REVIEW ARTICLE

Association of Physicians of India Consensus Recommendations for Vonoprazan in Management of Acid Peptic Disorders

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Abstract

The suppression of gastric acid secretion has long been the cornerstone of treatment for acid peptic disorders (APDs). Proton pump inhibitors (PPIs) have played a central role in managing these conditions, but their effectiveness can be hindered by notable limitations such as refractoriness or treatment failure due to inadequate acid suppression in some gastroesophageal reflux disease (GERD) patients, nonadherence to prescribed regimens due to the complexity of dosing, variability of response, and nocturnal acid breakthrough, etc. Vonoprazan is a first-in-class potassium-competitive acid blocker (P-CAB), recently introduced in India and also approved in several countries such as Japan, South Korea, and the USA. Extensive clinical evidence suggests that vonoprazan offers more potent acid suppression than PPIs. This consensus from the Association of Physicians of India (API) has been developed with the objective of providing key recommendations for the appropriate clinical usage of vonoprazan across various subsets of APDs, thereby optimizing the existing therapeutic options and improving the care and management of APD patients.

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Introduction

India is a land of multiple cultural practices with strong differences in foods consumed across different states and regions. Despite the lifestyle differences, acid peptic disorders (APDs) are widely prevalent across India.[1,2] Among various APDs, gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders globally and in India.[3] Consensus guidelines from the Association of Physicians of India (API) and the Indian Society of Gastroenterology (ISG) identified GERD prevalence as being around <10% in most population studies.[4] Besides GERD, peptic ulcer disease (PUD) has been a significant contributor to morbidity and mortality.[5] Amidst multiple risk factors, infection with *Helicobacter pylori* has been identified as a significant contributor to APDs and gastric malignancy.[6] Among all these APDs, inhibition of gastric acid secretion has been the mainstay of treatment. The self-medication of antacids in the setting of heartburn or similar symptoms is often insufficient, as individuals tend to stop drugs with some symptomatic relief. This leads to massive under-treatment of APDs. Over the last few decades, H_2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) have been the principal acid suppressants.[7] Despite their efficacy in APDs, nonresponsiveness to PPIs in GERD and *H. pylori* infection is not uncommon.[8–10] Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) recently approved in India and may represent a real breakthrough in acid suppression. Considering the pharmacological limitations of PPIs, there is a strong need to understand the pharmacokinetics, pharmacodynamics, and clinical evidence pertaining to the use of vonoprazan. It is necessary, on the part of the treating physicians, to adequately and safely use this new therapeutic entity in different subsets of APD patients. At present, there is no guidance document from India available regarding the appropriate clinical usage of vonoprazan.

Need for the Consensus

In India, primary care physicians or family physicians are the first point of contact for patients with complaints related to APDs. However, inappropriate use of PPIs is widely prevalent in the Indian setting.[11,12] This is of great concern considering the suboptimal dosing, insufficient acid suppression, adverse effects, and drug interactions associated with PPIs. Owing to such practices and concerns, Indian experts have published recommendations for the rational use of PPIs.[13] Another important aspect is the under-dosing of PPIs in indications requiring twice-daily dosing of PPIs. However, this has not been observed in routine clinical practices, probably because of physician unawareness, clinical inertia in prescribing

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twice-daily dosing of PPIs, or possible fear of adverse effects.

Vonoprazan, a first-in-class P-CAB, was first approved in Japan in 2015 and subsequently approved in more than 15 countries, including Russia, South Korea, and the USA.[14] Over the period of 8 years, vonoprazan has accumulated considerable clinical evidence globally in several acid-related disorders. In 2024, regulatory approval of vonoprazan was further expanded in India.[15] In clinical studies, vonoprazan has shown effectiveness in PPI-resistant erosive esophagitis (EE), nonerosive reflux esophagitis (NERD), as well as in *H. pylori* regimens.[16–18] Although substantial clinical studies on vonoprazan have been published globally, no guidance document on its usage in Indian clinical practice has been published or is available to date. Therefore, to ensure vonoprazan's appropriate clinical usage across various subsets of APDs and to optimize the existing therapeutic options, this consensus document has been developed to provide relevant guidance to Indian physicians on the use of vonoprazan in Indian clinical settings. In this context, the expert working group of API recognized an urgent need to develop this consensus to guide physicians across India in the appropriate use of vonoprazan for managing various APDs.

Approach to the Consensus Development

Expert Panel

For this consensus development, a multidisciplinary consensus working group was formulated by the lead expert from the API. Each expert involved in the consensus had vast clinical experience in the management of APDs in India. They also had experience with prescribing Vonoprazan in different patient profiles. The experts belonged to specialties such as internal medicine, gastroenterology, otorhinolaryngology, pulmonology, cardiology, rheumatology, and nephrology.

Conesus Statements

The lead expert, in discussion with others, developed the consensus statements. While deriving the consensus statements, the criteria of answerability, effectiveness, potential for translation to clinical practice, novelty, and potential impact on the healthcare burden were considered. A total of 13 statements were initially framed for presentation in the consensus working group meeting.

Arriving at a Consensus

We utilized the Delphi method for arriving at a consensus. The Delphi method is a scientifically proven technique that assists in the organization and management of structured group discussions. Often, it aims to generate insights on situations wherein there is limited information or there is a need to address current or future challenges in given situations. It has been frequently used in medicine.[19] In this consensus development, there were two rounds of consensus working group experts. In the initial round of discussion, the lead expert presented the clinical evidence pertaining to each consensus statement, followed by the discussion among the experts. After the discussion, each expert was asked to rate their opinion on a 5-point Likert scale as strongly disagree, disagree, neutral, agree, strongly agree.[20] The voted opinion was collated from each expert and was analyzed descriptively.

Acceptance Criteria

We used a 5-point Likert scale (strongly agree, agree, neutral, disagree, and strongly disagree) for expert voting.[21] The expert voting for agree/strongly agree for a given consensus statement was considered as acceptable. To finally accept or refute the consensus, a voting percentage of 85% was considered as the cutoff for accepting the consensus statement. Figure 1 provides the key steps in developing the consensus. Table 1 summarizes all the finally accepted consensus statements.

