

Journal of The Association of Physicians of India



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Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹15,000 (India). The Journal is dispatched within India by surface mail.

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Published and Edited by

Prof. Dr Jyotirmoy Pal, on behalf of **The Association of Physicians of India**, Journal of The Association of Physicians of India, Unit No. 3301, Prestige Turf Tower 'D', Shakti Mill Lane, Off. Dr. E. Moses Road, Near Mahalaxmi Station (West), Mumbai-400 011.

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Supplement Copy

Redefining Acid Suppression in Acid Peptic Disorders: The Emerging Role of Prazans

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Redefining Acid Suppression in Acid Peptic Disorders: The Emerging Role of Prazans



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Received: 27 June 2026; Accepted: 15 July 2026

ABSTRACT

Acid peptic disorders (APDs) affect approximately 38% of the population in India and commonly present with overlapping phenotypes, including gastroesophageal reflux disease (GERD), dyspepsia, and peptic ulcer disease (PUD), necessitating uniform and sustained acid suppression. Proton pump inhibitors (PPIs) have several clinical limitations, including a delayed onset of action of 3–5 days, incomplete 24-hour acid control with nocturnal acid breakthrough, high nonresponse rates of approximately 40% in GERD and 37% in nonerosive reflux disease (NERD), and variability related to cytochrome P450 2C19 (CYP2C19) metabolism, meal dependency, and drug interactions. Collectively, these limitations contribute to inconsistent real-world efficacy.

Potassium-competitive acid blockers: Mechanistic and pharmacodynamic superiority: Potassium-competitive acid blockers (P-CABs) directly and reversibly inhibit the H^+/K^+ -ATPase without requiring acid activation, thereby enabling a rapid onset of action from the first dose. Inhibition of both active and inactive proton pumps provides continuous and sustained acid suppression. P-CABs offer true 24-hour intragastric pH control, including nocturnal control, with a higher parietal-cell concentration of approximately 100,000-fold compared with approximately 1,000-fold for PPIs. Their meal-independent administration, low CYP-related variability, and minimal potential for drug interactions allow a more predictable response across patient populations.

Tegoprazan: Rapid onset, nocturnal control, and comorbidity advantages—Tegoprazan may be considered in the following clinical settings: symptomatic GERD and on-demand treatment of GERD/NERD, because its rapid onset of action within approximately 30 minutes may facilitate early symptom relief and flexible dosing; nocturnal acid breakthrough, because it provides nocturnal pH control, with an intragastric pH of ≥ 4 maintained for approximately 66% of the night; patients at cardiovascular risk receiving antiplatelet therapy, dual antiplatelet therapy, or atorvastatin, because its lower interaction potential involving CYP2C19 and CYP3A4 may reduce the risk of gastrointestinal bleeding and treatment failure related to dyslipidemia; and patients with renal or metabolic comorbidities, because it has shown favorable renal safety signals and a lower decline in serum creatinine levels.

Vonoprazan: Potency, high acid burden, and eradication efficacy—Vonoprazan may be preferred in the following situations: refractory GERD after PPI failure, because its potent and sustained acid suppression may overcome an inadequate response to PPIs; severe GERD and other high-acid-burden states, because it provides consistent and prolonged intragastric pH elevation; *Helicobacter pylori* eradication, because it may serve as a preferred treatment backbone, with reported eradication rates of approximately 92.6% through sustained maintenance of an intragastric pH > 6 ; nonsteroidal anti-inflammatory drug-associated ulcers, because it may reduce ulcer recurrence and the risk of gastrointestinal bleeding; complex or recurrent PUD, because its stronger acid suppression may support faster and more durable healing; and hepatic disease, because it has demonstrated favorable outcomes, with fewer liver-related complications than PPIs.

Fexuprazan—Stability and extraesophageal reflux phenotypes: Fexuprazan may be considered for extraesophageal reflux, including laryngopharyngeal reflux and atypical GERD, because it has been associated with improvements in reflux symptom indices and airway-related symptoms.

Conclusion: Tegoprazan may be preferred when rapid symptom relief, nocturnal acid control, and a favorable drug-interaction profile are required. Vonoprazan may be preferred when maximal acid suppression and enhanced *H. pylori* eradication efficacy are needed. Fexuprazan may be considered for laryngopharyngeal reflux and other atypical or extraesophageal GERD phenotypes.

Keywords: Acid peptic disorders, Fexuprazan, Potassium-competitive acid blockers, Proton pump inhibitors, Tegoprazan, Vonoprazan.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1676

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How to cite this article: Goenka M, Ghoshal UC, Yadav D, et al. Redefining Acid Suppression in Acid Peptic Disorders: The Emerging Role of Prazans. J Assoc Physicians India 2026;74(8): 6–26.

OVERVIEW OF ACID PEPTIC DISORDERS

Acid peptic disorders (APDs) arise when gastric acid overwhelms mucosal defense mechanisms, leading to symptomatic and structural gastrointestinal damage. They are characterized by epigastric pain associated with dyspepsia, bloating, abdominal fullness, nausea, or early satiety.^{1,2} APDs encompass a wide range of clinical conditions, which are illustrated in Figure 1.^{1,3–9} Due to their similar pathophysiological characteristics, functional dyspepsia and gastroesophageal reflux disease frequently coexist.⁴

Acid peptic disorders highly prevalent in India, with a cross-sectional study revealing an overall prevalence of 38.1%.¹⁰ Globally, the burden of gastroesophageal reflux disease (GERD) nearly doubled from 450 million cases in 1990 to over 825 million in 2021.¹¹ GERD prevalence in India ranges from 8%–28.5%, with a pooled prevalence

of 15.6%.¹² Peptic ulcer disease (PUD) continues to affect 8 million individuals annually, with a lifetime risk of 5%–10%.¹³ These conditions significantly impair the quality of life and healthcare utilization, thereby making a precise diagnosis and early treatment crucial.^{1,2,4}

Evolution of Acid Peptic Disorder Management

The goals of therapy for APD include symptom relief, promoting restoration of mucosal integrity, addressing underlying causes, and preventing complications and recurrence.^{1,14}

Gastric acid control remains the cornerstone of management of APDs. As illustrated in Figure 2, since the introduction of histamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), and more recently potassium-competitive acid blockers (P-CABs), gastric acid control has substantially

evolved over the past 5 decades.^{4,15,16,17,18} Adjunctive therapies including alginate-based formulations and prokinetics such as itopride and domperidone are particularly beneficial in managing dyspeptic symptoms.^{15,17,18}

Physiological Requirements for Effective Acid Control

Role of Intragastric pH in Restoration of mucosal integrity

Gastric acid secretion is controlled through an integrated network of neural, paracrine, and hormonal signals that ultimately regulate the activity of parietal cells, all of which converge at proton pump hydrogen–potassium adenosine triphosphatase (H⁺/K⁺-ATPase) in parietal cells (Fig. 3). As the terminal step in acid production, the proton pump represents the most critical target for pharmacological intervention.¹⁹

Under resting conditions, proton pumps remain within intracellular compartments

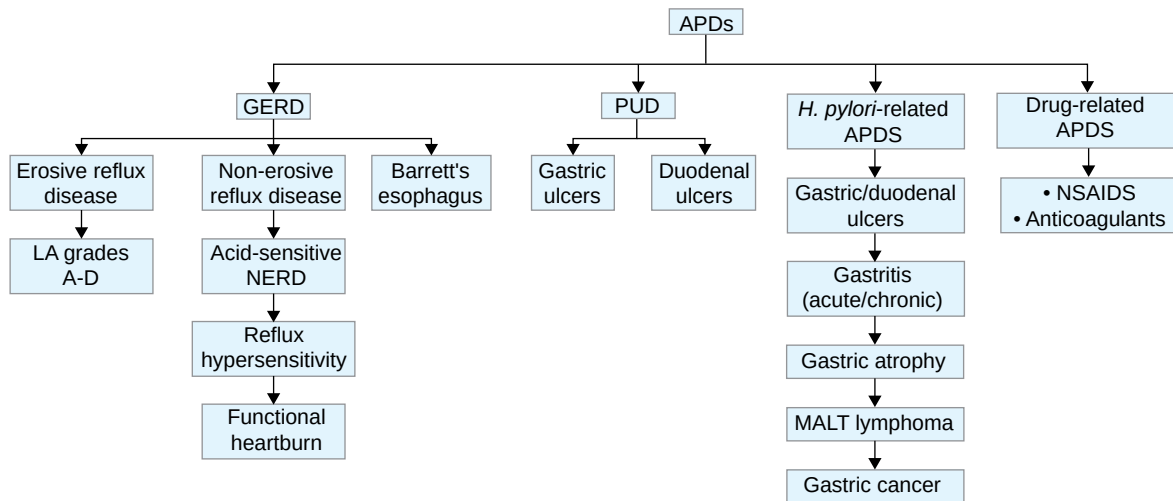


Fig. 1: Clinical conditions associated with acid peptic disorders^{1,6–9,14} [APD: Acid peptic diseases; GERD: Gastroesophageal reflux disease; *H. pylori*: *Helicobacter pylori*; LA: Los Angeles; MALT: Mucosa-associated lymphoid tissue; NERD: Non-erosive reflux disease; NSAID: Non-steroidal anti-inflammatory drugs; PUD: Peptic ulcer disease]

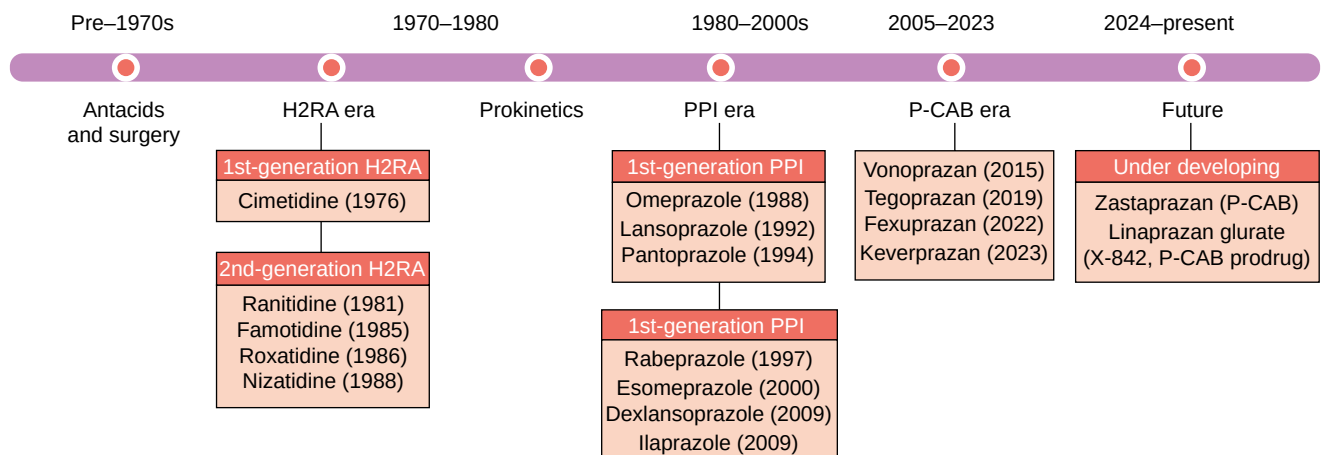


Fig. 2: Timeline of key discoveries in the management of acid peptic disorders^{15–17} [H2RA: Histamine-H2 receptor antagonist; PCAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor]

- Has been associated with robust efficacy in ulcer healing and *H. pylori* eradication, with rates of 96.4% and 94%, respectively.³⁵
- Primarily metabolized by CYP2C19 and CYP3A4 isoforms, which can result in drug interactions. It is therefore recommended to avoid coadministration with clopidogrel due to reduced antiplatelet efficacy and increased risk of cardiovascular events.²⁹

Pantoprazole

- Proven efficacy in erosive esophagitis, with a cumulative healing rate of 88% at 8 weeks with a 40 mg/day dose.³⁶
- Effective in acute duodenal ulcer healing in 71% at 2 weeks.³⁷
- Triple therapy regimens achieve 90.7% *H. pylori* eradication rates.³⁸
- Is effective against nonsteroidal anti-inflammatory drug (NSAID)-associated and peptic ulcer lesions.³⁹
- Does not attenuate the effect of clopidogrel or affect platelet aggregation in patients on dual antiplatelet therapy (DAPT).²⁹
- Use cautiously with diclofenac and monitor glycemic levels in patients on dipeptidyl peptidase-4 inhibitors.²⁹

Rabeprazole

- Among the most potent PPIs for 24-hr acid control.⁴⁰
- Lower CYP2C19 reduces interaction risk with clopidogrel vs. other PPIs.⁴¹
- Faster activation due to high pKa value (~5.0) and early onset of action.⁴²
- Demonstrates rapid and sustained relief of GERD symptoms, including improvement in sleep disturbances.^{42,43}

- Indian real-world study showed higher complete response rates with rabeprazole (83.3%) vs. pantoprazole (62.1%) and esomeprazole (65.7%).⁴²

