Potassium-Competitive Acid Blockers and Proton Pump Inhibitors: The Dynamic Duo of Acid Blockers

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Abstract: The management of acid-based disorders was transformed in the 1980s with the advent of proton pump inhibitors (PPIs), which target the hydrogen-potassium adenosine triphosphatase (proton pump) of the parietal cell. Potassium-competitive acid blockers (P-CABs), a newer class of medications, act at the same proton pump through a novel mechanism resulting in profound and sustained acid suppression. Although trials in Asian populations over the past decades have highlighted the potential benefit of P-CABs, clinical trials in Western populations have been initiated more recently. These trials evaluated vonoprazan in patients with *Helicobacter pylori* infection, erosive esophagitis, and heartburn with nonerosive reflux disease and have demonstrated promising results, culminating in US Food and Drug Administration approval for these indications. Adverse event profiles between PPIs and P-CABs appear comparable thus far, although additional long-term data on P-CABs are needed. While navigating the evolving landscape of acid suppression, it is crucial to identify which patients and diseases are poised to derive the most benefit from this emerging therapeutic option. This article seeks to highlight important pharmacologic properties of PPIs and P-CABs, understand the current literature with a focus on clinical trials in Western populations, and explore potential scenarios for integrating P-CABs into therapeutic regimens.

Keywords
Potassium-competitive acid blockers, proton pump inhibitors, gastroesophageal reflux disease, *Helicobacter pylori*, erosive esophagitis, nonerosive reflux disease

The landscape of treatment for acid-related disorders underwent significant transformation with the advent of proton pump inhibitors (PPIs) in the 1980s, with omeprazole leading the way as the first market entrant and demonstrating superior acid suppression compared with previous agents.[1,2] PPIs have remained integral to gastroenterology treatment strategies. Presently, 6 PPIs have gained approval from the US Food and Drug Administration (FDA) and are extensively utilized across various disease states, including erosive esophagitis, Barrett

Table. Phase 2 and 3 Clinical Trials Performed in Western Populations

Disease	Trial type, number	Location(s)	Interventions	Outcome measure(s)	Status
Erosive esophagitis	Phase 3, NCT04124926	United States	Vonoprazan 20 mg compared with lansoprazole 30 mg for healing; evaluate the efficacy and safety of vonoprazan (10 mg and 20 mg) compared with lansoprazole 15 mg for the maintenance of healing	Healing phase: percentage of participants with complete healing of erosive esophagitis by week 8; maintenance phase: percentage of participants maintaining complete healing of erosive esophagitis at week 24	Completed[20]
Helicobacter pylori	Phase 3, NCT04167670	United States, Europe	Vonoprazan dual therapy, vonoprazan triple therapy, lansoprazole triple therapy	Percentage of participants with successful *Helicobacter pylori* eradication in participants with and without a clarithromycin- or amoxicillin-resistant strain of *Helicobacter pylori* at baseline and at week 6	Completed[31]
Nonerosive reflux disease	Phase 3, NCT05195528	United States	Efficacy and safety of vonoprazan 10 mg and 20 mg compared with placebo	Percentage of days without daytime or nighttime heartburn	Completed[27]
Symptomatic gastroesophageal reflux disease with partial proton pump inhibitor response	Phase 2, NCT02743949	Europe	4 weeks of esomeprazole 40 mg daily, vonoprazan 20 mg daily, and vonoprazan 40 mg daily	Percentage of heartburn-free 24-hour periods (day and night) during 4 weeks of treatment	Completed, not published

esophagus (BE), *Helicobacter pylori* infection, and peptic ulcer disease.[3-6]

The more recent introduction of potassium-competitive acid blockers (P-CABs) has sparked interest in the gastroenterology community. These medications were first used in Asia, with revaprazan emerging in 2005 as the first P-CAB in clinical practice in Korea. The first P-CAB approved for use in the United States was vonoprazan (Voquezna, Phathom), first authorized by the FDA for *H pylori* combination therapy in 2022.[7] Vonoprazan is currently the most well-characterized P-CAB in Western populations (Table).[8] Other P-CABs on variable timelines of development and approval include linaprazan, keverprazan, tegoprazan, fexuprazan, and revaprazan.[9]

The remainder of this article will discuss the pharmacologic differences between PPIs and P-CABs. It will also explore evidence for the use of P-CABs across different clinical contexts, focusing on trials performed in Western populations (Table). Additionally, it will provide a succinct overview of the safety and potential future applications for P-CABs, recognizing that not all conditions have been longitudinally studied. This discussion will highlight how these medications may be utilized in the management of various gastrointestinal conditions.