Prevalence of Acid Peptic Disorders in India

Acid peptic disorders are widely prevalent in India. A meta-analysis of nine studies with 20,614 subjects reported a pooled GERD prevalence of 15.6%.[22] The ISG consensus on GERD in adults identified that GERD prevalence ranges between 7.6 and 30%, with most studies reporting it to be <10%.[23] In relation to GERD, EE and NERD are important contributors to symptomatology and morbidity. In EE diagnosed by upper GI (UGI) endoscopy, India ranks second in the world with a prevalence of 52% and is preceded by Indonesia (55%).[24] A multiethnic study from Malaysia involving 1000 patients reported NERD prevalence of 28.2, 32.1, and 16.8% in Malay, Indian, and Chinese ethnicities, respectively. The Indian race was also the strongest risk factor for NERD.[25] Based on the UGI endoscopy, EE is classified as grade A–D based on the size and extent of mucosal breaks (Table 2).[26] A recent study from South India involving 100 refractory GERD patients identified NERD in 33% and EE in 67% of cases. LA grade B was the most frequent EE (43%).[27] GERD has also been linked to the development of Barrett's esophagus (BE). A study from West India observed 278 patients with GERD over 2 years and reported BE in 16.54% of cases.[28] The API-ISG consensus also identifies BE prevalence in India to range from 2.6 to 9%.[4] Another important acid reflux disorder is laryngopharyngeal reflux disease (LPRD). A recent survey of 2300 individuals from India was performed to detect LPRD using the reflux symptom index (RSI). In 253 responders, RSI was >13, amounting to an 11% prevalence of LPRD with no difference in males and females (11.2 vs 10.6%, respectively).[29] The burden of *H. pylori* disease is enormous in India.[30,31] Recent global estimates indicate that the crude prevalence of *H. pylori* is 35.1%. In India, the pooled prevalence of *H. pylori* from 12 studies in adults was observed to be 59.5%.[32] *H. pylori* has been linked to the development of PUD. Over three decades (1990–2019), there has been a substantial reduction in PUD-related age-standardized mortality in India.[33] Nonetheless, the PUD burden still remains an important issue in the Indian setting.

- Consensus 1: There is a substantial presence of APDs in India [agree/strongly agree: 100%].

Limitations of Proton Pump Inhibitors

Since their introduction, PPIs have been used extensively across the globe and in India as well. Although proven effective in APDs, PPIs have notable limitations. One important limitation is the relative ineffectiveness of PPIs in GERD. Nearly 40% of patients with GERD do not respond to 8-week therapy of PPIs and are labeled as refractory GERD.[34,35] One possible reason for such inefficacy could be suboptimal

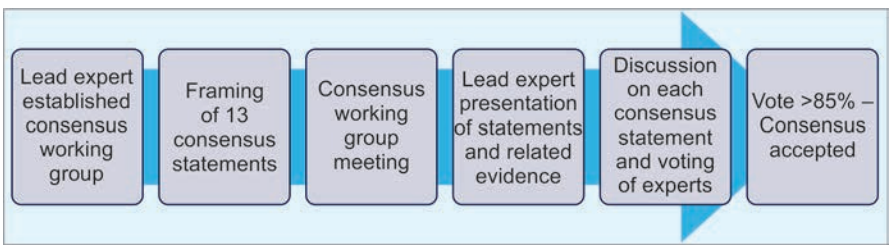

Fig. 1: Approach to the consensus development

Table 1: Consensus statements

PREVALENCE OF APDs IN INDIA
Consensus 1: There is a substantial presence of APDs in India [agree/strongly agree: 100%]
LIMITATIONS OF PPIs
Consensus 2: Currently available PPIs have certain limitations in management of GERD [agree/strongly agree: 100%]
FOOD AND PPIs ADMINISTRATION TIMING
Consensus 3: In real-world clinical practice, majority of GERD patients on PPI therapy do not comply with the advice of taking PPIs at least 30–45 minutes before meal that may lead to diminished treatment effectiveness and/or increased treatment failures [agree/strongly agree: 100%]
VONOPRAZAN PHARMACOLOGY
Consensus 4.1: In managing APDs, vonoprazan potentially overcomes the clinically relevant limitations of PPIs [agree/strongly agree: 100%]
Consensus 4.2: In managing GERD patients with predominant nocturnal acid breakthrough, vonoprazan may be considered as an alternative treatment approach to PPIs [agree/strongly agree: 100%]
Consensus 4.3: Vonoprazan can be administered irrespective of the meal timing [agree/strongly agree: 100%]
VONOPRAZAN AND REFRACTORY GERD
Consensus 5: In refractory GERD patients, switching from PPIs to vonoprazan (20 mg, once daily) is considered as the most suitable treatment approach [agree/strongly agree: 100%]
VONOPRAZAN & EROSIVE ESOPHAGITIS (EE)
Consensus 6.1: In mild EE (Los Angeles grade A and B), vonoprazan (20 mg, once daily) may be considered as an alternative to PPIs as it reduces the treatment duration by 4 weeks [agree: 91.7%/neutral:8.3%]
Consensus 6.2: Vonoprazan (20 mg, once daily) may be considered as an alternative to PPIs in mild EE (LA grade A/B) patients who are noncompliant to PPI dosing schedule [agree/strongly agree: 100%]
Consensus 7: Vonoprazan is recommended as the initial treatment approach for severe EE (LA grades C/D) [agree/strongly agree: 100%]
VONOPRAZAN & NON-EROSIVE REFLUX DISEASE (NERD)
Consensus 8.1: Vonoprazan may be considered as an alternative to PPIs in the treatment of NERD with excessive esophageal acid exposure [agree/strongly agree: 100%]
Consensus 8.2: In the long-term management of NERD, vonoprazan may be considered as an on-demand treatment approach [agree/strongly agree: 100%]
VONOPRAZAN & *H. PYLORI* ERADICATION REGIMENS
Consensus 9: In eradication regimens for *H. pylori* infection, vonoprazan is recommended in place of PPIs [agree/strongly agree: 100%]
VONOPRAZAN AND NSAID INDUCED PEPTIC ULCERS
Consensus 10: Vonoprazan can be an alternative to PPIs as a concomitant therapy in patients at a high risk of peptic ulcer with chronic use of NSAIDs [agree/strongly agree: 100%]
VONOPRAZAN & LARYNGOPHARYNGEAL REFLUX DISEASE (LPRD)
Consensus 11: Vonoprazan may be considered as an alternative to PPIs in the treatment of LPRD [agree: 100%]
VONOPRAZAN LONG TERM SAFETY
Consensus 12.1: In the maintenance therapy of GERD, vonoprazan is found to be safe (clinical evidence is up to 5 years–as per Japanese VISION trial) [agree/strongly agree: 100%]
Consensus 12.2: In patients with cardiovascular comorbidity receiving antiplatelet therapy, vonoprazan may be considered as a treatment option with careful monitoring [agree/strongly agree: 100%]
VONOPRAZAN IN HEPATIC AND RENAL IMPAIRMENT
Consensus 13.1: Vonoprazan can be considered in patients with renal impairment with careful monitoring (as per dosages suggested in Table 5) [agree/strongly agree: 100%]
Consensus 13.2 Vonoprazan can be considered in patients with hepatic impairment with careful monitoring (as per dosages suggested in Table 5) [agree/strongly agree: 100%]