Esomeprazole

- Provides the highest sustained acid control over 24-hours compared with standard doses of several other PPIs.⁴⁴
- Maintains the highest intragastric pH >4.0 for a mean of 14.0 h, when compared to those of other PPIs such as esomeprazole, rabeprazole, omeprazole, lansoprazole, and pantoprazole.³¹
- Has been associated with superior healing rates in erosive esophagitis at 4 and 8 weeks relative to comparator PPIs.⁴⁵
- CYP2C19 metabolism may reduce clopidogrel activity; interaction caution is needed.²⁹

Lansoprazole

- Effectively relieves dyspepsia in addition to reflux symptoms in patients with GERD, improving heartburn in 75.7% of patients and postprandial fullness in 68.7% of patients.⁴⁶
- Maintains long-term healing in duodenal ulcer disease, with 70%–85% of patients remaining ulcer-free at 12 months.⁴⁷
- Significantly reduces the percentage of days with upper abdominal discomfort vs. placebo (~34–35% vs. 19%) with a higher number of patients achieving complete symptom resolution (44% vs. 29%).⁴⁸

Adverse Effects Associated with Proton Pump Inhibitor Use

- Despite being widely available and frequently prescribed, PPIs have a number

of potentially serious complications that could have a long-term negative influence on patients (Fig. 4).⁴⁹

- The most frequently reported adverse events associated with PPI therapy are headache, abdominal pain, nausea, diarrhea, constipation, and flatulence, which are generally mild and self-limiting. Long-term PPI exposure has also been associated with an increased risk of enteric infections, vitamin B12 deficiency, hypomagnesemia, osteoporosis-related fractures, and iron deficiency.⁴⁹
- Several observational studies and meta-analyses have reported associations between prolonged PPI exposure and major adverse clinical outcomes. A meta-analysis involving more than 600,000 participants reported a modest increase in the risk of chronic kidney disease (HR approximately 1.26–1.35). Similarly, PPI use has been associated with a higher risk of acute kidney injury (adjusted RR approximately 1.6–2.0). Observational cardiovascular studies have reported a small increase in myocardial infarction and stroke risk, particularly among individuals receiving concomitant antiplatelet therapy; however, causality remains unproven. In patients with cirrhosis, long-term PPI exposure has been associated with an increased risk of hepatic encephalopathy and infections. Current evidence regarding hepatocellular carcinoma remains inconsistent, with no definitive causal relationship established. Therefore, PPIs should be prescribed at the lowest effective dose and for the shortest clinically appropriate duration.^{49–51}

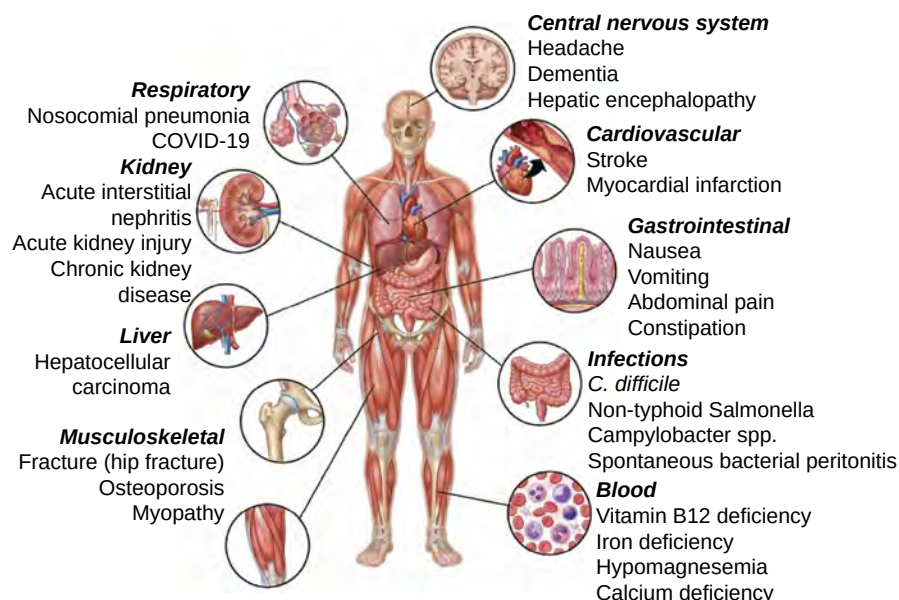


Fig. 4: Potential side effects associated with the use of proton pump inhibitors⁴⁹

UNMET CLINICAL NEEDS WITH PROTON PUMP INHIBITORS

Executive Summary

Proton pump inhibitors (PPIs) have long been the standard of care for acid-related disorders and are commonly used globally, including in India. However, despite their established efficacy, PPIs have several intrinsic limitations, including delayed onset of action, interpatient variability, and suboptimal control of nocturnal acid secretion, that may affect optimal acid control.^{15,52,53} Although strategies such as extended half-life PPIs and modified-release formulations were developed, they achieved only modest incremental improvements in acid control. These limitations underscore the need for more potent, rapid, and durable acid control strategies.¹⁵

Pharmacological Limitations of Proton Pump Inhibitors

Acid-labile Nature

Proton pump inhibitors are benzimidazole prodrugs that are acid-labile and are easily degraded in the gastric lumen. Therefore, PPIs need an enteric coating or co-administration with an acid-neutralizing agent such as sodium bicarbonate to survive gastric transit to achieve adequate systemic absorption after oral administration.^{50,54}

Slow Onset of Action

Proton pump inhibitors have a relatively slow onset of action and require 3–5 days on average to achieve optimum level of gastric acid secretion inhibition.⁵⁵ They are prodrugs that require activation in the acidic environment of the stomach, where they inhibit gastric acid secretion by forming a disulfide bond with H⁺/K⁺-ATPase.⁵⁶

Inadequate Night-time Acid Control

Proton pump inhibitors only inhibit actively secreting proton pumps; therefore, repeated dosing is necessary for adequate and complete acid inhibition.^{50,57} PPIs inhibit approximately 70% of active proton pumps at a steady state when administered once-daily, and nearly 25% of proton pumps are regenerated each day, allowing ongoing acid secretion.⁵⁸ Even with twice-daily dosing, only about 80% of pumps are inhibited, still leaving 20% active pumps at steady state.⁵⁹ In addition, the short plasma half-life of most PPIs (approximately 1–2 hours) limits their duration of action, contributing to nocturnal acid breakthrough despite additional evening dosing.²⁴

Meal-time Dependency

Conventional PPIs are prodrugs requiring protonation in an acidic environment to attain their pharmacologically active state. For optimal activation, the drug must reach the secretory canaliculi of stimulated parietal cells, where acid secretion is increased following a meal. Accordingly, PPIs are recommended to be administered approximately 30 minutes before meals to ensure maximal therapeutic effect.⁶⁰

Maintenance of 24-hour Intragastric pH Levels

Maintenance of intragastric pH >4.0 is a key pharmacodynamic marker for symptom control and restoration of mucosal integrity in GERD.²⁴ Comparative studies show that standard once-daily PPIs maintain pH >4 for only 10–14 hours over 24 hours, leaving prolonged periods of incomplete acid control.^{24,31}

For *H. pylori* eradication, sustained intragastric pH ≥6 is needed because bacterial replication occurs near neutral pH and antibiotic susceptibility improves.⁶¹ Conventional PPIs often fail to maintain pH >6 for >75% of the dosing interval, limiting eradication efficacy.⁶²

Variability Due to Cytochrome P450 2C19 (CYP2C19) Polymorphism

Multiple studies demonstrate considerable interindividual differences in the clinical response to PPIs, largely attributed to their hepatic metabolism via CYP2C19 enzymes. These enzymes can influence both the pharmacokinetic and pharmacodynamic profiles of PPIs, resulting in changes in their systemic exposure and acid-suppressive effects.^{63,64} It also increases the potential for clinically relevant drug–drug interactions, particularly with agents that inhibit or compete for this pathway (e.g., clopidogrel, certain antidepressants, and antifungal agents), which may further alter PPI efficacy or safety.^{63,64}

CYP2C19 polymorphisms result in distinct metabolizer phenotypes with significantly different pharmacokinetic profiles: homozygous extensive metabolizers (carrying two mutated alleles), heterozygous extensive metabolizers (carrying one mutant and one wild-type allele), and poor metabolizers (carrying two wild-type alleles).⁶⁵ A study involving 110 Indian patients reported that 23.64% were normal metabolizers, 47.23% were poor metabolizers, and 35.45% were ultra-rapid metabolizers.⁶⁴ Rapid metabolizers and ultra-rapid metabolizers may experience therapeutic failures because of increased metabolic inactivation, whereas intermediate and poor metabolizers may experience enhanced therapeutic effects, but with greater PPI-related side effects.^{66,67}

The impact of CYP2C19 polymorphism on the metabolism of PPIs varies, being greatest with omeprazole, followed by lansoprazole, dexlansoprazole, pantoprazole, esomeprazole, and rabeprazole.⁶⁷ Systemic exposure (AUC) to PPIs varies substantially across metabolizer phenotypes. For example, the AUC for omeprazole is approximately 7.5-times higher in poor metabolizers compared to that in homozygous extensive metabolizers, about 4.5-times higher for lansoprazole, and about 4-times higher for rabeprazole.⁶⁸

CYP2C19 phenotyping is not routinely conducted in clinical practice, limiting the reliability of PPIs as a consistent acid-suppressive strategy due to their unpredictable efficacy and safety.⁶⁴

Patient Subgroups with Inadequate Proton Pump Inhibitor Response

A prospective observational study conducted by Prabakar *et al.* over 6 months in an Indian tertiary care teaching hospital including 100 patients with gastrointestinal disorders revealed that only 16% of the patients were satisfied with the overall usage of PPIs. Common reasons for dissatisfaction with PPIs were inadequate symptom relief, dosing frequency, and long-term costs.⁶⁹

Gastroesophageal Reflux Disease

Many studies have shown that a substantial proportion of patients with GERD continue to experience persistent symptoms despite PPI therapy.

Approximately two-thirds fail to achieve symptom control after the first PPI dose in symptomatic patients, with ~50% continuing to report symptoms after 3 days.⁵⁵

Only 36% of patients receiving prescription therapy remain asymptomatic despite treatment.⁷⁰

More than half of patients on daily PPI continue to experience persistent, troublesome GERD symptoms.⁷¹

In severe erosive disease (LA grade C/D), 4%–15% fail to heal completely, and relapse remains common despite maintenance therapy.⁷²

Approximately 40% of patients with GERD experience an insufficient response to PPI therapy. Refractory GERD (rGERD) is characterized by the persistence of symptoms despite optimal PPI treatment for at least 8 weeks, along with documented ongoing gastroesophageal reflux. There are several limitations of PPIs that contribute to rGERD, including the requirement for a high PPI concentration in parietal cells, a short plasma half-life (1–2 hours), the need for dosing before meals, CYP2C19 polymorphism, instability in acidic environments, and a limited residence time in systemic circulation.⁵⁸

GERD imposes a substantial clinical and economic burden, with persistent symptoms impairing quality of life and increasing healthcare use, long-term medication, and productivity loss. Patients with refractory GERD incur up to 70% higher annual healthcare costs globally, with additional indirect productivity losses. Although India-specific data are limited, the overall burden remains considerable due to ongoing symptoms and long-term treatment needs.⁷³

Nocturnal Acid Breakthrough

Nocturnal acid breakthrough (NAB) is defined as intragastric pH <4 for more than 60 minutes overnight (approximately from 10 PM to 6 AM),

which remains a significant unmet need in the management of GERD.⁷⁴

In a group of adult patients experiencing heartburn at least once a week, 79% reported nocturnal symptoms, which impaired sleep in 75% and affected next-day functioning in 40%.⁷²

Several studies indicate that once-daily PPI therapy is less effective for nighttime heartburn (up to 53%) compared with daytime symptoms (up to 66%).⁷²

Nonerosive Reflux Disease

Nonerosive reflux disease (NERD) represents approximately two-thirds of GERD patients.⁷⁵

Estimates suggest a 2–3-fold longer lag time to symptomatic response to PPI therapy.⁷²

Based on the findings from the ReQuestTM questionnaire, the median time to first symptom relief was 2 days, whereas sustained symptom relief required 10–13 days for patients with NERD treated with either pantoprazole or esomeprazole.⁷²

Systematic review reveals a pooled response rate to PPI of approximately 37% at the end of 4 weeks.⁷²

H. pylori Infection

Twice-daily dosing of PPIs often achieves only up to 69% pH >6 HTR, after the first few days of treatment, which may be insufficient for effective *H. pylori* eradication.²⁷

Furthermore, PPI therapy may induce coccoid transformation of *H. pylori*, reducing antibiotic susceptibility and eradication rates.⁷⁶

Patients on Antiplatelet/Anticoagulant Therapy

In patients receiving dual antiplatelet therapy, PPIs are often prescribed to reduce gastrointestinal bleeding risk, but CYP2C19-mediated interactions may reduce clopidogrel activation.^{77,78}

Meta-analysis shows co-prescription of PPI and antiplatelet therapy may be associated with increased risk of MACE.⁷⁹ This was initially assumed to be associated with all PPIs but later found to be restricted to esomeprazole and omeprazole.^{77–79}

These findings underscore the importance of careful therapeutic selection for patients receiving antiplatelet therapy to balance gastrointestinal protection against potential cardiovascular risks (Fig. 5).⁷⁷

INTRODUCTION TO PRAZANS

Prazans (P-CABs) represent a novel class of acid-suppressant drugs demonstrating tremendous potential in improving the treatment of APDs. This class presently includes fexuprazan, keverprazan, revaprazan, tegoprazan, and vonoprazan, along with additional drugs under development (i.e., linaprazan, zastaprazan).^{53,80} Currently in India, only fexuprazan, vonoprazan, and tegoprazan are available.^{4,81}

Evolution of Prazans

Prazans, a novel class of antisecretory agents, were first developed in the early 1980s to target the gastric H⁺/K⁺-ATPase via competitive inhibition at the potassium-binding site. The earliest compound, SCH28080, established proof of concept but was discontinued due to hepatotoxicity. Subsequent agents, including AZD0865 (linaprazan), have demonstrated an early onset of action and efficacy comparable to that of PPIs. However, lack of clinical superiority and concerns regarding elevated hepatic transaminases limited further development. Other early molecules (e.g., soraprazan, CS526, YH-4808) similarly failed due to liver safety concerns.

