Potassium-Competitive Acid Blockers: Present and Potential Utility in the Armamentarium for Acid Peptic Disorders

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Abstract: Potassium-competitive acid blockers (P-CABs) such as vonoprazan represent a novel class of acid suppressants that show tremendous promise to enhance care of acid peptic disorders. P-CAB characteristics distinct from those of proton pump inhibitors—such as acid stability with dosing independent of food consumption, rapid onset of action, less variability with CYP2C19 polymorphisms, and extended half-lives—may add value in clinical practice. With recently reported data beyond Asian populations and expanding regulatory approval of P-CABs, clinicians should be aware of these medications and their potential roles in the management of acid peptic disorders. This article provides an up-to-date summary of the evidence around P-CABs for the treatment of gastroesophageal reflux disease (especially erosive esophagitis healing and maintenance), eosinophilic esophagitis, *Helicobacter pylori* infection, and peptic ulcer healing and secondary prophylaxis.

Keywords
Potassium-competitive acid blocker, gastroesophageal reflux disease, erosive esophagitis, eosinophilic esophagitis, gastric ulcer, peptic ulcer disease, *Helicobacter pylori*

Proton pump inhibitors (PPIs) have demonstrated good efficacy with excellent safety profiles for indications across acid peptic disorders, with widespread availability and use in clinical practice.[1,2] However, the potential for more rapidly acting, acid-stable, and/or increasingly potent antisecretory agents[3] to mitigate some limitations of PPI medications has fostered the development of and interest in novel potassium-competitive acid blockers (P-CABs).[4-6]

The evolving P-CAB class currently includes fexuprazan, keverprazan, revaprazan, tegoprazan, and vonoprazan, with others under development (ie, linaprazan, zastaprazan). Of these, vonoprazan has been the most extensively studied[4] and was initially approved in Japan in 2015 (Takecab, Takeda) for the treatment of acid-related diseases (gastric ulcer, duodenal ulcer, reflux esophagitis, prevention of recurrence of gastric or duodenal ulcer, adjunct to *Helicobacter pylori* [HP] eradication), with subsequent expansion of approvals to other countries.[7] Tegoprazan (K-Cab, HK inno.N/RaQualia Pharma) was approved in South Korea

Table 1. Potassium-Competitive Acid Blocker Indications and Approvals

Current Approval in the United States	Current Approval and/or Use Outside the United States	Potential Indications of Interest and/or Under Study
• *Helicobacter pylori* eradication	• *Helicobacter pylori* eradication • Erosive esophagitis • Nonerosive reflux disease • Peptic ulcer treatment and prophylaxis • Gastritis	• Eosinophilic esophagitis • Barrett esophagus • Nonvariceal gastrointestinal bleeding • Nonulcer dyspepsia • Use in pregnancy or lactation

in 2019. In May 2022, the US Food and Drug Administration approved 2 vonoprazan-containing HP treatment regimens (vonoprazan plus amoxicillin and clarithromycin [Voquezna Triple Pak, Phathom] and vonoprazan plus amoxicillin [Voquezna Double Pak, Phathom]), and accepted filing of a New Drug Application for vonoprazan for the treatment of erosive esophagitis (EE) (Table 1).[8,9]

Mechanism of Action

P-CABs act at the H+/K+ ATPase transporter on the luminal membrane of gastric parietal cells, the same proton pump targeted by PPIs. After systemic absorption, P-CABs concentrate in parietal cell canaliculi and ionically bond to H+/K+ ATPase transporters to prevent acidifying proton secretion. Once bound, the P-CAB blocks K+ ion access to the proton pump. Unlike PPIs, P-CABs are acid-stable and thus do not require enteric coating or optimal dosing administration 30 minutes prior to meals. Additionally, P-CABs are not prodrugs and act immediately at the proton pump. These P-CAB mechanistic differences facilitate more rapid attainment of peak plasma levels and onset of action (Table 2).[4-6]