Mechanisms of Action: Proton Pump Inhibitors vs Potassium-Competitive Acid Blockers

Gastric acid secretion occurs in parietal cells located in the oxyntic glands of the stomach corpus.[10] This is where PPIs target the hydrogen-potassium adenosine triphosphatase (H+/K+ ATPase) enzymes (proton pump), binding irreversibly to inhibit hydrogen ion secretion. As prodrugs that are acid labile, PPIs require activation by an acidic environment before inhibiting the final step of acid secretion in a dose-dependent manner.[11] These mechanisms of action of PPIs result in many unique properties. The acid-labile nature necessitates unique delivery systems capable of bypassing the stomach to facilitate absorption in the small bowel. The binding of PPIs exclusively to active proton pumps results in a short plasma half-life (1-2 hours) as new proton pumps are continuously synthesized.[11] Additionally, PPIs exhibit variable effectiveness related to food intake, with 60% to 75% of proton pumps active and susceptible to inhibition by a single PPI dose.[12] In fact, PPIs reach a steady-state and maximum effect after 3 to 5 daily doses. These attributes underscore the rationale for preprandial dosing and the observed improvement in efficacy with prolonged therapy over multiple

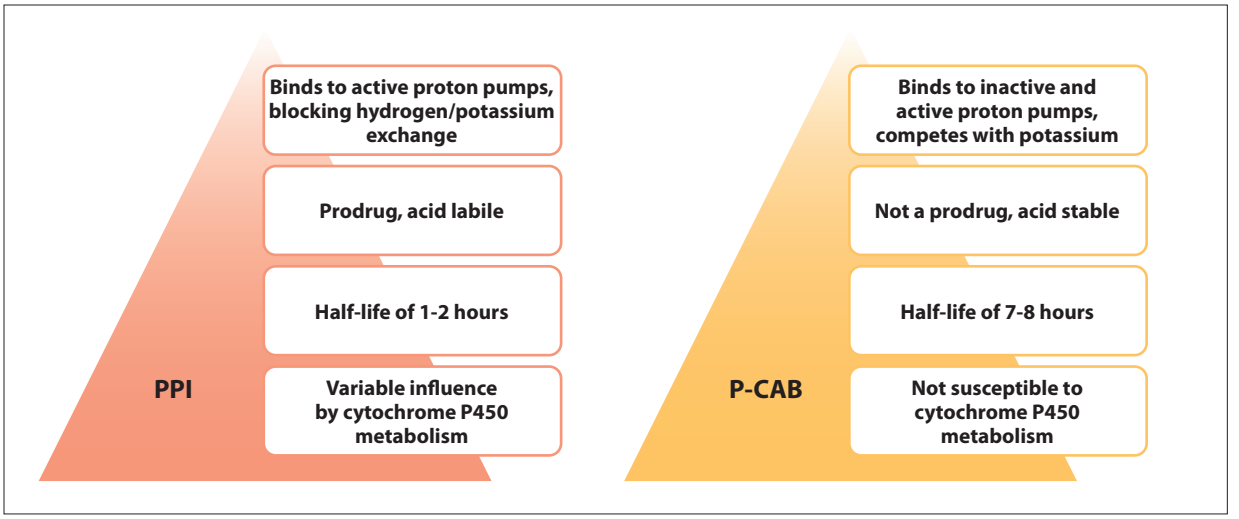

Figure 1. Comparison of PPI and P-CAB key pharmacologic properties.