Revaprazan (YH-1885) became the first PCAB introduced into clinical practice in South Korea and India, although it did not demonstrate clear advantages over PPIs. A major breakthrough followed with vonoprazan fumarate (TAK-438), introduced in Japan in 2015, which rapidly gained acceptance due to its faster onset, longer duration, and more potent and consistent acid control. This success renewed interest in this class of drugs and facilitated the development of newer agents, including tegoprazan, which demonstrated efficacy comparable to that of esomeprazole in phase III trials and was approved in South Korea in 2018 for NERD and erosive esophagitis. Since then, additional

P-CABs such as fexuprazan, keverprazan, and emerging molecules (e.g., DWP14012, KFP-H008) have expanded the therapeutic landscape, underscoring the growing potential of this class of drugs in APDs.^{52,55,82}

Mechanism of Action of Prazans

Prazans inhibit gastric acid secretion by competitively and reversibly blocking the potassium ion binding site of the H⁺/K⁺-ATPase proton pumps on the luminal membrane of gastric parietal cells (Fig. 6).^{80,83}

After systemic absorption, P-CABs rapidly concentrate within the parietal cell canaliculi and ionically bind to the proton pump, thereby preventing the exchange of K⁺, which in turn inhibits proton secretion. In contrast to PPIs, P-CABs remain stable in acidic environment and do not require activation in an acidic environment. Therefore, they do not require enteric coating or optimal dosing administration 30 minutes prior to meals. Furthermore, they exert an early onset of action, since they are not prodrugs. In addition, P-CABs inhibit both resting and actively secreting proton pumps and remain within the secretory canaliculi for prolonged periods, allowing prolonged acid control of newly synthesized pumps, resulting in long-lasting gastric acid inhibition.^{80,83}

Prazans have several physicochemical properties that enable them to inhibit gastric acid production faster, longer, and more potently than PPIs (Table 3). They have been shown to accumulate up to 100,000-fold within parietal cells relative to plasma concentrations, substantially exceeding the intracellular accumulation observed with PPIs, due to their high lipophilicity and low pKa.⁵²

Key Pharmacological Advantages

Prazans represent a significant advancement in the pharmacological management of APDs, addressing several mechanistic and clinical limitations of PPIs. Unlike PPIs, which require 4–5 days to achieve maximal acid control and 3–5 days to reach pharmacodynamic steady state, P-CABs achieve maximal acid inhibition from the first dose. Their acid stability and food-independent administration enable sustained and predictable 24-hour gastric acid control.⁵

In the management of APDs, sustained gastric acid control is more clinically relevant than pharmacokinetic parameters such as plasma half-life. Although the plasma half-life of tegoprazan is only ~3–5 hours, this does not limit its therapeutic efficacy because its pharmacodynamic effect on gastric acid control persists for ≥24 hours, achieving a 24-hour intragastric pH >4 holding time of approximately 65%. This apparent dissociation between plasma half-life and duration of action is characteristic of drugs that bind their targets

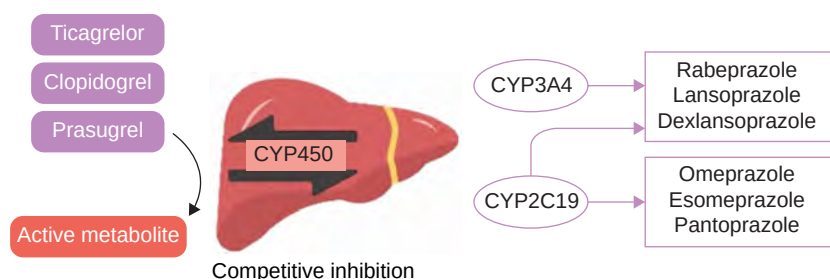


Fig. 5: Mechanistic basis of proton pump inhibitor–clopidogrel interaction via hepatic CYP450 pathways⁷⁷

with high affinity and accumulate at the site of action, enabling prolonged pharmacodynamic effects despite shorter systemic exposure, as seen with tegoprazan.^{5,24,84}

Metabolized primarily via CYP3A4 rather than CYP2C19, P-CABs demonstrate reduced susceptibility to genetic polymorphism, improving consistency of response across populations. In erosive reflux disease, P-CABs showed superior early healing (RR 1.09 at 2 weeks; 1.03 at 8 weeks vs PPIs) and improved outcomes in severe disease (LA grade C/D).⁵ P-CABs significantly increased the likelihood of achieving complete relief from nighttime heartburn, when compared with PPIs (RR 2.29).⁸⁵ In PPI-refractory GERD, symptom improvement reached 86.3%, with 90.7% improvement in erosive cases. For peptic ulcer prevention in NSAID users, recurrence risk was significantly reduced (RR 0.45), and delayed bleeding after artificial ulcers was lower (RR 0.35). In *H. pylori* eradication, P-CAB-based regimens achieved 100% eradication in

clarithromycin-sensitive infections and >90% eradication in 14-day dual rescue therapy.⁵

Short- and long-term safety profiles are comparable to PPIs, with serious adverse reactions occurring in <2% of cases and a 12-month adverse drug reaction incidence of 0.71%. Collectively, current evidence positions P-CABs as a fast-acting, pharmacogenetically stable, and clinically robust alternative to PPIs in the evolving management of APDs.⁵

Therapeutic Areas Covered by Prazans

For further details, refer to Table 4.

PHARMACOLOGICAL AND CLINICAL OVERVIEW OF AVAILABLE PRAZANS

Tegoprazan

Tegoprazan was first marketed in Korea in 2019 and has since been introduced in

other Asian and Central/South American Countries.⁵² It has been approved by the Korean Ministry of Food and Drug Safety for the treatment of GERD, gastric ulcer, and *H. pylori* eradication.^{89,90} Structurally, tegoprazan belongs to the benzimidazole-derivative class of P-CABs, distinguishing it from sulfonyl pyrrole P-CABs such as vonoprazan and fexuprazan.⁵² This structural modification of tegoprazan helps mitigate the hepatotoxic effect associated with SCH28080 and related P-CABs.⁹⁰ Tegoprazan has a pKa of approximately 5.1, which closely aligns with the intraluminal pH of the proximal duodenum, thereby facilitating faster absorption and early onset of action compared to other P-CABs.^{52,91} The strong and sustained effect of tegoprazan is attributable to its ability to accumulate in high concentrations in the gastric parietal cells, leading to slow clearance from the gastric glands and exerting its effects independent of acid levels.⁵²

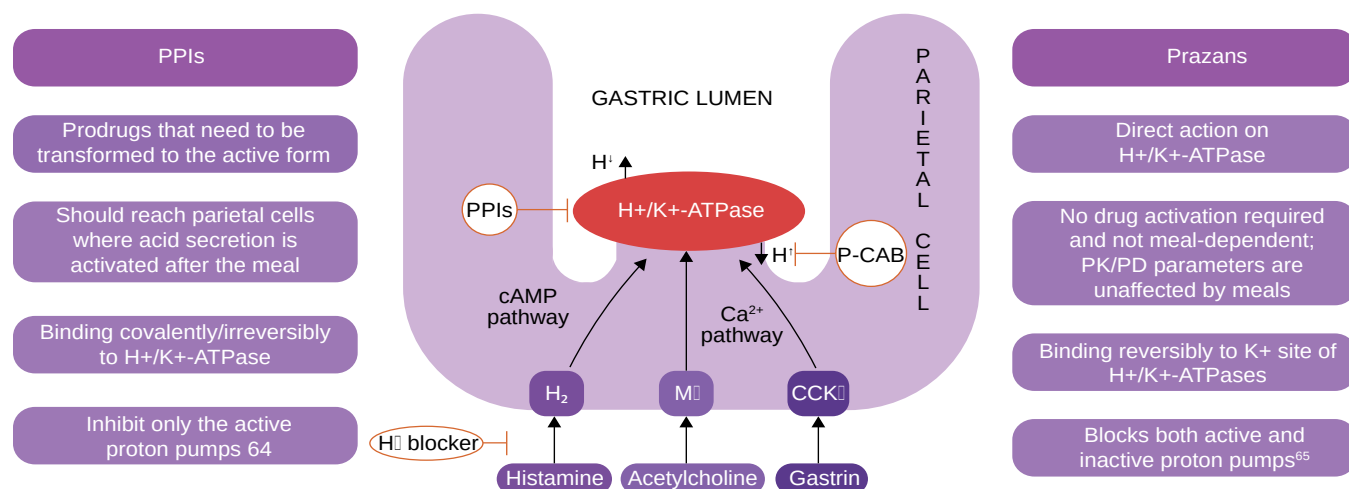


Fig. 6: Comparison of mechanism of action of prazans vs proton pump inhibitors⁵⁶

Table 3: Comparison of the pharmacodynamic properties of prazans and proton pump inhibitors^{5,56,57}

Parameter	PPIs	Prazans
Mechanism	A prodrug; needs an acidic environment for conversion to the active form, sulfenamide	Active drug that concentrates in the parietal cell canaliculi; no acid activation needed and is instantaneously protonated
Binding mechanism	Irreversible covalent inhibition of H ⁺ /K ⁺ -ATPase	Reversible ionic competitive inhibition of H ⁺ /K ⁺ -ATPase
Effect on new pumps	Does not inhibit newly synthesized pumps	Inhibits newly synthesized pumps
Onset of action	1.5–3 hours	0.5–2 hours
Maximal acid suppression after dosing	Maximal effect in 3–5 days	Full effect from first dose
Parietal cell accumulation	~1000-fold vs. plasma	~100,000-fold vs. plasma
Metabolic pathway	Primarily CYP2C19	Primarily CYP3A4
Genetic polymorphism influence	Affected by CYP polymorphism	Minimal impact of CYP polymorphism
Drug–drug interaction potential	Potential for CYP2C19-mediated drug interactions	Low potential for drug interactions due to low <i>in vitro</i> CYP2C19 inhibition potential
Duration of control	Predominantly daytime acid suppression	Sustained 24-hour acid suppression
Influence of meal timing	Best taken before meals for optimal effect	Can be administered regardless of meals
Acid stability	Acid-labile, traditionally administered with pH-dependent enteric coating	Acid-stable, do not require enteric coating

Table 4: The current approval status of prazans

P-CAB	Globally approved indications	Approval status in India
Vonoprazan ^{5,81,86,87}	Healing and maintenance of healing of erosive GERD Gastric and duodenal ulcer Treatment of <i>H. pylori</i> infection in combination with antibiotics NSAID-induced PUD Reflux esophagitis	Healing and maintenance of healing of erosive GERD Gastric and duodenal ulcer Treatment of <i>H. pylori</i> infection in combination with antibiotics NSAID-induced PUD
Tegoprazan ^{5,81,88}	Treatment and maintenance of erosive GERD Treatment of nonerosive GERD Gastric ulcers Duodenal ulcers Eradication of <i>H. pylori</i> in patients with PUD and/or chronic atrophic gastritis	Treatment of nonerosive GERD Gastric ulcer
Fexuprazan ^{5,81}	Erosive esophagitis	Erosive esophagitis

GERD: Gastroesophageal reflux disease; *H. pylori*: Helicobacter pylori; NERD: Nonerosive reflux disease; NSAID: Nonsteroidal anti-inflammatory drug

Table 5: Dose-response relationship of tegoprazan following single and multiple dosing⁹²

Dosing	Baseline	Tegoprazan 50 mg (n = 6)	Tegoprazan 100 mg (n = 6)	Tegoprazan 200 mg (n = 6)	Tegoprazan 400 mg (n = 6)
Single dose on day 1 (n = 31)					
Median pH	1.3 ± 0.5	3.6 ± 1.3	5.3 ± 0.9	5.8 ± 0.4	5.8 ± 0.2
Time pH >4 (%)	12.3 ± 10.3	48.9 ± 12.0	76.5 ± 17.7	82.0 ± 7.9	87.4 ± 8.0
Multiple doses (n = 23)					
Day 1 Median pH	1.4 ± 0.4	—	4.9 ± 1.1	5.8 ± 0.4	—
Time pH >4 (%)	10.3 ± 8.6	—	62.3 ± 15.0	76.8 ± 10.4	—
Day 7 Median pH	—	—	5.2 ± 0.5	6.4 ± 0.3	—
Time pH >4 (%)	—	—	70.4 ± 14.4	94.6 ± 3.5	—

Table 6: Potential drug interactions

Interacting drug	Clinical impact
Clopidogrel ⁹⁸	Tegoprazan does not impact the peak plasma concentration of the active metabolite of clopidogrel, unlike esomeprazole, which resulted in a 2.6 times higher reduction. Hence, tegoprazan can be safely coprescribed with clopidogrel
Atorvastatin ⁹⁸	Plasma concentration profile of atorvastatin remains consistent when administered with tegoprazan, ensuring predictable therapeutic outcomes
NSAIDs ⁹⁹	Co-administration of tegoprazan with naproxen, aceclofenac, or celecoxib did not alter the systemic exposure of either tegoprazan or the respective NSAIDs. Tegoprazan can therefore be co-administered with these NSAIDs without the need for dose adjustment.