Table 2: Los Angeles (LA) Grading of Erosive Esophagitis (EE)

LA grade	*UGI endoscopy finding*
A	≥1 mucosal breaks, <5 mm long, no extension between tops of 2 mucosal folds
B	≥1 mucosal breaks, >5 mm long, no extension between tops of 2 mucosal folds
C	≥1 mucosal breaks, continuous between tops of 2 or more mucosal folds, involves <75% of the esophageal circumference
D	≥1 mucosal breaks, continuous between tops of 2 or more mucosal folds, involves at least 75% of the esophageal circumference

adherence and inappropriate use of PPIs.[36] PPIs are prodrugs and provide effective acid suppression only after protonation to form disulfide bonds with cysteines of the H^+, K^+-ATPase pump. As PPIs irreversibly inhibit the active proton pump, it is necessary to administer PPIs 30–45 minutes before a meal to achieve peak concentration at gastric canaliculi.[37] This limits the PPIs administration in relation to food. In addition, the stability of the binding of PPIs to the proton pump determines the duration of pump inhibition.[37] Additionally, the short half-life of PPIs is a concern, as once- or twice-daily administration may not achieve complete acid suppression. Nearly 20% of pumps are synthesized in 24 hours, and it takes 48–73 hours for PPIs to reach the steady-state phase of acid inhibition.[37] Another limitation is nocturnal acid-breakthrough (NAB), which occurs in

40–70% of GERD patients receiving PPIs.[38,39] This can contribute to esophageal mucosal damage. Another important limitation with PPIs is drug-drug interactions involving CYP2C19 and CYP3A4 metabolism. Liver function impairment and older age impact the clearance of PPIs. Mutations in CYP2C19 also affect the metabolism of PPIs, and 15–20% of Asians are known to be rapid metabolizers, increasing the risk of side effects.[40]

- Consensus 2: Currently available PPIs have certain limitations in the management of GERD [agree/strongly agree: 100%].

Food and Proton Pump Inhibitors Administration Timing

PPIs need to be administered 30–45 minutes before a meal to achieve the inhibition of active proton pumps. A survey of 100 GERD patients who had persistent symptoms despite PPIs was conducted to identify suboptimal dosing of PPIs. Suboptimal dosing was considered when PPIs were taken >60 minutes prior to meals, after meals, as needed, and at bedtime before sleeping. About 54% of respondents were dosed suboptimally, whereas only 12% were taking PPIs in a manner that maximized acid suppression.[41] The OSCAR trial reported that the administration of PPIs 30 minutes before breakfast, compared to any other time of administration, is associated with improvement in GERD symptoms.[42] In India, studies have identified that incorrect timing of PPI administration contributes significantly to the persistence of GERD symptoms.[27] Further, studies identify a strong need for patient education and reinforcement of dosing instructions by treating physicians in relation to PPI dosing.[43]

- Consensus 3: In real-world clinical practice, the majority of GERD patients on PPI therapy do not comply with the advice of taking PPI at least 30–45 minutes before a meal, which may lead to diminished treatment effectiveness and/or increased treatment failures [agree/strongly agree: 100%].

Vonoprazan: A Potassium-competitive Acid Blocker

P-CABs are a new class of drugs that target the potassium binding sites of proton pumps to exhibit acid suppression. Vonoprazan is the first P-CAB with initial global approval in Japan (2015)[44] and has been approved in the USA.[45] In the gastric parietal cells, the H^+–K^+ ATPase pumps (proton pumps) are stored in tubulovesicles and are inactive. Once pumps are inserted in the canalicular membrane at luminal borders, the proton pumps are activated. Part of the pump that protrudes in the lumen is the extra-cytoplasmic secretory canaliculus. This section is acidic as it is exposed to the gastric lumen. PPIs, being prodrugs, are converted to sulfenamide, a step necessary for the drug to bind to cysteines on active proton pumps. The site of accumulation and activation of PPIs is therefore the extra-cytoplasmic secretory canaliculus. The binding of PPIs to cysteine residues is by covalent disulfide bonds and is irreversible. Vonoprazan, a P-CAB, is not a prodrug, and there is no need for its activation or acid dependence for proton pump binding. Vonoprazan binds to both active pumps present at the membrane of parietal cells as well as the pumps that are inactive in the tubulovesicles. The binding of vonoprazan is ionic and is thus reversible. Vonoprazan blocks the access of potassium (K^+) ions to the potassium-binding site of the pump that is necessary for the exchange of H^+ into the lumen. This results in reduced entry of H^+ ions into the gastric lumen and helps to reduce both basal and stimulated gastric acid secretion (Fig. 2).[46,47]