P-CAB pharmacodynamics and pharmacokinetics convey other potentially clinically beneficial properties. Notably, the longer half-lives of P-CABs allow prolonged inhibition of newly synthesized proton pumps and thus longer durations of action than PPIs.[4] In healthy male subjects, the P-CAB tegoprazan more effectively and durably suppressed intragastric acidity than the PPI esomeprazole.[10] Similarly, among a population of healthy adults in the United States, vonoprazan demonstrated more rapid and potent acid suppression than lansoprazole.[11] Patients randomized to a 7-day course of vonoprazan 20 mg once daily (vs lansoprazole 30 mg once daily) demonstrated increased proportions of times with intragastric pH greater than 4 on both day 1 (63% vs 23%) and day 7 (88% vs 42%), with separation of intragastric pH starting 2 to 3 hours after the initial dose. Notably, in vitro analysis showed that vonoprazan is primarily metabolized by CYP3A4, with contributions by CYP2B6, CYP2C19, and CYP2D6, suggesting that CYP2C19 genotype status may have less influence on gastric acid suppression by P-CABs than by PPIs.[12] Gastric acid suppression with vonoprazan has been evaluated among healthy Japanese volunteers and confirmed to be effective irrespective of CYP2C19 genotype.[13]

Safety

Most of the safety data for P-CABs are from studies of vonoprazan, with excellent short-term and medium-term safety comparable with that of antisecretory PPI formulations. A 24-week trial in Japan showed similar safety profiles of vonoprazan and lansoprazole; nasopharyngitis represented the most common adverse event reported in each treatment group.[14] More broadly, a meta-analysis of vonoprazan vs PPI for gastroesophageal reflux disease (GERD) showed similar safety outcomes between vonoprazan and PPI therapy groups, with a risk ratio of adverse events of 1.08 (95% CI, 0.96-1.22).[15] Similarly, meta-analyses for HP treatment regimens have shown generally comparable rates of adverse events between vonoprazan- and PPI-based regimens,[16,17] as have trials of peptic ulcer prevention.[18,19]

Beyond vonoprazan, a multicenter Korean trial randomizing patients with EE to tegoprazan 50 mg or 100 mg once daily or esomeprazole 40 mg once daily found comparable rates of adverse events among the groups.[20] There were no serious adverse events reported in a tegoprazan study with healthy Chinese patients.[21] Similarly, tegoprazan was well tolerated in a multiple-ascending-dose study, with most adverse events reported as mild and resolving without sequelae.[10] Likewise, tegoprazan at 50 mg or 100 mg once daily did not significantly differ from placebo in the incidence of treatment-emergent adverse events in a 4-week treatment trial for nonerosive reflux disease (NERD).[22]

However, longer-horizon safety data for P-CABs are warranted and emerging. A 1-year study of vonoprazan

Table 2. Comparison of Potassium-Competitive Acid Blocker (P-CAB) and Proton Pump Inhibitor (PPI) Drug Classes

	P-CAB Class	PPI Class
Examples of Medications	Fexuprazan, keverprazan, revaprazan, tegoprazan, vonoprazan	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
Prodrug	No	Yes
Acid Stability	Yes	No
Inhibition and Binding	Reversible, ionic	Irreversible, covalent
Maximal Acid Suppression After Dosing[5,6]	1 day (vonoprazan)	3-5 days
Half-Life[4,6]	6-9 hours (vonoprazan)	1-2 hours
Significantly Affected by CYP2C19 Polymorphism	No	Yes
Optimal Dosing Administration	Independent of mealtimes (before or after meals)	30-60 minutes prior to mealtimes (for most PPIs)

vs lansoprazole for maintenance therapy for EE revealed low rates of adverse events in both groups.[23] The VISION study aims to investigate the long-term safety of vonoprazan as maintenance therapy for EE over 5 years.[24] Although increases in serum gastrin levels (potentially greater than those seen with PPIs) have been observed in some cohorts of patients receiving P-CABs, other data suggest that these increases may be comparable with those of patients treated with lansoprazole,[25] without observed clinically significant associated effects on gastric mucosa histopathology.[14] Nonetheless, further high-quality and longer-term data on the potential effects of hypergastrinemia and/or hypochlorhydria with prolonged P-CAB use are warranted.

Given its importance in human health and disease, the impact of P-CABs on the gut microbiome represents an intriguing area of investigation. As acid suppression with PPI use can predispose patients to enteric infections, P-CAB use may also induce clinically relevant alterations of the gut microbiome. Analysis of P-CAB effects on microbiota composition revealed an association between vonoprazan use and microbiota changes that may decrease defense against enteric infections (such as significantly decreasing *Clostridioides difficile*–protective *Blautia* and *Coprococcus* genera).[26]

Data for P-CABs in pregnant and lactating populations are sparse. An animal study suggested that vonoprazan exposure levels similar to those indicated clinically in humans did not result in maternal or developmental toxicity effects.[27] Although longer-term safety data (and additional data in non-Asian populations) are warranted and emerging, the overall safety profile of P-CABs based on available evidence appears favorable and comparable with that of PPIs.

