: rethinking acid suppression for gastroesophageal reflux disease and Helicobacter pylori. Postgrad Med. 2024;136(2):131-40.

24. Howden CW. The Role of P-CABs in GERD. Am J Gastroenterol. 2025;120(5):993-8.

25. Jang Y, Park J, Kang D, Kim JH, Choi HS, Jeon HL, et al. Safety of Potassium-Competitive Acid Blockers Compared With Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease and Peptic Ulcer Disease: A Systematic Review and Meta-Analysis. J Gastroenterol Hepatol. 2026;41(1):28-40.

26. Tietto A, Faggin S, Scarpignato C, Savarino EV, Giron MC. Safety of potassium-competitive acid blockers in the treatment of gastroesophageal reflux disease. Expert Opin Drug Metab Toxicol. 2025;21(1):53-68.

27. Fung S. Vonoprazan: A Review in Erosive Esophagitis and Non-Erosive Gastro-Esophageal Reflux Disease. Drugs. 2025;85(7):945-55.