Pharmacodynamic Effects

Compared to PPIs, vonoprazan is shown to have rapid and potent antacid activity as measured by 24-hour gastric pH measurements. Better gastric acid suppression than lansoprazole has been reported in the US study.[47] In another randomized, cross-over study from Japan, a comparatively better acid suppressive effect of vonoprazan than either esomeprazole or rabeprazole was reported (Fig. 3). The likelihood of NAB with vonoprazan was lower as the duration of vonoprazan was 4 hours longer to maintain pH >4.[48] These studies prove that vonoprazan has a significantly rapid impact on intragastric pH and the effect is sustained for 24 hours. Based on the results of the US study, vonoprazan can be taken irrespective of fed or fasted conditions.[49] Table 3 provides a comparative assessment of PPIs vis-à-vis vonoprazan.[50]

- Consensus 4.1: In managing APDs, vonoprazan potentially overcomes the clinically relevant limitations of PPIs [agree/strongly agree: 100%].
- Consensus 4.2: In managing GERD patients with predominant NAB P, vonoprazan may be considered as an alternative treatment

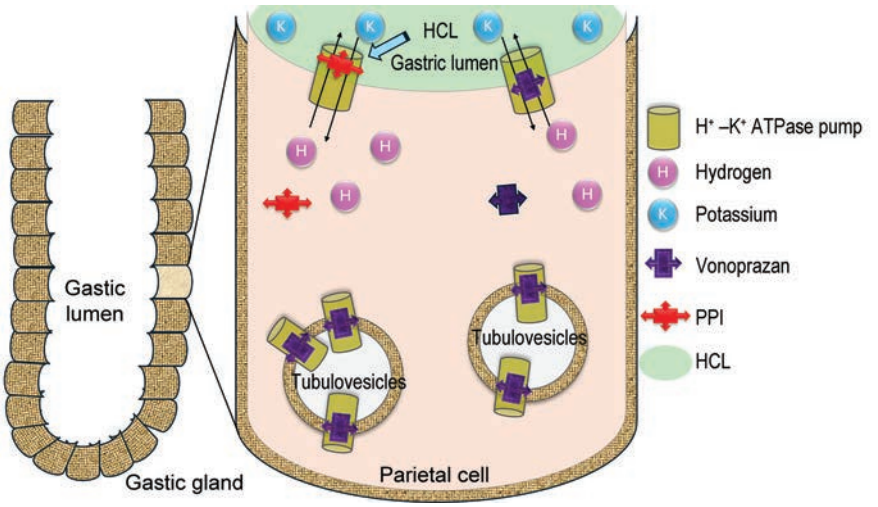

Fig. 2: Mechanism of action of vonoprazan: In the gastric parietal cells, PPI block the H^+–K^+ ATPase pump from the luminal side after their activation in the gastric acid. PPIs do not affect the resting or inactive pumps in the tubulovesicles. Vonoprazan blocks both active and inactive pumps in the parietal cells at the active site of potassium. Entry of potassium inside the cell is inhibited and hydrogen exchange fails leading to lesser hydrogen concentration in the lumen and thereby decreased acid output.

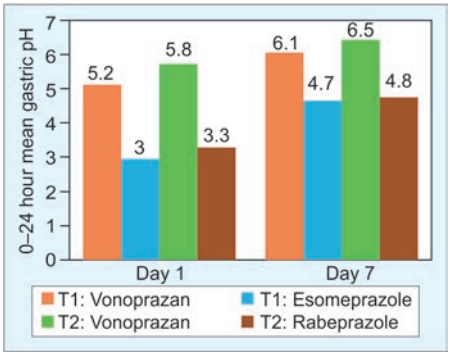

Fig. 3: 0–24 hour mean gastric pH in vonoprazan, esomeprazole and rabeprazole groups: T1—first time period of the study; T2—second time period of the study

approach to PPIs [agree/strongly agree: 100%].

- Consensus 4.3: Vonoprazan can be administered irrespective of the meal timing [agree/strongly agree: 100%].

Vonoprazan and Refractory GERD

Gastroesophageal reflux disease (GERD) is termed refractory when there are typical or atypical symptoms of GERD with no response to twice-daily PPI therapy for a minimum of 8 weeks.[27] Besides noncompliance and improper or underdosing of PPIs, residual reflux, esophageal hypersensitivity to weakly acidic reflux, chronic and persistent breach in the mucosal integrity of the esophagus, and concomitant psychological distress are the major factors identified to be contributory to refractory GERD.[35] Management of such refractory GERD is difficult. Possible approaches for the management of refractory GERD are summarized in Figure 4.

Multiple studies have shown the short-term (4–12 weeks) as well as long-term (1 year) efficacy of vonoprazan in PPI-refractory GERD.[51,52] A systematic review and meta-analysis of three observational studies reported that vonoprazan 20 mg for 4–8 weeks was associated with symptom improvement in a significant proportion of patients (86.3%) with PPI-resistant GERD.[16] These studies are further supported by the international recommendations. Guidelines from the Japanese Society of Gastroenterology (2021) advised that vonoprazan can be considered for PPI-refractory GERD. In addition, guidelines indicate that the use of prokinetics and Japanese herbal medicine can be considered.[53] The American Gastroenterology Association (AGA) clinical practice update also recommends that vonoprazan can be used in patients who have acid reflux despite twice-daily therapy with PPIs.[50]

- Consensus 5: In refractory GERD patients, switching from PPIs to vonoprazan is considered the most suitable treatment approach [agree/strongly agree: 100%].