Potassium-Competitive Acid Blockers for Gastroesophageal Reflux Disease

Nonerosive Reflux Disease

GERD remains one of the most common diseases managed by gastroenterologists, wherein PPI formulations represent standard treatments for gastric acid suppression and symptom relief.[1,2] The utility and efficacy of P-CABs for gastric acid suppression has translated to effective treatment in EE, with less clear benefits for patients without visible mucosal injury (ie, NERD). Tegoprazan effectively and durably suppressed acid among healthy volunteers, based on intragastric pH monitoring[10]; these findings suggest that P-CABs should have good efficacy for symptoms stemming directly from esophageal acid exposure. However, P-CAB studies have not consistently demonstrated benefits for NERD cohorts. In a South Korean trial in which 324 participants with NERD were randomized to 4 weeks of tegoprazan 50 mg or 100 mg once daily or placebo, the tegoprazan groups experienced higher rates of complete heartburn resolution at 4 weeks (43%-49% vs 24%).[22] A phase 3 trial of vonoprazan vs placebo for NERD among Japanese patients showed that patients in the vonoprazan group experienced fewer heartburn symptoms at week 4 and an overall greater improvement in heartburn symptoms.[28] However, there was no significant difference in the primary endpoint of heartburn-free days in the full analysis. Although some studies have noted improvement in GERD symptoms among PPI-resistant NERD patients with P-CABs, the underlying etiologies of persisting symptoms despite P-CAB therapy in these cohorts may be unrelated to acid reflux.[29-31] The recent Japanese Society of Gastroenterology practice guidelines for GERD acknowledged

the need for more data on the role of P-CABs in NERD diagnosis and treatment.[29]

Erosive Esophagitis

For patients with endoscopic evidence of mucosal injury (EE), PPI medications have been the mainstay for mucosal healing.[1] P-CAB studies for EE have focused on establishing noninferiority compared with PPI-based standard-of-care treatments.[15,23,32] Attention has also been focused on populations with potentially more robust opportunities for EE healing beyond available PPI therapies, such as patients with more advanced grades of esophagitis and/or CYP2C19 extensive metabolizers.[23] The recently updated American College of Gastroenterology GERD guidelines do not directly address the use of P-CABs but note that they represent promising new management options for GERD.[1] The value of P-CABs for treating Barrett esophagus has not been well established and was not specifically discussed in current American College of Gastroenterology guidelines.[33]

Vonoprazan has demonstrated noninferiority to lansoprazole as a first-line treatment for EE.[23,32] The noninferiority of vonoprazan for initial EE healing over 8 weeks has also been established for Asian patients outside Japan, such as in China, with slightly higher but not statistically significant rates of endoscopic healing at 2 and 4 weeks compared with lansoprazole.[32] Other P-CABs have also shown noninferiority to PPI formulations for initial EE healing, including tegoprazan in Korean patients and keverprazan in Chinese patients.[20,34] Importantly, smaller studies have demonstrated successful mucosal healing of EE with vonoprazan in PPI-refractory patients with EE.[35] A randomized study of Japanese patients also established the efficacy of vonoprazan for EE in CYP2C19 extensive metabolizers, with higher rates of EE healing with vonoprazan than with lansoprazole at 2 weeks (90% vs 79%), 4 weeks (96% vs 91%), and 8 weeks (99% vs 95%).[23]

Emerging data suggest that P-CABs may be more effective than PPIs for the healing of more advanced or severe EE. A meta-analysis of both Japanese and non-Japanese Asian patients showed that patients with more severe Los Angeles (LA) grades C and D esophagitis had higher rates of mucosal healing with vonoprazan than with PPIs, with a risk ratio of efficacy of 1.14.[15] In a subgroup analysis, vonoprazan 20 mg once daily was superior to lansoprazole 30 mg once daily for the healing of severe (LA grades C and D) EE at 2 weeks (88% vs 64%), 4 weeks (96% vs 81%), and 8 weeks (99% vs 88%), among a multicenter Japanese population.[23] Another subgroup analysis evaluated initial EE healing rates among a multicenter Chinese study population randomized to vonoprazan 20 mg once daily or lansoprazole 30 mg once daily for 8 weeks, revealing higher healing rates for vonoprazan at 2 weeks (62% vs 52%), 4 weeks (73% vs 67%), and 8 weeks (84% vs 81%), among those with baseline LA grades C and D esophagitis.[32]