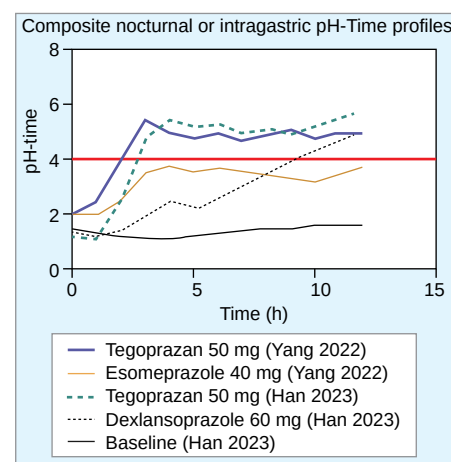
Clinical Pharmacology

Pharmacokinetic/pharmacodynamic profile: Tegoprazan has a median T_{max} of 1 hour (0.5 to 1.5 hours) after dosing, with a mean elimination half-life ranging from 3.65 to 5.39 hours.⁹² Its bioavailability is estimated to be 86%–100%.⁵² After single and multiple oral doses of tegoprazan, it shows a linear PK/PD profile with rapid and dose-dependent acid control over 24 hours (Table 5). Furthermore, tegoprazan does not significantly accumulate in the plasma after once-daily (OD) multiple dosing.⁹² It is primarily metabolized by CYP3A4 in the liver and is mainly excreted through the feces, with minimal renal excretion (3%–6%).^{89,92}

Early onset of action: Tegoprazan demonstrates rapid acid control, achieving intragastric pH >4 in approximately 30 minutes of administration. In contrast,

conventional PPIs and some other P-CABs require several hours (up to approximately 4 hours) to achieve comparable acid control (Fig. 7).^{92–96} Once achieved, tegoprazan maintained sustained acid control, with pH >4 remaining consistent throughout the 12-hour observation period. Furthermore, the antisecretory effect of tegoprazan begins on day 1 of administration, whereas PPIs take around 4–5 days to show maximal effects.⁹⁷

Meal-independent administration: Clinical studies assessed the effect of meal timing on PK and PD of tegoprazan (after single oral doses of 50 and 200 mg). The studies showed that absorption was delayed under fed conditions compared with fasting conditions. However, no significant differences were observed in the AUC and 24-h gastric acid control. Therefore, tegoprazan can be

**Fig. 7:** Composite nocturnal or intragastric pH-time profiles⁹⁶

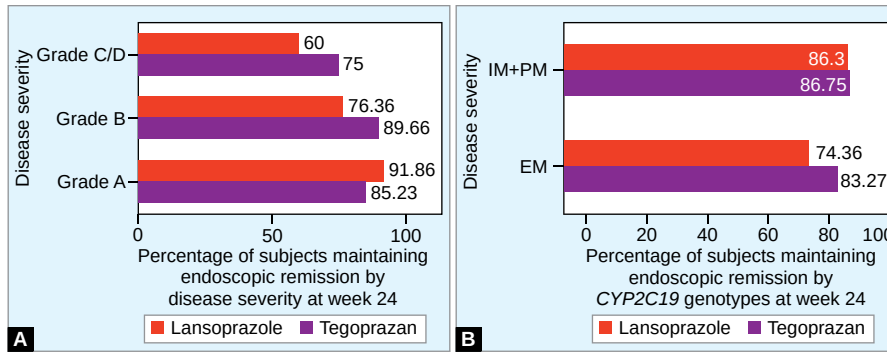
administered regardless of meal timing since it displays a meal-independent effect on acid secretion.⁸⁹

Low potential for drug interactions: Tegoprazan is predominantly metabolized via the CYP3A4 pathway and is independent of CYP2C19, making it less susceptible to potential drug interactions (Table 6).^{65,98,99}

Clinical Efficacy

Gastroesophageal reflux disease:

- **Erosive esophagitis:** A multicenter randomized controlled trial (RCT) by Lee *et al.* evaluated the noninferiority of



Figs 8A and B: (A) Maintenance rates with tegoprazan and lansoprazole according to disease severity; (B) Maintenance rates with tegoprazan and lansoprazole according to CYP2C19 genotypes¹⁰² [EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer]

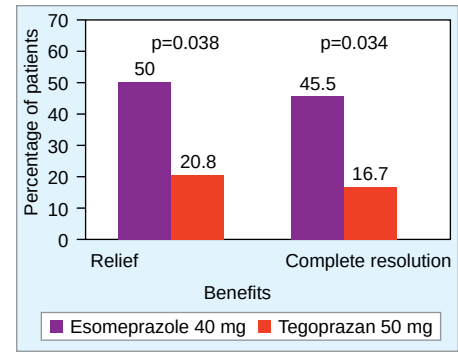


Fig. 10: Percentage of subjects with complete resolution and relief of nighttime heartburn¹⁰⁶

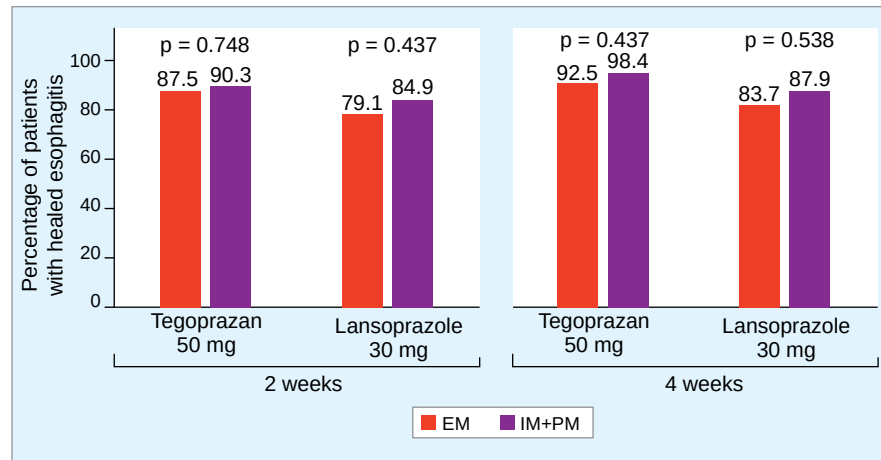


Fig. 9: Restoration of mucosal integrity rates by CYP2C19 genotypes¹⁰³

tegoprazan 50 mg OD to esomeprazole 40 mg OD in 302 patients with erosive esophagitis (EE) (LA grade A–D) for 4 and 8 weeks. It revealed that approximately 99% of patients treated with tegoprazan achieved restoration of mucosal integrity by week 8. Significant reductions in regurgitation severity, with nearly 71% improvement and a 57% reduction in frequency vs. the esomeprazole group, were also noted.¹⁰⁰

- **Maintenance therapy for erosive esophagitis:** An RCT evaluated the effect of long-term acid control using either tegoprazan 25 mg or lansoprazole 15 mg on the maintenance of endoscopic remission in patients with healed EE. It reported an endoscopic remission rate of 90.6% for tegoprazan and 89.5% for lansoprazole after 24 weeks. Subgroup analysis revealed that tegoprazan's efficacy remained stable irrespective of the disease severity (Fig. 8A) and CYP2C19 genotype (Fig. 8B), highlighting its advantage over PPIs.¹⁰¹
- **Maintenance of healing in gastroesophageal reflux disease:** The TRIUMPH program included two phase III multicenter, double-blind studies for GERD, evaluating the safety and efficacy of tegoprazan in EE

and NERD. After an initial healing phase (up to 8 weeks), patients with healed EE were assigned randomly to maintenance treatment with either tegoprazan (100 mg), tegoprazan (50 mg), or lansoprazole (15 mg) for 24 weeks. The EE trial was conducted in 1,250 patients (463 with LA Grade C/D), with complete endoscopic healing at week 8 as the primary endpoint. The NERD trial enrolled 800 patients and assessed the percentage of 24-hour heartburn-free days as the primary endpoint, and the percentage of days without night-time heartburn or regurgitation as the key secondary endpoints.¹⁰²

- Both tegoprazan doses (100 mg and 50 mg) were comparable in efficacy to lansoprazole in maintaining healing at 24 weeks across all LA Grades (A–D) and were statistically superior in sustaining healing over the 24-week period. Tegoprazan also showed a favorable safety profile, with low rates of TEAEs and no new safety concerns.¹⁰²
- **Restoration of mucosal integrity in erosive esophagitis based on CYP2C19 genotype:** A multicenter, randomized, double-blind, comparative efficacy trial showed that tegoprazan achieved higher restoration of mucosal integrity rates than lansoprazole

up to week 4 (95.2% vs 86.2%) and a greater proportion of heartburn-free days. In severe EE (LA grade C/D), healing rates were numerically higher with tegoprazan at weeks 2 and 4. Healing rates with tegoprazan were consistent across CYP2C19 genotypes (EM and IM+PM) (Fig. 9).¹⁰³

- **On-demand treatment for gastroesophageal reflux disease:** An RCT assessed the efficacy of on-demand tegoprazan therapy in GERD and revealed that tegoprazan offers faster onset of action (within 30 minutes) with sustained relief for 24 hours from GERD symptoms, such as heartburn and regurgitation, compared to PPIs. Nearly 1.6 times more patients had symptom improvement within 30 minutes with tegoprazan as compared to esomeprazole (26.2% vs 16.1%), with sustained symptom resolution for 24 hours.¹⁰⁴
- **Nonerosive reflux disease:** A phase III study evaluated the therapeutic effect of tegoprazan 50 mg and 100 mg for 4 weeks in comparison with that of placebo in 324 patients with NERD. Patients treated with tegoprazan consistently showed higher daily heartburn-free rates than placebo from day 1 through week 4. The complete resolution rates of major GERD symptoms were significantly higher in patients receiving both tegoprazan doses than in patients receiving placebo, as measured by the RDQ score ($p < 0.05$).¹⁰⁵

Nocturnal Acid Breakthrough

A multicenter, double-blind RCT involving patients with EE compared the efficacy of tegoprazan with that of esomeprazole in relieving nighttime heartburn and sleep disturbances. Tegoprazan has been associated with a shorter median time to the first heartburn-free interval (1.5 days vs 3.0 days) and a higher percentage of heartburn-free days (57.8% vs 43.1%). Subgroup analysis also showed ~2.5-fold more patients achieved nighttime heartburn relief and nearly threefold more achieved complete resolution with tegoprazan (Fig. 10).¹⁰⁶

Healing of Erosive Gastroesophageal Reflux Disease

A multicenter, randomized, double-blind phase III trial involving 255 patients, conducted across India, Russia, and South Africa, showed that tegoprazan 50 mg OD was comparable in efficacy to esomeprazole 40 mg in healing erosive GERD over a treatment period of 8 weeks (99.1% vs 97.2%). Symptom relief, GERD-HRQL improvement, and rescue medication use were comparable between groups.¹⁰⁷

Peptic Ulcer Disease

H. pylori eradication: A phase III multicenter RCT conducted in South Korea showed that 14-day tegoprazan (50 mg and 100 mg)-based triple therapy was comparable in efficacy to lansoprazole (30 mg)-based therapy for first-line *H. pylori* eradication. The *H. pylori* eradication rates were 86.0%, 85.5%, and 78.7% for tegoprazan (50 mg BD), tegoprazan (100 mg BD), and lansoprazole (30 mg BD), respectively. Tegoprazan also showed numerically higher efficacy in clarithromycin-resistant strains.¹⁰⁸

A systematic review and meta-analysis of six low-bias RCTs in 2025 treatment-naïve *H. pylori* patients showed higher eradication rates with tegoprazan-based therapy than PPI-based regimens (83.36% vs 80.06%; RR 1.045) (Fig. 11). Overall, tegoprazan-based therapy has been associated with superior eradication efficacy with a similar safety profile compared to PPI-based regimens.¹⁰⁹

A multicenter, double-blind, double-dummy RCT was conducted across 41 centers in China between October 2022 and September 2023, enrolling 561 patients with *H. pylori* infection. They were randomized (1:1) to receive either TACB (tegoprazan 50 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and bismuth 220 mg) or EACB (esomeprazole 20 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and bismuth 220 mg), administered twice daily for 14 days. The *H. pylori* eradication rate was assessed using the 13C-urea breath

test at 4–8 weeks after treatment. Eradication rates were 93.5% in the TACB group and 86.4% in the EACB group, with TACB demonstrating comparable efficacy and a numerically higher eradication rate of 7% (Fig. 12).¹¹⁰

Endoscopic treatment of bleeding peptic ulcers vs intravenous proton pump inhibitors:

- A retrospective study involving 105 patients with nonvariceal upper gastrointestinal bleeding revealed.¹¹¹
- Pre-endoscopic oral administration of tegoprazan (50 mg) led to significantly lower odds of requiring endoscopic therapy (OR=0.272) and reduced rates of rebleeding (OR = 0.14), compared to pantoprazole [80 mg administered intravenously (IV) as a bolus followed by a continuous infusion of 8 mg/h for 48 hours].
- The frequency of therapeutic endoscopy, determined using ulcer bed evaluation during emergency endoscopy, was considerably higher in the PPI group than in the PCAB group (54.1% vs 22.7%) (Fig. 13).
- Rebleeding rate was also significantly higher with PPIs compared with P-CABs (21.3% vs 4.5%) (Fig. 13).