Table 3: Pharmacokinetic and pharmacodynamic comparison between PPIs and vonoprazan

Parameter	*PPIs*	*Vonoprazan (P-CAB)*
Acid stability	Labile (enteric coating must)	Stable
Prodrugs	Yes	No
Activation in acid environment	Required	Not required
Binding to H^+–K^+ ATPase pump	Covalent, irreversible	Ionic, reversible
Proton pump inhibition	Only active	Both active and inactive
Time of administration	30–60 minutes before meal	Food independent
Half life	1–2 hours	6–9 hours
Onset of action	Delayed	Rapid
Time to maximal acid suppression	3–5 days	1 day
24-hour acid suppression	Not achieved	Achieved
Nocturnal acid breakthrough	More likely	Less likely
Duration of acid suppression	Shorter	Longer
CYP2C19 related interactions	Yes	No

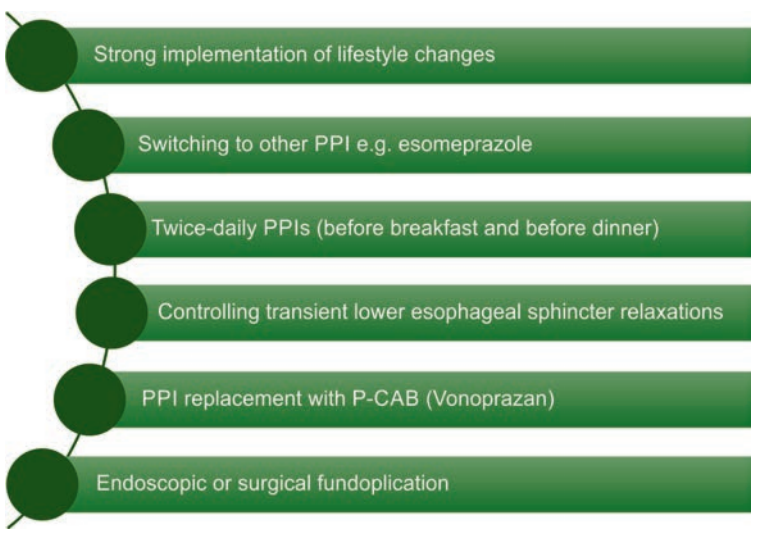

Fig. 4: Possible approaches to manage refractory GERD

Vonoprazan in Erosive Esophagitis

Mild Erosive Esophagitis (Los Angeles Grade A and B)

The 2021 Japanese Society of Gastroenterology guidelines have recommended the use of either PPI for 8 weeks or vonoprazan for 4 weeks. This suggests that vonoprazan can help reduce the treatment duration by 4 weeks. After 4 weeks, maintenance therapy with vonoprazan can be considered to prevent recurrences. Patients who do not respond to 8 weeks of standard-dose PPI therapy can be switched to vonoprazan 20 mg daily.[53] The AGA practice update also recommends that clinicians may use P-CABs in selected patients who fail therapy with twice-daily PPIs.[50] Thus, vonoprazan can be an alternative to PPIs.

- Consensus 6.1: In mild EE (Los Angeles grade A and B), vonoprazan 20 mg, once daily, may be considered an alternative to PPIs as it reduces the treatment duration by 4 weeks [agree: 91.7%/neutral: 8.3%].
- Consensus 6.2: Vonoprazan (20 mg once daily) may be considered an alternative to PPIs in mild EE (LA grade A/B) patients who are noncompliant with the PPI dosing schedule [agree/strongly agree: 100%].

Severe Erosive Esophagitis (Los Angeles Grade C and D)

In severe EE, PPIs have been standard treatment for a long time. However, nearly 15% of EE patients do not achieve complete healing even after 8 weeks of PPIs. Even with continuation of PPIs, relapse within 6 months is seen in 24–41% of EE patients with LA grade C and D.[54] With severe EE, failure of PPI calls for effective therapy. Vonoprazan has been shown to be effective in both healing and maintenance of healing in severe EE grades.[55] In another double-blind trial from

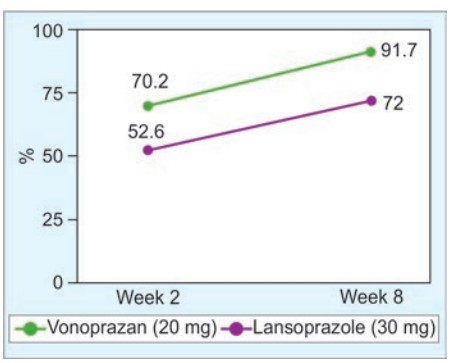

Fig. 5: Healing rates in Los Angeles grade C/D EE with vonoprazan and lansoprazole