P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

days.[11] Additionally, PPIs are subject to variable clinical efficacy owing to metabolism by cytochrome P450 (CYP) 2C19 in the liver.[13]

In contrast, P-CABs suppress luminal acid secretion by competing with potassium to reversibly bind and inhibit the H+/K+ ATPase enzyme (Figure 1).[13] They are acid stable and do not require pH levels for activation. Additionally, they are primarily metabolized by CYP3A4 and therefore less susceptible to CYP polymorphisms.[13] Given these properties, P-CABs demonstrate a rapid onset of action, increasing intragastric pH as quickly as within 2.5 hours of administration.[14] Furthermore, P-CABs display a plasma half-life of approximately 7 to 8 hours, promoting prolonged duration of gastric acid inhibition.[13-15] Their metabolic properties allow for fewer drug interactions and decreased interindividual variability.[16] Both P-CABs and PPIs act on the final step of acid secretion, but their unique pharmacologic properties are important to keep in mind when considering their use in specific disease states.

Erosive Esophagitis

The current management of erosive esophagitis typically involves 8 to 12 weeks of PPI therapy to facilitate healing.[4] However, up to 30% of patients with high grades of erosive esophagitis (Los Angeles [LA] grade C and D; Figure 2) may not achieve complete resolution. Several randomized controlled trials have compared the effectiveness of P-CABs with PPIs in this context, with initial studies in Asia showing noninferiority of vonoprazan to lansoprazole in both healing and maintenance.[17-19] More recently, a landmark study by Laine and colleagues randomized patients with erosive esophagitis to either vonoprazan or lansoprazole in both an 8-week healing phase and a 24-week maintenance phase. During the healing phase, patients were assigned 1:1 to daily vonoprazan 20 mg or lansoprazole 30 mg. Endoscopies at weeks 2 and 8 evaluated for healing of esophagitis, with the primary endpoint being the noninferiority of vonoprazan in the proportion of healed esophagitis. After achievement of healing, patients were randomized to once-daily doses of vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg for 24 weeks in the maintenance phase.[20]

This pivotal trial found that vonoprazan was noninferior to lansoprazole for both healing and maintenance of erosive esophagitis.[20] Additionally, vonoprazan demonstrated a significantly higher rate of healing LA grade C and D esophagitis compared with lansoprazole at 8 weeks, consistent with earlier investigations.[17] Ultimately, these studies suggest that vonoprazan is at least equivalent to lansoprazole in terms of efficacy for erosive esophagitis healing and maintenance. Ultimately, vonoprazan was FDA approved for this indication in late 2023.

Although P-CABs display effective healing in severe, LA grade C and D esophagitis, their effects in milder, LA grade A esophagitis do not appear to surpass those of standard PPI therapy. An investigation by Tack and colleagues noted that esomeprazole had similar efficacy rates for healing of low-grade esophagitis.[21] Regarding maintenance of healing, higher doses of vonoprazan did not demonstrate superior efficacy, leading to FDA approval of the 10-mg maintenance dose. Further research is necessary to clarify the optimal positioning of P-CABs in the spectrum of erosive esophagitis populations, especially when compared with high-potency PPIs such as esomeprazole.

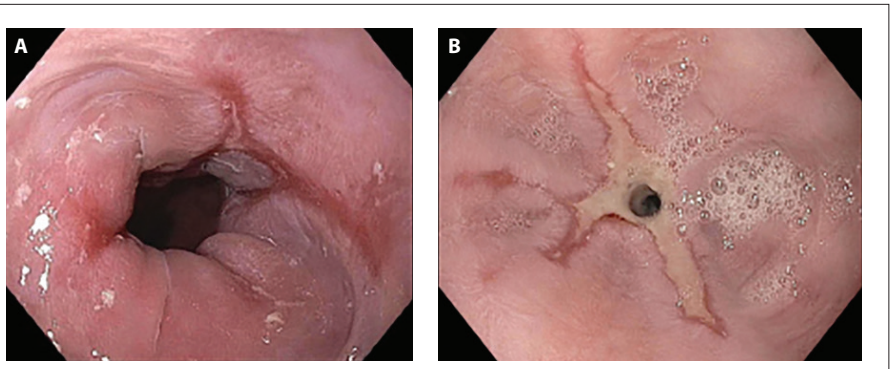

Figure 2. A: Endoscopic representation of Los Angeles grade C erosive esophagitis. **B:** Endoscopic representation of Los Angeles grade D erosive esophagitis.

Courtesy of the University of Pennsylvania Esophageal Center.