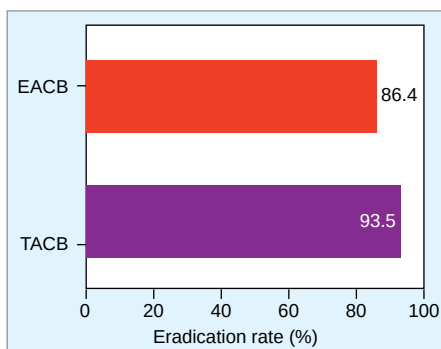


Fig. 12: Eradication efficacies of tegoprazan- vs esomeprazole-based triple therapy in treatment-naïve patients with *H. pylori* infection [EACB: Esomeprazole 20 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and bismuth 220 mg; TACB: Tegoprazan 50 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and bismuth 220 mg]

- These results suggest a potential advantage of tegoprazan over IV PPIs in pre-endoscopic management of bleeding peptic ulcers.¹¹¹

Functional Dyspepsia

A prospective multicenter study evaluated the efficacy and safety of tegoprazan (50 mg OD) for 8 weeks in patients with functional dyspepsia (FD), which was diagnosed using the Rome IV criteria. A total of 173 patients were included in the per-protocol analysis, and satisfactory symptom relief rates were 86.7% at 8 weeks and 74.6% at 4 weeks. There were significant improvements in Nepean Dyspepsia Index-Korean (NDI-K) and gastroesophageal reflux disease–health-related quality of life (GERD–HRQL) scores compared with baseline. Tegoprazan showed a remarkable improvement in FD symptoms, regardless of the FD subtype or *H. pylori* status. In patients with overlapping FD and GERD, a significantly greater symptom improvement was observed than in those with FD alone.¹¹²

Safety Profile of Tegoprazan

Across numerous clinical trials, tegoprazan has been associated with a good tolerability profile with no major adverse events reported.⁵⁵

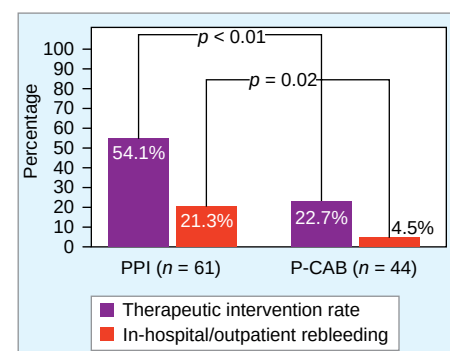


Fig. 13: Clinical outcomes with proton pump inhibitor vs PCAB therapy [PCAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor]

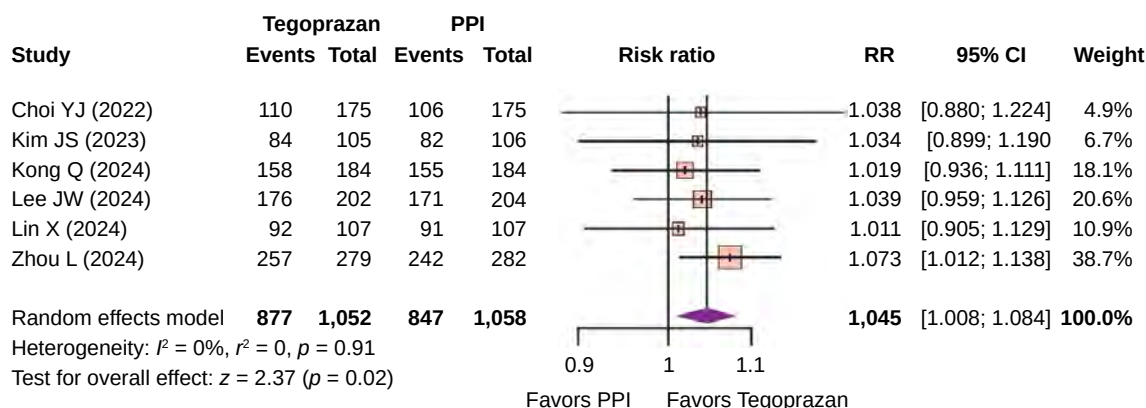


Fig. 11: Forest plot demonstrating the eradication rate in tegoprazan-containing therapy compared to proton pump inhibitor-containing therapy¹⁰⁹

Hepatotoxicity		Total number (P-CAB)	Total number (PPIs)	Risk ratio (95% CI)
Tegoprazan vs. 6 PPIs				
Tegoprazan vs. 6 PPIs		9169	75,171	0.73 (0.72–0.75)
Tegoprazan vs. dexlansoprazole		9169	13,017	0.70 (0.69–0.72)
Tegoprazan vs. esomeprazole		9169	11,385	0.81 (0.79–0.83)
Tegoprazan vs. lansoprazole		9169	15,066	0.61 (0.59–0.63)
Tegoprazan vs. omeprazole		9169	7880	1.17 (1.13–1.20)
Tegoprazan vs. pantoprazole		9169	15,232	0.61 (0.59–0.62)
Tegoprazan vs. rabeprazole		9169	12,591	0.73 (0.71–0.75)

Fig. 14: The risk ratio of hepatotoxicity for tegoprazan vs the six existing PPIs¹¹³

Hepatic safety: A nationwide population-based retrospective study of 50 million inhabitants in Korea, conducted between January 2019 and December 2020, has been associated with a favorable hepatic safety profile for tegoprazan compared with six PPIs (namely, dexlansoprazole, lansoprazole, esomeprazole, omeprazole, pantoprazole, and rabeprazole). Tegoprazan showed a significantly lower likelihood of hepatotoxicity, in comparison with PPIs (Fig. 14). The RR for tegoprazan vs. the six available PPIs was 0.73, corresponding to a 27% lower cumulative incidence of overall hepatotoxicity, in comparison with the PPIs.¹¹³

Renal safety: A retrospective cohort study of 6941 patients with esophageal or gastric diseases treated with tegoprazan or esomeprazole between 2019 and 2023 (mean follow-up: 21 months) evaluated renal outcomes associated with long-term acid control therapy. Tegoprazan was associated with a 0.58-times lower risk for serum creatinine doubling and a 0.50-times lower risk for eGFR decline (log-rank $p = 0.001$). After adjusting for multiple covariates including baseline eGFR, prescription days, major comorbidities, and concomitant use of other medications, hazard ratios for creatinine doubling and eGFR decline were 0.52 and 0.63, respectively. Although limited by its single-center retrospective design, relatively short follow-up, and potential residual confounding, these findings suggest that P-CAB therapy may represent a safer option for preserving renal function in patients at risk of CKD progression requiring long-term acid control.¹¹⁴

Hypergastrinemia: Tegoprazan 25 mg can be administered for a long period without risking gastrin elevation, unlike PPIs.¹⁰¹ Administration of tegoprazan for 4–8 weeks

maintains gastrin plasma concentration within the normal range of <200 pg/mL.¹¹⁵

Vonoprazan

Vonoprazan fumarate is a first-in-class P-CAB that was launched in Japan in February 2015 for the treatment of APDs and as an adjunct to *H. pylori* eradication.¹¹⁶ Structurally, it belongs to the sulfonyl pyrrole class of P-CABs.⁵²

Clinical Pharmacology

Pharmacokinetic/Pharmacodynamic Profile Vonoprazan demonstrates approximately 350-fold greater potency than lansoprazole in inhibiting the H^+/K^+ -ATPase.^{116,117} This reversible interaction allows vonoprazan to produce an earlier onset of action and sustain acid control for a longer duration compared with PPIs. Additionally, its capacity to inhibit the proton pump at all stages of the catalytic cycle, without requiring acid-mediated activation, contributes to its potent and prolonged acid-suppressive effect.¹¹⁸

Clinically, vonoprazan achieves sustained intragastric pH ≥ 4 holding time, improving from ~63% on Day 1 to over 83% by Day 7 at 24 hours. The antisecretory activity of vonoprazan was evaluated in a systematic review comprising six study arms and 864 patients. The analysis showed a linear correlation between drug dose and antisecretory activity, indicating that therapeutic efficacy in GERD is dose-dependent.⁵²

Onset of Control and Duration of Action: Vonoprazan is absorbed rapidly and achieves its peak plasma concentration within 1–2 hours after oral administration.¹¹⁸ It has a high pKa of 9.06 that enables rapid protonation and accumulation within gastric parietal cells under acidic conditions, explaining its sustained 24-hour acid control (following a single dose

and at steady state) and maintenance of elevated intragastric pH for approximately 24–48 hours after discontinuation.¹¹⁹

Drug–drug Interaction and Cyp450 Metabolism Profile: CYP2C19 polymorphism contributes to variability in the pharmacokinetics and pharmacodynamic response of traditional PPIs. In contrast, vonoprazan is predominantly metabolized by CYP3A4 and shows minimal CYP2C19 dependence, leading to reduced interindividual variability and fewer related drug interactions.^{116,120}

Vonoprazan is a weak CYP3A inhibitor, producing a <2-fold increase in exposure of substrates such as midazolam. Although *in vitro* activity of CYP2C19 inhibition is limited, clinical data suggest potential inhibition at therapeutic doses, as reflected by altered proguanil pharmacokinetics and reduced antiplatelet effects of clopidogrel and prasugrel. Increased tacrolimus concentrations have also been reported in renal transplant recipients, warranting monitoring. In *H. pylori* regimens, clarithromycin-based regimens demonstrate increased vonoprazan exposure, whereas metronidazole-based regimens show minimal interaction. Importantly, co-administration with low-dose aspirin and NSAIDs results in minimal and clinically insignificant changes, supporting its use in gastroprotection settings.⁵²

Clinical Evidence

Gastroesophageal reflux disease: PPI-resistant gastroesophageal reflux disease: In a study involving 124 patients with persistent GERD symptoms despite prior PPI therapy and pathological esophageal acid exposure (EAET) $\geq 4\%$, administration of vonoprazan (20 mg OD) for 8 weeks led to a significant decrease in gastroesophageal acid exposure time (GAET), compared with continued PPI therapy (median GAET: 23.8% vs

41.1%). Vonoprazan 10 mg also achieved lower median EAET (4.5% vs 10.6% with PPIs). Almost 46% of patients achieved normalization of EAET and complete acid control, alongside improvements in reflux symptoms and EE, indicating vonoprazan as an effective choice for superior acid control and symptom improvement in PPI-resistant GERD.¹²¹

Symptomatic nonerosive reflux disease: In a phase II, double-blind study involving 207 patients with symptomatic NERD, vonoprazan (10 mg or 20 mg for 6 weeks) has been associated with significantly greater complete relief of heartburn episodes compared to placebo (56.0% with 10 mg vs. 60.6% with 20 mg vs. 27.3% with placebo). Differences in symptom relief were observed as early as 1 hour after treatment, supporting its use as an on-demand therapy.¹²²

Reflux esophagitis, nonerosive reflux disease, and proton pump inhibitor-resistant gastroesophageal reflux disease: An open-label, single-center observational study including 200 patients (47 with reflux esophagitis [RE], 49 with NERD, and 104 with PPI-resistant GERD) showed that vonoprazan was associated with statistically significant improvement in FSSG scores across all three groups, including the PPI-resistant cohort (Fig. 15). These findings support vonoprazan's efficacy in PPI-resistant GERD, symptomatic RE, and NERD.¹²³