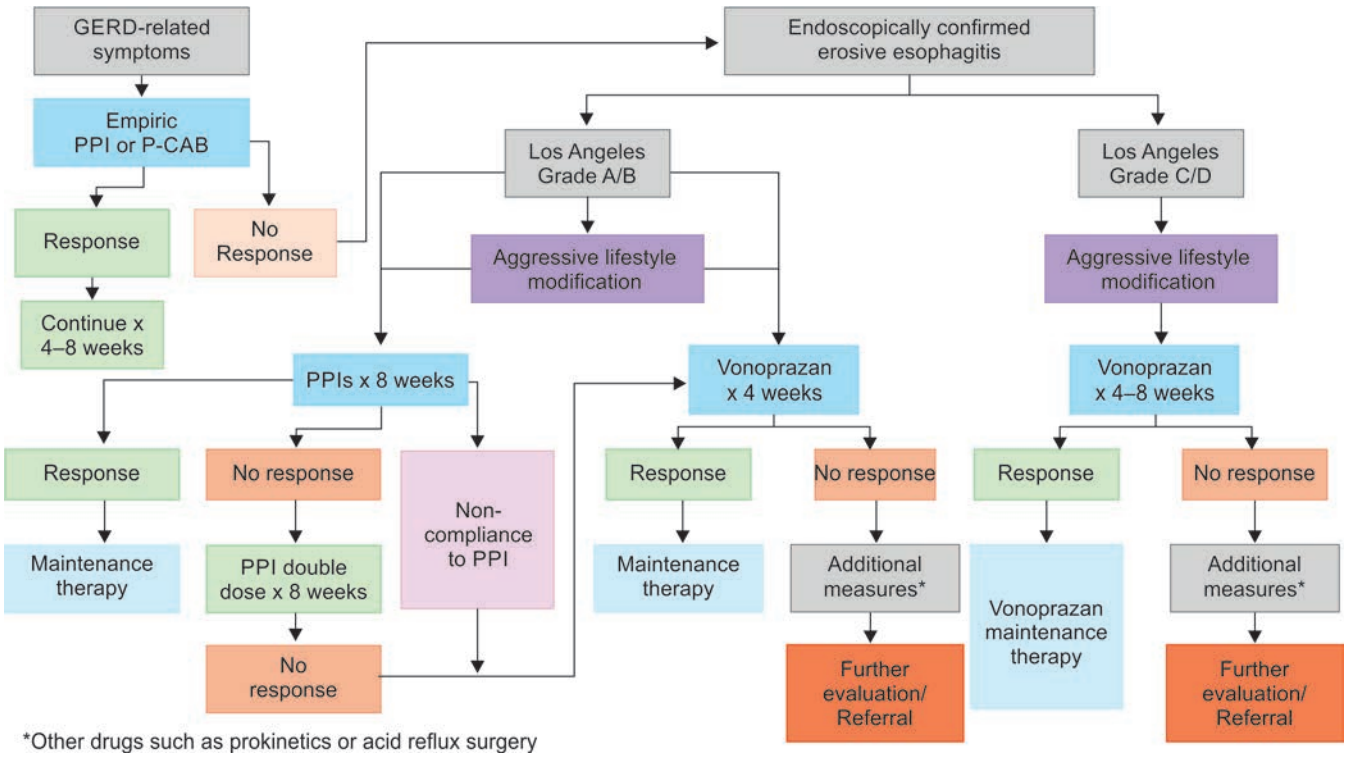

Fig. 6: Approach to the management Erosive Esophagitis (EE)

the US, Laine et al. reported greater overall EE healing rates (all grades A–D) at 8 weeks with vonoprazan than lansoprazole (92.9 vs 84.6%). Figure 5 provides healing rates for grade C/D EE in two groups. During the maintenance phase, healing rates of grade C/D EE at 24 weeks were significantly better with vonoprazan 20 mg (77.2%) and 10 mg (74.7%) than lansoprazole 15 mg (61.5%). Also, the heartburn-free days were substantially higher with both doses of vonoprazan.[56] These findings indicate that vonoprazan has substantial promise as starting therapy for severe EE. This is confirmed by the Japanese Gastroenterology Guidelines[53] as well as the AGA practice update recommendations.[50] Also, vonoprazan has been approved for this indication by the United States Food and Drug Administration (USFDA).[45] Figure 6 provides the approach to the management of EE.

- Consensus 7: Vonoprazan is recommended as the initial treatment approach for severe EE (Los Angeles grades C/D) [agree/strongly agree: 100%].

Vonoprazan in Nonerosive Reflux Disease

NERD does not involve the acidic erosion of the esophageal lining, and thus the absence of erosion on endoscopy is classified as NERD. It commonly occurs because of nonacid or weak acid reflux, causing symptoms such as heartburn. PPIs have long been used in heartburn due to NERD.[57] Vonoprazan has been evaluated in phase 2 and phase 3 trials for heartburn in NERD. A phase 2 trial involved 458 patients with NERD having heartburn for ≥6 months or during any ≥4 days of consecutive seven days in the screening period with normal endoscopic features. In a 4-week run-in period, all patients received vonoprazan 20 mg daily and were randomized at the end of 4 weeks to vonoprazan 10, 20, and 40 mg groups and placebo as "on-demand" therapy (to be taken only when heartburn occurs). After 6 weeks, complete and sustained relief was reported by 56, 60.6, and 70% of patients from the three vonoprazan dose groups, respectively. Compared to the response rate of 27.3% in the placebo group, all vonoprazan doses provided significantly better results. There were no serious adverse events related to the treatments.[58] The PHALCON-NERD-301 trial confirmed the effectiveness of vonoprazan in NERD. The trial included patients similar to the phase 2 study. Patients were randomized to vonoprazan 20 mg, 10 mg, and placebo. Patients in the placebo arm were rerandomized to either vonoprazan 10 or 20 mg. All patients continued treatment for 20 more weeks. Vonoprazan significantly improved the primary efficacy results of 24-hour heartburn-free days (Fig. 7) in NERD patients. The effect on reducing 24-hour heartburn was evident on day 1. In the extension phase, patients shifted from placebo to vonoprazan rapidly responded and joined

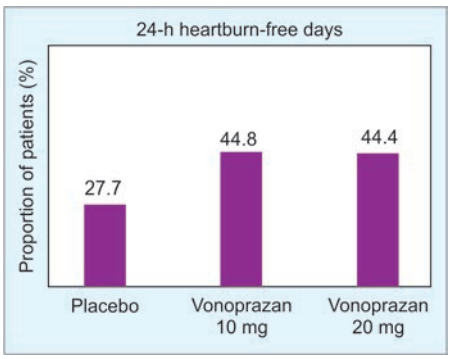

Fig. 7: Vonoprazan effect on 24-hour heartburn-free days in NERD patients in 4-week

the previously continued vonoprazan group in terms of the efficacy endpoint. The study concluded that NERD patients derived benefit in terms of relief from heartburn as early as day 1, and benefits persisted over a period of 24 weeks. Both doses of vonoprazan were effective.[59] This led to the indication approval for vonoprazan by the USFDA.[45] The Japanese guidelines also indicated that P-CABs like vonoprazan may also be effective in NERD with excessive esophageal acid exposure.[53]

- Consensus 8.1: Vonoprazan may be considered as an alternative to PPIs in the treatment of NERD with excessive esophageal acid exposure [agree/strongly agree: 100%].
- Consensus 8.2: In the long-term management of NERD, vonoprazan may

be considered as an on-demand treatment approach [agree/strongly agree: 100%].