Nonerosive Reflux Disease

Nonerosive reflux disease (NERD) is defined as troublesome symptoms related to gastroesophageal reflux disease in the absence of esophageal mucosal breaks. The Rome IV criteria note that true NERD patients also demonstrate elevated esophageal acid exposure on pH testing.[22] A prospective, randomized, open-label comparative study of Japanese patients with gastroesophageal reflux disease symptoms found that vonoprazan provided symptomatic relief comparable with esomeprazole.[23] A randomized controlled trial by Oshima and colleagues demonstrated that vonoprazan had a faster onset of heartburn relief compared with lansoprazole.[24] These studies predominantly included patients with no or mild esophagitis (LA grade A and B), suggesting the potential utility of vonoprazan in symptomatic NERD populations. Initial trials in Japan focusing on NERD patients alone, however, did not show superiority of vonoprazan over placebo for the treatment of reflux symptoms.[25,26]

Following their study on erosive esophagitis, Laine and colleagues sought to evaluate the utility of vonoprazan in Western populations that experienced reflux symptoms without erosive findings on endoscopy.[27] The initial phase of the study randomized patients with heartburn to placebo, vonoprazan 10 mg, or vonoprazan 20 mg, with the placebo group crossing over to active treatment during the extension period. Results showed quicker sustained heartburn resolution and a higher proportion of heartburn-free days in the vonoprazan groups compared with placebo. Patients rerandomized to active treatment rapidly reached similar proportions of heartburn-free days as patients already on therapy. Notably, efficacy was comparable between the higher and lower doses of vonoprazan. These findings provided novel evidence for the efficacy of vonoprazan in treating NERD in a Western population and were critical to the 2024 FDA approval of vonoprazan for heartburn relief in patients with NERD. Future studies that incorporate ambulatory pH testing will further elucidate the role of P-CABs in NERD management.

Helicobacter pylori Therapy

H pylori is one of the most common bacterial infections in the world, with significant potential gastrointestinal sequelae including peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Eradication of *H pylori* requires multiple antibiotics coupled with an acid-suppressive medication. PPIs have traditionally been the cornerstone acid-suppressive medication for *H pylori* eradication since the 1990s. However, triple therapy–based regimens encompassing PPIs, clarithromycin, and amoxicillin or metronidazole have decreased in efficacy over the past decades, with current eradication rates below 70% in Europe and the United States. Clarithromycin-resistant strains are considered contributory to this declining efficacy rate.[28] Thus, US guidelines have evolved to recommend bismuth-based quadruple therapy with PPI as the preferred initial empiric therapy for eradication.[6]

Vonoprazan initially gained approval for *H pylori* treatment in several Asian countries, where vonoprazan-based triple therapy was shown to have higher eradication rates than PPI-based regimens.[29,30] The first phase 3 clinical trial in the United States and Europe aimed to compare eradication rates of PPIs and P-CAB–based therapies in treatment-naive patients with *H pylori* infection.[31] Patients were randomized to receive vonoprazan dual therapy (vonoprazan 20 mg twice daily and amoxicillin 1 g thrice daily), vonoprazan triple therapy (vonoprazan, amoxicillin, and clarithromycin 500 mg once daily), or lansoprazole triple therapy (lansoprazole 30 mg twice daily with amoxicillin and clarithromycin) for 14 days. Vonoprazan triple and dual regimens demonstrated noninferiority to lansoprazole triple therapy, with eradication rates of 84.7%, 78.5%, and 78.8%, respectively. In patients with clarithromycin-resistant strains, the highest eradication rate of 65.8% was demonstrated in the vonoprazan triple-therapy group. Per-protocol analysis showed superiority of vonoprazan dual and triple therapy compared with the PPI regimen in all groups.

Serious treatment-emergent adverse events (TEAEs) occurred in less than 2% of the population.

Although empiric *H pylori* regimen selection is guided ideally by regional eradication rates, such data collection in the United States is suboptimal, given the lack of routine verification of *H pylori* cure as well as the dearth of surveillance registries.[32] Overall, head-to-head studies comparing approved first-line empiric therapies and further investigations into susceptibility-tailored therapies are needed to optimize *H pylori* therapy regimens.