Acid control based on CYP2C19 genotype: A randomized crossover study in 28 healthy volunteers assessed acid control with vonoprazan and esomeprazole across CYP2C19 genotypes. Vonoprazan 20 mg twice daily achieved near-complete acid control (100% pH $\geq$ 4 holding time) and was superior to vonoprazan od and esomeprazole one- or twice-daily regimens, with consistent effects across genotypes. In contrast, esomeprazole showed genotype-dependent variability,

highlighting vonoprazan's potent, genotype-independent acid inhibition.¹²⁴

Erosive esophagitis: Two phase I RCTs involving healthy adult male subjects from Japan ($n = 60$) and the UK ($n = 48$) evaluated the dose-dependent acid control with vonoprazan 10–40 mg OD.⁹³ The 24-hour pH >4 holding time increased dose-dependently, reaching 100% (Japan) and 93.2% (UK) at 40 mg (Fig. 16A). Nighttime pH control showed a similar trend, achieving up to 100% and 90.4%, respectively (Fig. 16B).^{93,120} These findings indicate potent, sustained acid control with near-complete achlorhydria.¹²⁰

Healing rates in erosive esophagitis: A multicenter RCT involving 305 patients with EE (LA grades A to D) compared the safety and efficacy of vonoprazan (20 mg od) and lansoprazole (20 mg od) for 8 weeks and showed comparable healing rates for mild EE (99.2% vs. 100%). However, vonoprazan had significantly higher EE healing rates of 98.7% for severe EE (LA grades C/D) compared to 87.5% with lansoprazole. Furthermore, recurrence remained low with vonoprazan (4.1–6% at 24 weeks and ~9% at 52 weeks) during the maintenance phase among healed patients, demonstrating durable remission.¹²⁵

Sustained night-time acid control vs proton pump inhibitors: An RCT compared the efficacy of vonoprazan and lansoprazole in relieving heartburn among patients with endoscopically confirmed EE who experienced heartburn at least once a week. The study reported that vonoprazan rendered 33.3% of patients with complete relief from nocturnal heartburn compared to only 9.1% of patients with lansoprazole on day 1 of treatment. Furthermore, a significantly higher number of patients achieved complete nocturnal heartburn relief with vonoprazan compared with those treated with lansoprazole till day 7 (HR 6.2).¹²⁶

Peptic Ulcer Disease

Triple Therapy for *H. pylori* Infection: A multicenter, double-blind, randomized study assessed whether vonoprazan 20 mg was comparable in efficacy to lansoprazole 30 mg as part of first-line triple therapy (with amoxicillin and clarithromycin) in *H. pylori*-positive patients with a history of gastric or duodenal ulcer. Among 650 subjects, the *H. pylori* eradication rate was significantly higher for vonoprazan (92.6%), compared to that for lansoprazole (75.9%), with a 16.7% treatment difference, confirming comparable efficacy. In clarithromycin-resistant strains, vonoprazan triple therapy has been associated with a markedly improved eradication rate of 82%, in contrast to 40% achieved with lansoprazole triple therapy, thereby supporting its use as both first- and second-line therapy for *H. pylori* eradication.¹²⁷

Dual therapy for *H. pylori* eradication: A prospective, open-label, single-arm pilot study enrolling 50 South Indian patients showed that vonoprazan–amoxicillin dual therapy achieved a high *H. pylori* eradication rate of 90%, exceeding historical PPI-based regimens (~70%). Significant improvements were observed in dyspeptic symptoms and quality of life, alongside marked increases in intragastric pH. The regimen showed high adherence of 94% and a favorable safety profile. These findings highlight vonoprazan-based dual therapy as an effective, well-tolerated alternative in high antibiotic resistance settings.¹²⁸

High-dose dual therapy for *H. pylori* eradication: In a prospective, multicenter, randomized trial involving treatment-naïve patients, dual regimens combining P-CABs with amoxicillin were evaluated. Vonoprazan-based therapy achieved significantly higher eradication rates compared with tegoprazan across intention-to-treat (89.3% vs 76.1%), modified intention-to-treat (94.6% vs 80.8%), and per-protocol analyses (95.1% vs 81.0%).

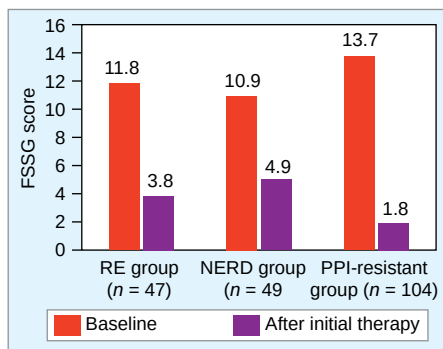


Fig. 15: FSSG at baseline and after initial vonoprazan therapy¹²³ [NERD: Non-erosive reflux disease; PPI: Proton pump inhibitor; RE: Reflux esophagitis]

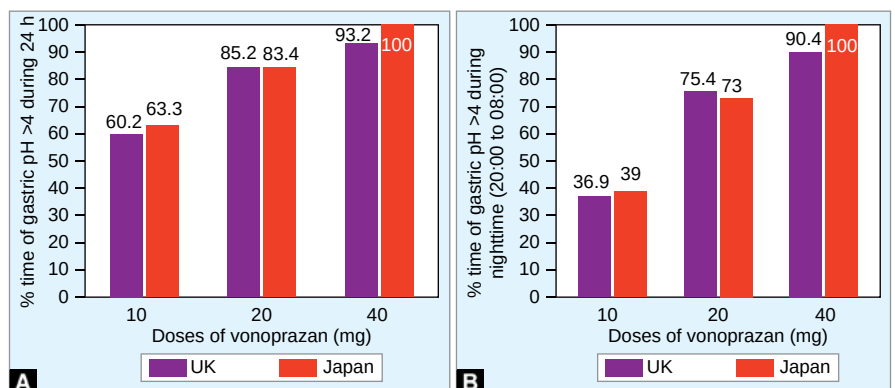


Fig. 16: Vonoprazan dose-dependently prolonged 24 h (A) and nighttime (B) intragastric pH >4 holding time in healthy adult male subjects^{93,120}

Overall adverse event rates and treatment compliance were comparable between groups, although tegoprazan was associated with fewer gastrointestinal adverse events. These findings suggest that vonoprazan–amoxicillin dual therapy provides robust eradication with a favorable safety profile.¹²⁹

Safety

Postmarketing surveillance including >128 million patients exposed to vonoprazan worldwide has shown no new or unexpected safety concerns, with the safety profile consistent with clinical trial findings.⁵¹

Short-term safety: Vonoprazan exhibits a broad safety profile comparable to PPIs in the short term, with pooled incidences of adverse events (AEs), drug-related AEs, serious AEs, and AEs leading to discontinuations of ~20%, 7%, 1%, and 1%, respectively. Common AEs include gastrointestinal symptoms (diarrhea, abdominal pain, nausea, dyspepsia), hepatic enzyme elevations, skin reactions (rash, dermatitis, urticaria), and nonspecific effects such as headache, dizziness, and fatigue, with occasional infections (e.g., respiratory or urinary). Notably, a higher risk of hemorrhagic enterocolitis has been reported, while no clear association with interstitial lung disease has been observed.¹¹⁸

Long-term safety: Long-term data indicate a generally favorable safety profile, with high treatment persistence (>85% at 6 months), low adverse reaction rates, and no new safety signals over up to 3 years of maintenance therapy. The study also reported an overall low incidence of hemorrhagic lesions (1.04%), corroborating the safety and efficacy of vonoprazan in real-world clinical practice. Although sustained acid control may lead to hypergastrinemia and histological changes such as parietal and G-cell hyperplasia, no neoplastic progression has been identified to date.¹¹⁸

Hepatic safety: In a cohort study of 35,056 patients with cirrhosis (31,688 receiving PPIs and 3,368 receiving P-CABs), treatment with vonoprazan was associated with significantly better clinical outcomes compared with PPIs. Adjusted analyses showed lower risks of mortality (adjusted HR [aHR] 0.36–0.39), infections (aHR 0.60–0.67), liver complications (aHR 0.16–0.18), and liver-related hospitalizations (aHR 0.12–0.13) at 6 and 12 months. These results suggest that vonoprazan may be associated with improved outcomes in patients with cirrhosis compared with conventional PPIs.¹³⁰

Fexuprazan

Fexuprazan was launched in South Korea in 2022 for the treatment of GERD.^{5,16} It is a

sulfonyl pyrrole derivative, demonstrating stronger and more sustained antisecretory activity compared with lansoprazole.⁵²

Clinical Pharmacology

Pharmacokinetic/pharmacodynamic profile: After both single and multiple oral doses (20–160 mg), the pharmacokinetics of fexuprazan are linear and remain unaffected with a high-fat meal. The drug produces a dose-dependent, rapid, and prolonged acid control of gastric acid secretion, lasting over 24 hours after both single and repeated dosing, with the 40 mg and 80 mg doses showing no NAB.⁵²

Onset of control and duration of action: Fexuprazan exhibits rapid absorption, with a median T_{max} ranging from 1.75 to 3.50 hours across single-ascending dose (SAD; 10–320 mg) and multiple-ascending dose (MAD; 20–160 mg) investigations. Intra-gastric pH >4 is achieved within approximately 2 hours of the first dose, as confirmed by 24-hour pH monitoring in SAD and MAD studies.⁹³ Multiple-dose administration demonstrates predictable accumulation, with approximately twofold increases in C_{max} and AUC_{0-12h} at steady state.¹³¹ Clinically, acid control persists for more than 24 hours after od dosing, providing effective control throughout the dosing interval, including overnight.^{93,132} Importantly, acid control parameters remain unaffected by high-fat meals, and reversible potassium-competitive inhibition allows acid secretion to resume upon drug clearance.⁹³

Drug–drug Interaction and CYP450 metabolism profile: Fexuprazan is primarily metabolized via CYP3A4; therefore, co-administration with strong CYP3A4 inhibitors such as clarithromycin may increase systemic exposure and should be monitored.^{133–135}

Importantly, its CYP3A4-dominant metabolic pathway minimizes genotype-dependent variability in drug exposure and acid control that characterizes PPI therapy, supporting predictable, once-daily dosing without the need for dose adjustment based on CYP2C19 genotype.^{132,133,136} Additionally, no clinically significant interaction with PPIs is anticipated, and available pharmacokinetic data suggest that pH-related changes are unlikely to meaningfully affect NSAID absorption.¹³³

Clinical Evidence

Fexuprazan based on the timing of administration in erosive esophagitis: A multicenter, open-label, phase III, comparable efficacy study involved 186 patients with endoscopically confirmed EE who were randomized to receive fexuprazan 40 mg either 30 minutes before or after a meal. Week

4 healing rates were 98.77% (pre-meal) and 100.00% (post-meal), confirming comparable efficacy with similar rates at Week 2 (95.77% and 97.14%, respectively). These findings show that fexuprazan provides effective restoration of mucosal integrity regardless of meal timing, offering a practical advantage over PPIs that require pre-meal dosing.¹³⁶

Fexuprazan vs esomeprazole in erosive esophagitis: In a phase III double-blind, multicenter, RCT ($n = 263$), fexuprazan 40 mg OD was found to be comparable in efficacy to esomeprazole 40 mg OD in EE healing at Week 8. The difference in percentages of patients with complete absence of mucosal breaks, adjusted for baseline LA grade, was 0.9% between the fexuprazan 40 mg group and the esomeprazole 40 mg group (Fig. 17). Fexuprazan provided faster symptom relief, with significantly more patients being symptom-free by day 3 compared to esomeprazole (22.4% vs 7.9%, night-time 34.5% vs 17.5%). Overall symptom scores (reflux disease questionnaire, gastroesophageal reflux disease–health-related quality of life) improved similarly in both groups and serum gastrin elevations were comparable between treatments.¹³²

Genotype-independent efficacy of fexuprazan: In a phase III RCT subgroup analysis ($n = 107$), fexuprazan showed consistent EE healing across CYP2C19 metabolizer groups. In EM subgroup ($n=88$), Week 4 and 8 healing rates were comparable to esomeprazole (91.7% vs. 89.4% and 100% vs. 98.1%). Similar results were observed in poor metabolizers ($n=14$), indicating minimal genotype-dependent variability in response.¹³²

On-demand fexuprazan in gastroesophageal reflux disease maintenance: In a prospective real-world cohort study ($n = 31$), patients with symptomatic GERD and confirmed EE experienced significant improvement after 4 weeks of fexuprazan 40 mg od (gastroesophageal reflux disease questionnaire: 9.0→6.5; patient assessment of upper gastrointestinal symptom severity index: 29.0→10.8). Following symptom control, 67.7% of patients transitioned to on-demand therapy based on preference. Symptom scores remained stable during maintenance, with no significant differences between continuous and on-demand regimens at 8 weeks. Importantly, no adverse events were reported. These findings demonstrate that approximately two-thirds of patients can successfully adopt an on-demand strategy, maintaining symptom control while reducing medication burden.¹³⁷

Nocturnal Acid Breakthrough

In a randomized, open-label, prospective crossover study ($n = 39$), GERD patients with