Vonoprazan in *H. Pylori* Infection

As discussed previously, the *H. pylori* burden is substantial in India. Current management of *H. pylori* is dependent on the use of PPIs and antibiotics. It has been shown that acid suppression is of prime importance in *H. pylori* eradication. *H. pylori* has the ability to survive in an acidic environment. It has acid acclimation activity by which the bacteria are able to maintain vitality but not growth. The bacteria raise the cytoplasmic pH moderately against external acidic pH. With the rise in pH after the use of PPIs it grows in the less acidic pH in the stomach with a doubling time of 4–6 hours.[60] It is at this phase that antibiotics such as amoxicillin and clarithromycin effectively exert antibacterial activity. The current 2024 regimens recommended by the American College of Gastroenterology (ACG) are shown in Table 4.[61] The American Gastroenterological Association recommends that P-CAB (vonoprazan) should be used in place of PPIs for most patients with *H. pylori*.[50] This has also been supported by the US FDA approval of vonoprazan use in combination with clarithromycin and amoxicillin as triple therapy or with amoxicillin as double therapy for adults with *H. pylori*.[45]

One of the key problems with *H. pylori* is the recurrence of disease. Multiple recurrences are common in previously treated individuals. To differentiate reinfection and recrudescence, a duration of 1 year has been considered. Recurrence of *H. pylori* after 1 year of initial eradication should be labeled as reinfection.[62] In India, there is significant recurrence of *H. pylori*, and rates may go as high as 60%.[63] It should be noted that asymptomatic *H. pylori* infection does not demand treatment. It is only symptomatic infection, with or without complications, that necessitates *H. pylori* treatment. It is recommended that after therapy of *H. pylori*, the test of cure (e.g., urea breath test, fecal antigen test, etc.) should be performed after 4 weeks of completion of treatment.[61] With respect to the use of vonoprazan in *H. pylori*, Indian studies are required. Nonetheless, it can be considered over PPIs in *H. pylori* management.

- Consensus 9: In eradication regimens for *H. pylori* infection, vonoprazan is recommended in place of PPIs [agree/strongly agree: 100%].

Vonoprazan and NSAID Induced Peptic Ulcers

Chronic use of painkillers such as nonsteroidal anti-inflammatory drugs (NSAIDs) or even low-dose aspirin carries a substantial risk of PUDs. Vonoprazan has been evaluated in this indication in multiple randomized studies. In one study from Japan by Mizokami et al., 642 patients on long-term NSAIDs who were at risk of PUD recurrence were enrolled. Initially, patients were randomized to vonoprazan (10–20 mg) or lansoprazole (15 mg daily) for a 24-week double-blind period, followed by an extension study. During the 24 weeks, both doses of vonoprazan were noninferior to lansoprazole. Endoscopically confirmed ulcers were observed in 3.3, 3.4, and 5.5% of the three groups, respectively. During the extension period, also, vonoprazan was effective and safe.[64] A postmarketing surveillance study of 1 year with the use of vonoprazan in patients with a history of PUD who were receiving NSAIDs also reported an ulcer recurrence rate of 1.04% and a better safety profile. The rate of adverse drug reactions was 0.71%.[65] These data are further supported by a systematic review of 10 articles demonstrating vonoprazan as an effective and safe initial and maintenance therapy for PUD related to chronic use of aspirin or NSAIDs.[66] The AGA practice update guidelines recommend that vonoprazan may be useful in PUD patients who fail to respond to PPIs.[50]

- Consensus 10: Vonoprazan can be an alternative to PPIs as a concomitant therapy in patients at high risk of peptic ulcer with chronic use of NSAIDs [agree/strongly agree: 100%].

Vonoprazan and Laryngopharyngeal Reflux Disease

As discussed previously, LPRD is not an uncommon entity, and adequate treatment of reflux is necessary to provide symptomatic relief. LPRD should be diagnosed adequately in a clinical setting. Primary care physicians should consider the referral of such patients to the otorhinolaryngologist. An interesting observation from Humayun et al. is that most otorhinolaryngologists had prescribed suboptimal PPI dosing in LPRD patients. In their study, PPIs were used once or twice daily in 63 and 31% of patients, respectively.[67] In LPRD, vonoprazan has been evaluated in a small number of studies. In 89 Chinese patients with LPRD, vonoprazan 20 mg once daily was compared to esomeprazole 20 mg twice daily. After 8 weeks, symptom relief, as indicated by the RSI and reflux finding score (RFS), was significant with both therapies. The effective rate of the two treatments was 86.7 and 77.3%, respectively. Thus, vonoprazan once daily was considered noninferior to esomeprazole twice daily for the treatment of LPRD.[68] Another study compared similar treatments for the relief of gastroesophageal reflux-related cough (GERC). By the end of 2 months, vonoprazan was similar in efficacy to esomeprazole in terms of cough symptoms score. However, the reflux symptoms and quality of life were better with vonoprazan.[69] Considering this, there is a need to further explore vonoprazan in Indian patients with LPRD.

- Consensus 11: Vonoprazan may be considered as an alternative to PPIs in the treatment of LPRD [agree: 100%].

Vonoprazan: Long-term Safety

In the randomized clinical trials of vonoprazan for EE, NERD, and *H. pylori*, no major safety

Table 4: *H. pylori* treatment approaches recommended by ACG 2024 clinical guideline

Regimen	*Treatment naïve*	*Previously treated*	
		Empiric therapy	Antibiotic sensitivity proven
Bismuth Quadruple*	Recommended (14 days)	Suggested (14 days)	
Rifabutin triple[#]	Suggested (14 days)	Suggested (14 days)	
Vonoprazan triple**	–	–	Suggested (14 days)
Vonoprazan + amoxicillin	Suggested (14 days)	May be considered if other treatments are not available	
Levofloxacin triple[!]		–	Suggested[a] (14 days)

*Bismuth salt + nitroimidazole (e.g. metronidazole, tinidazole) + tetracycline (e.g. tetracycline, doxycycline) + PPI; [#]rifabutin + amoxicillin + PPI; **vonoprazan (20 mg) + clarithromycin (500 mg) + amoxicillin (1000 mg) (proven clarithromycin sensitivity); [!]levofloxacin/moxifloxacin (500/400 once) + amoxicillin (500 mg, twice daily)/nitroimidazole + PPI (proven levofloxacin sensitivity); [a]only when Bismuth quadruple or rifabutin therapies have failed or unavailable

Table 5: Indication-wise vonoprazan dosing recommendation in hepatic and renal impairment