Nonvariceal Upper Gastrointestinal Bleeding and Peptic Ulcer Disease

Exploring the potential utility of P-CABs vs PPIs for nonvariceal upper gastrointestinal bleeding has been a logical endeavor. Previous studies indicate that higher intragastric pH may improve clot formation and facilitate platelet aggregation, prompting the recommendation for high-dose PPIs after hemostasis is achieved. Data supporting the use of P-CABs in these conditions are still emerging, and FDA approval for this scenario is currently lacking. However, a recent multicenter study in Thailand compared vonoprazan and conventional PPI therapy following hemostasis in Forrest Classification Ia/Ib or IIa/IIb peptic ulcers.[33] Results showed noninferiority of oral vonoprazan in preventing 30-day rebleeding compared with the PPI regimen, which encompassed both intravenous and oral PPI administration. These findings suggest a possible future role for oral management via vonoprazan in management of bleeding ulcers, with further studies in the Western population needed to help generalize the results.

Other Diseases

Ongoing studies worldwide are exploring how P-CABs compare with PPIs in various esophageal and acid-related conditions. Likely research directions include the evaluation of P-CABs in diseases where PPIs are the standard first-line treatments, such as BE. Another intriguing avenue is the potential for P-CABs in other esophageal disorders such as eosinophilic esophagitis (EoE); a small Japanese study indicated that vonoprazan is comparable to PPIs in inducing remission in EoE.[34] However, further data are necessary in patients with BE, EoE, and other acid-related disorders to understand the prospect of P-CABs as a potential therapeutic option.

Adverse Events and Safety

Because PPIs have a well-established safety profile,[35] understanding any adverse events unique to P-CABs will be crucially important. A systematic review with meta-analysis by Cheng and colleagues noted that the most common TEAEs associated with P-CABs include nasopharyngitis, headache, upper respiratory infection, and gastroenteritis, with a risk ratio for TEAEs of 1.08 (95% CI, 0.96-1.22; P=.20).[36] Other reported adverse reactions to P-CABs include abdominal pain, nausea, and urinary tract infection.[8,37] Additionally, acute tubulointerstitial nephritis has been associated with vonoprazan use.[38] In general, current data show comparable rates of TEAEs with P-CABs in clinical trials when compared with PPIs.[39]

Given the potent acid suppression of vonoprazan, not surprisingly serum gastrin has been found elevated in patients receiving vonoprazan, with a dose-dependent relationship noted in short-term studies.[19] Regarding long-term evaluation of adverse effects, the VISION study was designed to evaluate nearly 200 patients receiving vonoprazan 10 mg daily or lansoprazole 15 mg daily for 260 weeks at 33 centers in Japan.[40] An interim analysis at 3 years found that the cumulative incidence of parietal cell, gastrin-producing cell, and enterochromaffin-like cell hyperplasia was similar between the vonoprazan and lansoprazole groups after 3 years of maintenance therapy. Gastric polyp rates were also similar between the groups (81% in the lansoprazole group vs 72% in the vonoprazan group).[41] No neoplastic changes were noted in either group. Contrastingly, a single retrospective cohort analysis suggested a possible association with gastric cancer.[42] Ultimately, more long-term data on the use of P-CABs will be essential for establishing their true adverse event profile and determining how it compares with that of PPI agents.

Conclusion

The introduction of PPIs several decades ago marked a significant advancement in the treatment of acid-based disorders. The potent and prolonged acid suppression offered by P-CABs necessitates consideration of their role in managing these conditions. Recent data have shown their efficacy in healing and maintenance in erosive esophagitis, particularly in severe, LA grade C and D populations. There is growing momentum for the use of P-CABs in *H pylori* treatment with the emergence of vonoprazan-based regimens, especially for clarithromycin-resistant strains. The real-world effects of the recent FDA approval for the use of vonoprazan in patients with heartburn without erosive esophagitis remain to be seen. The potential role of P-CABs in patients with NERD and positive pH testing, EoE, BE, and other upper gastrointestinal conditions warrants continued investigation. Numerous clinical trials are underway across various disease states to clarify the comparative positioning of

P-CABs vs PPIs in this rapidly evolving landscape of acid-suppression therapy.

Disclosures

Dr Ketchem has no relevant conflicts of interest to disclose. Dr Lynch has served as a consultant to Medtronic and Sanofi and on the medical advisory board of Phathom.

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