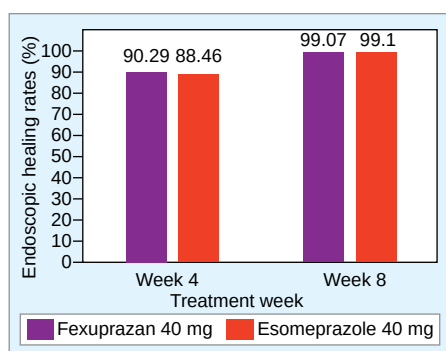


Fig. 17: Erosive esophagitis healing rate at weeks 4 and 8

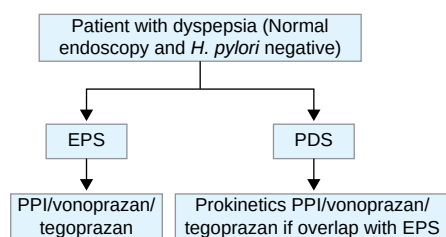


Fig. 18: Suggested algorithm for the treatment of patients with dyspepsia who had a normal endoscopy^{112,141,142,147} [In a patient with dyspepsia, endoscopy should be considered if the patient has alarm symptoms or has not responded satisfactorily to a 2–4-week course of symptomatic treatment with once daily PPI/vonoprazan/tegoprazan¹⁴⁷]

nocturnal reflux received either fexuprazan 40 mg or esomeprazole 40 mg for 4 weeks each, then underwent a 4-week washout period before switching to the other medication for an additional 4 weeks, concluding with a final washout to complete the sequence. Fexuprazan has been associated with significantly greater nocturnal symptom severity reduction (81.3% vs 64.1%). In patients with severe baseline symptoms (score ≥ 7), fexuprazan provided superior improvement ($p = 0.008$). After crossover, fexuprazan again showed greater reductions in nocturnal severity and frequency, confirming sustained superiority. Patients switching from esomeprazole preferred fexuprazan. These benefits are supported by its longer half-life (~7–10 hours) and sustained nighttime pH ≥ 4 control without NAB.¹³⁸

Laryngopharyngeal symptom control: A randomized, double-blind, multicenter Phase 4 trial involving 161 patients with GERD-related chronic cough showed that fexuprazan 40 mg OD had efficacy comparable to that of esomeprazole 40 mg over 8 weeks. Improvements in cough-related quality of life were similar between both groups (mean Leicester Cough Questionnaire score change: 4.9 ± 4.0 vs 5.3 ± 3.8), with comparable reductions in cough severity and reflux symptom scores. The incidence of TEAEs

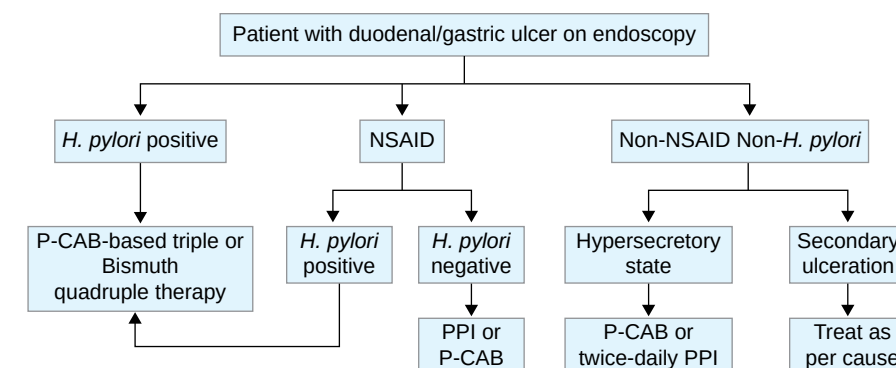


Fig. 19: Suggested algorithm for the treatment of patients with duodenal and gastric ulcers^{4,5,108,147,146,148,149} [*H. pylori*: *Helicobacter pylori*; NSAID: Nonsteroidal anti-inflammatory drug; P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor [Note: P-CABs include vonoprazan, tegoprazan, and fexuprazan;⁸⁰ Only vonoprazan is currently available in two strengths viz 10 mg and 20 mg;⁸¹ Tegoprazan and fexuprazan are available as single strength tablets of 50 mg and 40 mg, respectively;⁸¹ Choice of *H. pylori* treatment could be dependent on local resistance patterns of *H. pylori* to antibiotics;¹⁴⁵ In gastric ulcer, tegoprazan and vonoprazan are supported by clinical evidence and global regulatory approvals, whereas equivalent evidence and approvals are not yet available for fexuprazan⁵

was also similar, with mostly mild events and no serious adverse events reported in the fexuprazan group, indicating comparable efficacy and safety to PPIs in this population.¹³⁹

Another prospective, double-blind, multicenter RCT involving 136 patients with laryngopharyngeal reflux disease (LPRD) showed that fexuprazan 40 mg OD had efficacy comparable to that of esomeprazole 40 mg over 8 weeks, with significant improvements in reflux symptom index (RSI) and reflux finding score in both groups. Notably, among patients with severe symptoms (RSI ≥ 18), fexuprazan produced greater and faster improvement in RSI at 4 weeks, indicating effective and well-tolerated therapy for LPRD.¹⁴⁰

Safety

The overall TEAE profile of fexuprazan was mild-to-moderate in severity with no treatment-related deaths and no serious adverse drug reactions reported.^{132,136} Common events reported included epigastric discomfort, dyspepsia, nausea, headache, GI disorders, and skin events. The gastrin-increasing effect was similar to PPIs and lower than that of vonoprazan and returned within the normal range in all subjects after 48 hours of the last dose.^{93,132}

Long-term safety considerations: As with other potent acid-suppressive therapies, potential class-related concerns may include alterations in gut microbiota, enteric infections, and possible nutritional deficiencies; however, a definitive causal relationship with infections such as *Clostridioides difficile*, pneumonia, or fracture risk has not been established. Dizziness has been reported as an observed adverse event with fexuprazan. Ongoing post-marketing surveillance and long-term studies will further clarify its extended safety profile.¹³⁴

TRANSLATING EVIDENCE INTO PRACTICE: POSITIONING PRAZANS IN ACID DISORDERS

The use of prazans can be considered in the following clinical scenarios:

- **Functional dyspepsia:** Patients with dyspeptic symptoms and a normal endoscopy, with an *H. pylori* negative status.^{112,141,142}
- **GERD:** Patients with reflux symptoms who have undergone an endoscopy.^{4,7,53,103–105,125,143,144}
 - Erosive reflux disease on endoscopy.
 - Nonerosive reflux disease.
- **PUD:** Patients with endoscopically confirmed duodenal or gastric ulcers.^{4,5,108,110,127,145,146}
 - *pylori*-positive ulcers.
 - NSAID-associated ulcers (irrespective of *H. pylori* status).
 - Non-NSAID, *H. pylori*-negative ulcers, including hypersecretory states or secondary (non-peptic) ulcers of inflammatory, infective, or neoplastic etiologies.

Patient with Dyspepsia Who Had a Normal Endoscopy

For further details, refer to Figure 18.

Patients with Duodenal and Gastric Ulcers

For further details, refer to Figure 19.

Patients with Gastroesophageal Reflux Disease

For further details, refer to Figure 20.

Suggested Algorithm for the Treatment of Refractory Gastroesophageal Reflux Disease

For further details, refer to Figure 21.

Guideline-Endorsed Role of Prazans in Modern Acid Peptic Disorder Management

- Vonoprazan is recommended as an alternative therapeutic option in patients experiencing nocturnal acid breakthrough.
- Prazans, including vonoprazan, can be administered irrespective of meal timing.
- Switching to vonoprazan 20 mg od is advised for patients with refractory GERD.
- Vonoprazan is strongly endorsed as a component of *H. pylori* eradication regimens. It is considered a safe option for long-term maintenance therapy in GERD when used at the lowest effective dose.
- Vonoprazan may be used in patients with cardiovascular comorbidities receiving antiplatelet therapy, and in those with renal or hepatic impairment, with appropriate clinical monitoring.
- *API consensus included only vonoprazan and not other prazans.

American Gastroenterological Association (AGA) Clinical Practice Update¹⁵⁵

Prazans may be considered in patients with objectively documented acid reflux who do not show improvements with twice-daily PPI therapy.

Although evidence for first-line on-demand prazan use is limited, their early onset of action may benefit selected patients with heartburn who previously responded to antisecretory therapy.

Prazans can be used in place of PPIs in *H. pylori* eradication regimens.

American Foregut Society Recommendations¹⁴³

- Prazans can be administered irrespective of meals, unlike most PPIs.
- They achieve rapid and potent acid control within a few hours of the first dose.
- Vonoprazan provides more sustained acid inhibition than conventional once-daily PPIs.
- Tegoprazan 50 mg and vonoprazan 20 mg demonstrate efficacy comparable to that of PPIs in enhancing the healing of EE, across all severity grades.
- Vonoprazan is superior to lansoprazole in individuals with LA grade C or D esophagitis,

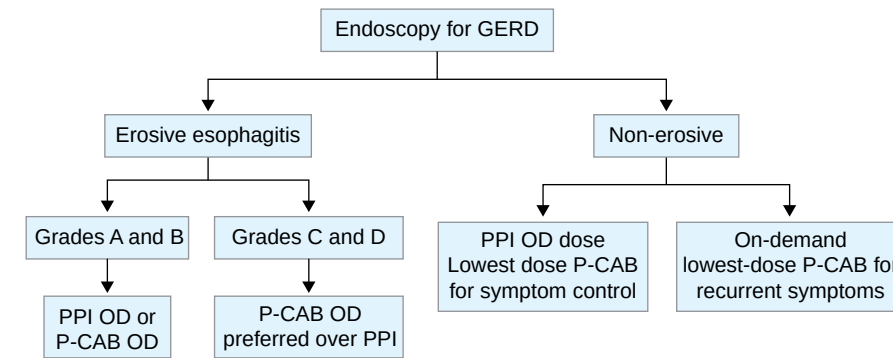


Fig. 20: Suggested algorithm for the treatment of patients with gastroesophageal reflux disease^{4,7,8,14,53,100,101,104,150–154} [OD: Once-daily; P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor. *Note:* P-CABs include vonoprazan, tegoprazan, and fexuprazan;⁸⁰ For symptom control, PCAB may be recommended over PPI as on-demand treatment in view of faster onset of action and long acid holding time;^{143,144} Choose the lowest dose of PPI to manage symptoms for NERD;¹⁴⁴ In NERD, more robust clinical evidence is available for tegoprazan, followed by vonoprazan, while comparable supporting data for fexuprazan remains limited.^{5,105,122} Tegoprazan is the only PCAB that has received approval from the DCGI approval for the treatment of NERD in India.⁸¹ Continuous daily PCAB is recommended for maintenance treatment of Grade C and D esophagitis.¹⁴⁴ On-demand PCAB is preferred over maintenance treatment for NERD.^{143,144,150} It is recommended for patients with GERD requiring long-term maintenance treatment to use the lowest effective dose that alleviates symptoms and maintains restoration of mucosal integrity^{4,144}]

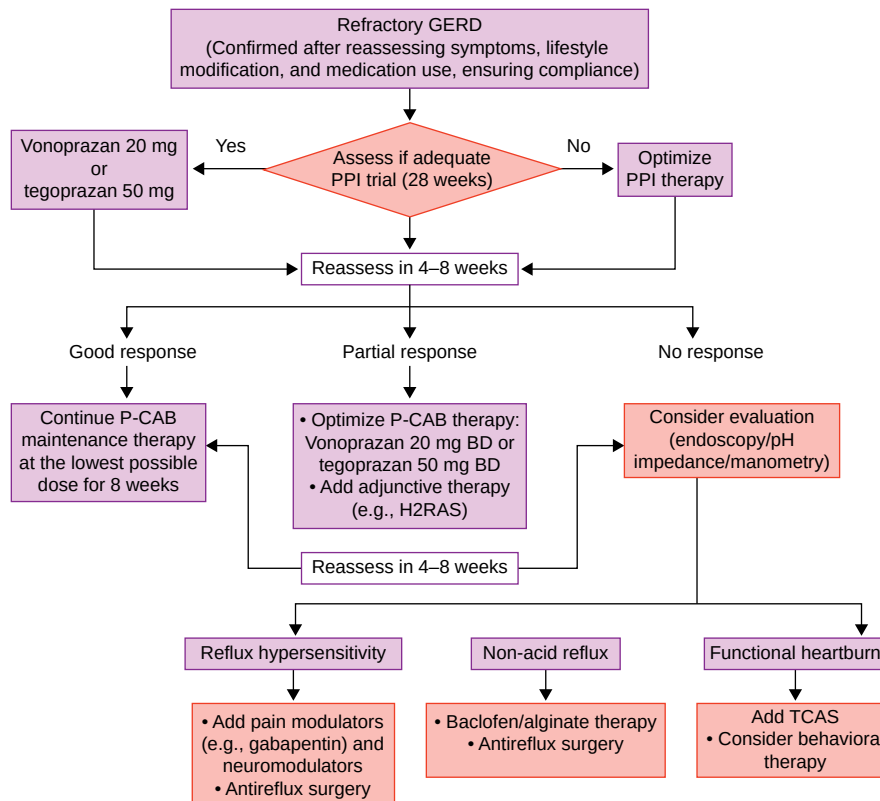


Fig. 21: Suggested algorithm for the treatment of patients with refractory gastroesophageal reflux disease^{4,5,14,58,143} [Bd: Twice-daily; H2RA: Histamine-2 receptor antagonist; P-CAB: Potassium-competitive acid blocker; PPI: Proton pump inhibitor; TCA: Tricyclic antidepressant. *Notes:* Vonoprazan provides more potent gastric acid control, enhanced symptom improvement, and better esophagitis healing than PPIs in patients with PPI-refractory GERD (median GAET: 23.8% vs. 41.1%, median EAET: 4.5% vs. 10.6% with PPIs). Additionally, 46% of patients achieved normalization of EAET and complete acid control, with significant improvements in reflux symptoms and erosive esophagitis.¹²¹ Expert recommendations advocate P-CABs over PPIs as the preferred therapy in refractory GERD for improved healing and symptom relief^{4,58,143}]

- with statistically significant healing benefits observed as early as week 2.
- For maintenance therapy, P-CABs have efficacy comparable to that of PPIs, with vonoprazan showing greater efficacy in patients with previously severe EE.
- Vonoprazan 20 mg is effective in treating patients with PPI-refractory EE.
- In non-erosive disease, prazans offer early heartburn relief, with symptom improvement from day 1 of therapy.
- For patients with NERD, mild EE, and severe EE, once-daily prazan therapy for 4–8 weeks is recommended as the first-line treatment option.
- Prazans demonstrate superior restoration of mucosal integrity compared with PPIs in patients with severe EE.
- On-demand prazan therapy is advised for long-term management in patients with NERD and mild EE.