Disease	*Indication*	
	EE	*H. pylori*
Hepatic impairment		
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
Renal impairment		
eGFR ≥30 mL/minute	20 mg OD	20 mg BD
eGFR <30 mL/minute	10 mg OD	Not recommended

eGFR: estimated glomerular filtration rate

Table 6: Salient features of vonoprazan

* Rapid onset of action (within 30 minutes)
* Acid stable, no need of enteric coating; PPIs are acid labile
* No impact of food, administered with or without food
* Inhibits both active and inactive proton pumps; PPIs inhibit only the active pumps
* Longer lasting acid suppression (durable 24-hour acid control)
* Effective control of nocturnal acid breakthrough
* More rapid healing of EE than PPIs
* First choice (over PPIs) in patients with more severe EE (Los Angeles Grade C & D)
* Improved GERD symptom relief after switching from PPIs
* Effective alternative to high-dose IV PPIs for the prevention of re-bleeding after endoscopic haemostasis in high-risk PU bleeding
* Clinical use in Japan for more than 8 years, approved in 15+ countries including the USA and India
* 5 years safety (Japanese VISION trial), no increased risk of malignant alterations
* No CYP2C19 related drugs interactions, can be administered with antithrombotic drugs like clopidogrel

concerns were reported with its use for up to 1 year. A recent VISION trial was a 5-year open-label randomized trial of vonoprazan for maintenance of EE. Adult patients who had healed EE on endoscopy entered the maintenance phase and were randomized to vonoprazan 10 mg or lansoprazole 15 mg once daily. At the end of 5 years, cumulative recurrence of EE was significantly lower with vonoprazan. Adverse events leading to treatment discontinuation were 4.4 and 1.5% in the two groups, respectively. Compared to lansoprazole, a higher proportion of vonoprazan patients had parietal cell hyperplasia and foveolar hyperplasia, with similar rates of enterochromaffin-like cell hyperplasia and G-cell hyperplasia. Though median serum gastrin levels were significantly higher, there was no increased risk of malignant transformations or gastric neuroendocrine tumors.[70] Another randomized trial assessed vonoprazan compared to PPI for prevention of high-risk PU rebleeding after endoscopic hemostasis. The population included elderly, hemodynamically unstable patients, indicating severe profiles. All patients had endoscopically confirmed high-risk bleeding PU and were randomized to vonoprazan (20 mg twice daily for 3 days followed by 10 mg once daily for 28 days) or pantoprazole (8 mg/hour intravenous for 3 days followed by 20 mg twice daily for 28 days). Patient profiles included some with coronary artery disease, cerebrovascular disease, and other comorbidities. Few patients were receiving aspirin, NSAIDs, warfarin, and direct oral anticoagulants. Thirty-day rebleeding rates were similar in the two groups (7.1 vs 10.4%, respectively), and vonoprazan was considered noninferior to pantoprazole.[71] Another study evaluated vonoprazan for bleeding after endoscopic submucosal dissection (ESD)-induced gastric ulcers in patients who were receiving antithrombotic therapy. Data synthesis from a randomized trial and observational study reported post-ESD bleeding in 8/86 patients in the vonoprazan group and 18/86 patients in the PPI group. This indicated better efficacy of vonoprazan than PPIs in preventing post-ESD bleeding among patients who are receiving antithrombotic medications.[72] Another nationwide database study from Japan identified that in 16,145 patients with ischemic heart disease who were receiving >2 antithrombotic agents (clopidogrel, ticagrelor, ticlopidine, prasugrel, or a low-dose aspirin), vonoprazan was noninferior to PPI in terms of UGI bleed occurrence at 6 months (3.14 vs 4.17%, respectively).[73] These data indicate that there is a less likely possibility of drug-drug interactions with vonoprazan, especially with antithrombotic drugs such as clopidogrel. Given the minimal activity of CYP2C19 in metabolizing vonoprazan, interaction based on CYP2C19-metabolizing medications is minimal. Also, the substantial inclusion of patients with established cardiovascular disease in these studies indicated no likely increased risk of cardiovascular abnormalities. However, further long-term studies are necessary with vonoprazan.

- Consensus 12.1: In the maintenance therapy of GERD, vonoprazan is found to be safe (clinical evidence is up to 5 years—as per Japanese VISION trial) [agree/strongly agree: 100%].
- Consensus 12.2: In patients with cardiovascular comorbidity receiving antiplatelet therapy, vonoprazan may be considered as a treatment option with careful monitoring [agree/strongly agree: 100%].

Vonoprazan in Hepatic and Renal Impairment

As per the approved USFDA label,[45] dosing recommendations for different indications are shown in Table 5.

- Consensus 13.1: Vonoprazan can be considered in patients with renal impairment with careful monitoring (as per dosages suggested in Table 5) [agree/strongly agree: 100%].
- Consensus 13.2: Vonoprazan can be considered in patients with hepatic impairment with careful monitoring (as per dosages suggested in Table 5) [agree/strongly agree: 100%].

Summary

Vonoprazan is a first-in-class P-CAB that is now clinically being used in India. Based on its pharmacology and currently available clinical evidence in different APDs, Table 6 brings some salient features of vonoprazan in comparison to PPIs.

Conclusion

This is the first consensus from India that provides a unified approach for the use of vonoprazan, a novel P-CAB, in the management of different APDs. The unique action of vonoprazan inhibiting active and

inactive proton pumps at gastric parietal cells provides effective acid suppression. Combined with its improved efficacy and safety in mild to severe APDs like GERD, EE, NERD, and *H. pylori* infection, vonoprazan holds promise to be a frontline therapy in APD management. Increasing evidence from the studies for de novo PUD and NSAID-induced ulcers shows substantial promise of this molecule in these indications as well. With a comparable safety profile to those of PPIs and better efficacy, vonoprazan has emerged as an excellent alternative to PPIs in mild to severe forms of APDs. In the Indian context, physicians should ensure the appropriate use of vonoprazan to gain maximum therapeutic benefits in APD patients.

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Author Contributions

All authors contributed to the development of this consensus. All authors read and approved the final manuscript.

Conflict of Interest

Ashwin Kotamkar, Shailesh Pallewar and Amit Qamra are full-time employees of Macleods Pharmaceuticals Ltd.

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