- Continuous daily prazan therapy is recommended to maintain symptom control and restoration of mucosal integrity in patients with severe EE.
- For chronic therapy, the lowest effective dose should be used to minimize overuse and potential long-term risks.

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- P-CABs are recommended as effective alternatives to PPIs for GERD and peptic ulcer disease.
- Vonoprazan demonstrates superior healing rates in severe erosive esophagitis (LA Grade C/D).
- Maintenance therapy with P-CABs is recommended in patients with recurrent or severe reflux esophagitis.
- Vonoprazan-based regimens are recommended as first-line options for H.

pylori eradication because of superior acid suppression and higher eradication rates.

COMPARISON OF AVAILABLE PRAZANS IN INDIA

In contrast to currently available PPIs, which are all benzimidazole derivatives, P-CABs belong to distinct chemical classes (Table 7). Although they target the same H⁺/K⁺-ATPase proton pump, they are structurally diverse and represent a heterogeneous group of molecules.⁵²

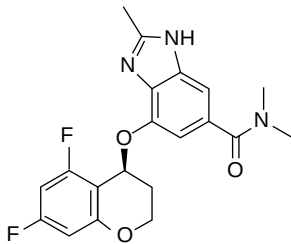
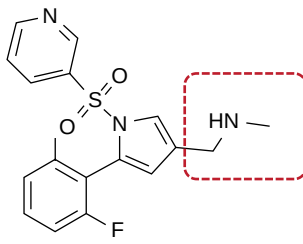
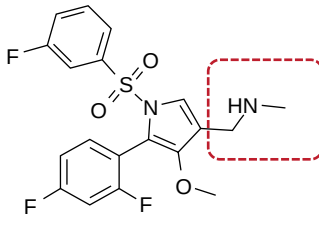
How Prazans Overcome the Unmet Needs with Proton Pump Inhibitors

For further details, refer to Table 7.

Determining the Most Appropriate Prazans in Various Acid Peptic Disorders

For further details, refer to Table 8.

Table 7: Comparison of the currently available prazans

Criteria	Tegoprazan	Vonoprazan	Fexuprazan
Structure ⁵²			
Class ⁵²	Benzimidazole derivative	Sulfonyl pyrrole derivative	Sulfonyl pyrrole derivative
pKa ⁵²	5.10	9.06	8.40
T _{max}	0.5–1 h ⁹²	4 h ⁹³	4 h ⁹⁴
Maintenance of intragastric pH >4 with single dose ⁵²	54.5 ± 17.9	63.3 ± 17.9	44.6 ± 22.9
DDI potential	Atorvastatin: No effect ⁹⁹ NSAIDs: Systemic exposure remains unchanged ⁹⁹ Proguanil: No effect ¹⁵³	Atorvastatin ⁹⁸ : Clarithromycin ¹⁵⁷ Proguanil ¹⁵⁶	Clarithromycin ¹⁵⁷
Influence on CYP3A ⁵²	No effect	No effect	No effect
Approved global indications ⁵	Erosive and nonerosive GERD Maintenance of healed erosive GERD Gastric ulcer disease Treatment of <i>H. pylori</i> infection	Healing and maintenance of all grades of erosive GERD and relief of heartburn associated with GERD Treatment of <i>H. pylori</i> infection NSAID-induced PUD Gastric and duodenal ulcers	Erosive GERD
Safety outcomes ^{5,114}	TEAEs mainly diarrhea, nausea, vomiting Hypergastrinemia less pronounced than vonoprazan Low incidence of liver TEAEs Better renal safety vs. PPIs	Mild–moderate AEs common; lower incidence of diarrhea than PPIs Hypergastrinemia more frequent Rare serious ADRs (<2%) include QT prolongation, nephritis, hypomagnesemia	Hyperuricemia, liver dysfunction, dizziness reported ≥2% Lower incidence of hypergastrinemia than vonoprazan

AE: Adverse event; DDI: Drug–drug interaction; EE: Erosive esophagitis; GERD: Gastroesophageal reflux disease; *H. pylori*: *Helicobacter pylori*; LA: Los Angeles; NERD: Non-erosive reflux disease; NSAID: Non-steroidal anti-inflammatory drug; P-CAB: Potassium-competitive acid blocker; PUD: Peptic ulcer disease; TEAE: Treatment-emergent adverse event; T_{max}: Time to maximum plasma concentration

Table 8: Determining the most appropriate prazans in various acid peptic disorders

Indication	Appropriate molecule	Justification
GERD	Tegoprazan	The rapid suppression of gastric acid secretion and rapid relief of heartburn with a single dose of P-CAB make it a suitable option for on-demand GERD therapy ¹⁴³ A significantly higher number of patients treated with tegoprazan show rapid symptom resolution within 30 minutes as compared to esomeprazole (26.2% vs. 16.1%) ¹⁰⁴ In patients with all grades of erosive esophagitis, P-CABs (including fexuprazan 40 mg, tegoprazan 50 mg or 100 mg, and vonoprazan 20 mg) are comparable in efficacy to PPIs for healing of EE ¹⁴³ Offers better cumulative healing rates up to week 4 compared to PPIs in severe (LA grades C/D) esophagitis (95.2% [98/103] vs. 86.2% [94/109], difference: 8.91%) ¹⁰³
Patients with NAB	Tegoprazan	Tegoprazan offers rapid nighttime acid control within 1 hour compared to 4 hours with vonoprazan and PPIs ⁹⁵ Tegoprazan produces more potent and sustained night-time acid control compared to PPIs and vonoprazan. The percentage of time at pH ≥ 4 during night was 66.0% for tegoprazan, 60.5% for vonoprazan, and 36.1% for esomeprazole ⁹⁵ The time to first nighttime heartburn-free interval was quicker with tegoprazan (in just 1.5 days) compared with 3 days with esomeprazole ¹⁰⁶
<i>H. pylori</i> -eradication therapy	Vonoprazan	The eradication rate of <i>H. pylori</i> eradication was notably greater with vonoprazan-based triple therapy, compared to that with lansoprazole-based triple therapy (92.6% vs. 75.9%; treatment difference 16.7%) ¹²⁷
NSAID-associated PUD	Vonoprazan	Vonoprazan is comparable in efficacy to PPIs for preventing NSAID-induced peptic ulcers and significantly reduces the risk of ulcer recurrence (RR 0.55) and gastrointestinal bleeding (RR 0.40) compared with PPIs ¹⁵⁸
APD with CV comorbidities	Tegoprazan	Tegoprazan offers a safer choice for patients requiring antiplatelet therapy who are at an increased risk for GI complications, as it reduces the risk of GI bleeding by 28% (HR 0.72) and the risk of major bleeding by 31% (HR 0.69) compared with PPIs, without an increased risk of ischemic events in AMI patients receiving DAPT after PCI ^{159,160}
Patients with symptoms of laryngopharyngeal reflux disease	Fexuprazan	Significant improvements were observed in mean change in RSI, RFS, and LPR-related questionnaires after 4 and 8 weeks with fexuprazan. For those with severe symptoms (RSI ≥ 18), fexuprazan showed more improvement in the mean change and change rate in the RSI than PPIs ^{139,140}
APD with renal disease	Tegoprazan	Tegoprazan has a 0.58-fold lower risk of doubling of creatinine and 0.50-fold lower risk of decline of eGFR compared to PPIs, offering a relatively safer option for preserving kidney function ¹¹⁴
APD with hepatic disease	Vonoprazan	Conventional PPIs are associated with risk of hepatotoxicity with long-term use. Vonoprazan is associated with substantially lower 6- and 12-month risks of mortality (aHR 0.36–0.39), infections (aHR 0.60–0.67), liver complications (aHR 0.16–0.18), and liver-related hospitalizations (aHR 0.12–0.13) compared with PPIs, making it a suitable option for patients with hepatic diseases ¹³⁰
APD with diabetes	Tegoprazan	Tegoprazan has been associated with renal and hepatic safety across clinical trials, making it a safer alternative in patients with comorbid diabetes ~27% lower risk of hepatotoxicity compared with PPIs ¹¹³ ~48% lower risk of doubling of creatinine and 37% lower risk of decline in eGFR of $\geq 50\%$ compared to PPIs ¹¹⁴

aHR: Adjusted hazard ratio; AMI: Acute myocardial infarction; APD: Acid peptic disorder; CV: Cardiovascular; DAPT: Dual antiplatelet therapy; eGFR: Estimated glomerular filtration rate; GERD: Gastroesophageal reflux disease; GI: Gastrointestinal; LA: Los Angeles; LPR: Laryngopharyngeal reflux; NAB: Nocturnal acid breakthrough; NSAID: Non-steroidal anti-inflammatory drug; PCI: Percutaneous coronary Intervention; PPI: Proton pump inhibitor; PUD: Peptic ulcer disease; RFS: Reflux finding score; RR: Relative risk; RSI: Reflux symptom index

Precautions for Vonoprazan Use in Hepatic and Renal Impairment^{116,118}

Exposure to vonoprazan increases in patients with moderate-to-severe hepatic impairment. Therefore, caution is advised when prescribing vonoprazan in patients with Child–Pugh class B or C hepatic dysfunction.

Current prescribing information recommends: • Child-Pugh A: Standard dosing can be used.

Hepatic impairment severity	Erosive esophagitis	<i>H. pylori</i>
Child-Pugh class A	20 mg OD	20 mg BD
Child-Pugh class B	10 mg OD	Not recommended
Child-Pugh class C	10 mg OD	Not recommended

- Child-Pugh B or C: Exposure may increase significantly; dose reduction or avoidance should be considered depending on indication.

Renal impairment severity	Erosive esophagitis	<i>H. pylori</i>
eGFR ≥ 30 mL/min/1.73 m ²	20 mg OD	20 mg BD
eGFR < 30 mL/min/1.73 m ²	10 mg OD	Not recommended

- eGFR ≥ 30 mL/min/1.73 m²: No dose adjustment generally required
- eGFR < 30 mL/min/1.73 m²: Limited data are available; cautious use is recommended
- End-stage renal disease: Clinical experience remains limited

CONFLICT OF INTEREST

None.

SOURCE OF FUNDING

This work was supported by Dr. Reddy's Laboratories Ltd., Hyderabad, Telangana, India.

AUTHORS' CONTRIBUTIONS

MG contributed to conceptualization, methodology, and data collection. MG, UCG, and VPK contributed to the overall drafting and review of the manuscript. RSB, PR, and SS contributed to data analysis, interpretation of results, manuscript review, and editing of the section "Overview of Acid Peptic Disorders." NP and HM contributed to the section "Unmet Clinical Needs with Proton Pump Inhibitors." VS and SP contributed to the section "Introduction to Prazans (P-CABs)." VGM and DY contributed to the section "Pharmacological and Clinical Overview of Tegoprazan." RP and MKP contributed to the sections "Pharmacological and Clinical Overview of Vonoprazan" and "Pharmacological and Clinical Overview of Fexuprazan." PL, MK, and BSR contributed to the sections "Translating Evidence into Practice: Positioning Prazans in Acid Disorders" and "Comparison of P-CABs." All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors thank Dr. Reddy's Laboratories Ltd. for its support and assistance during the preparation of this manuscript.

AI DISCLOSURE

The authors confirm that no artificial intelligence-assisted technologies were used in the preparation of this manuscript.

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