In addition to initial healing, data have been reported for EE maintenance therapy, although fewer studies of P-CABs for this indication have been conducted and published compared with studies for initial healing to date. Vonoprazan has shown at least noninferiority to lansoprazole for maintenance therapy of healed EE. A study of 607 patients with endoscopically healed EE showed that 24-week EE recurrence was significantly reduced with vonoprazan compared with lansoprazole, with recurrence rates of 16.8% for lansoprazole 15 mg once daily, 5.1% for vonoprazan 10 mg once daily, and 2.0% for vonoprazan 20 mg once daily.[14] Regarding longer maintenance intervals, data from 305 Japanese patients with EE randomized to vonoprazan 10 mg or 20 mg once daily and followed for a 52-week maintenance period revealed recurrence rates of 9.4% in the vonoprazan 10 mg group and 9.0% in the vonoprazan 20 mg group.[23]

P-CABs have also been evaluated for symptomatic endpoints beyond endoscopic healing in the setting of EE. Vonoprazan appears noninferior to PPIs for subjective GERD symptoms in the setting of EE.[32] Blinded data showed that Japanese patients with EE receiving vonoprazan were more likely to experience heartburn resolution in the first week of treatment than patients with EE receiving lansoprazole.[36] This same trial demonstrated that patients were more likely to have nocturnal heartburn improvement and sleep improvement with vonoprazan than with lansoprazole during the first 2 weeks of EE treatment.

Finally, in terms of evaluating P-CAB efficacy for the healing of EE in Western populations, the recently presented phase 3 PHALCON-EE trial evaluated EE healing in the United States and Europe.[37] Among 1024 subjects randomized to vonoprazan 20 mg once daily or lansoprazole 30 mg once daily for 8 weeks, vonoprazan was noninferior to lansoprazole for EE healing at 8 weeks (93% vs 85%), superior for healing at week 2 (74% vs 68%), and superior for the healing of more advanced LA grades C and D esophagitis by week 8 (92% vs 72%). P-CABs appear to have excellent efficacy for both initial and maintained healing of EE across different populations, with promise for enhancing the management of more advanced esophagitis.

Potassium-Competitive Acid Blockers for Eosinophilic Esophagitis

Given the effectiveness of PPIs in the treatment of eosinophilic esophagitis (EoE) through likely anti-inflammatory and acid-suppressive effects,[38,39] there is interest in the

potential efficacy of P-CABs in the context of EoE. At present, however, limited evidence exists to guide the use of P-CABs in EoE management. A Japanese case series assessed the efficacy of vonoprazan in 4 patients with EoE who were nonresponsive to 3 months of omeprazole 20 mg once daily; the authors reported that symptoms and histologic eosinophilia improved in 3 of the patients after 2 months of vonoprazan treatment.[40] Later, a more robust retrospective cohort study of 118 Japanese patients with EoE compared the efficacy of vonoprazan 20 mg once daily with rabeprazole 10 mg or 20 mg once daily and esomeprazole 20 mg once daily.[41] This analysis revealed similar therapeutic efficacy for all medications with regard to clinical symptoms, endoscopic findings, and histologic remission after treatment. However, these conclusions may have been limited by the lower PPI dosages used in the studied populations than typically utilized in clinical practice.[41,42] These findings overall suggest that P-CABs may represent an effective alternative to PPI therapy in patients with EoE. However, current studies remain limited, and more rigorous data that incorporate larger and more diverse populations and directly compare outcomes with higher-dose PPIs are warranted to better understand the potential roles for P-CABs in the management of EoE.

Potassium-Competitive Acid Blockers in *Helicobacter pylori* Eradication Therapy

First-Line Therapy

Potential indications for the testing and treatment of HP infection have increased, and the need for increasingly complex regimens to combat antibiotic resistance (especially for clarithromycin) highlights the potential utility of P-CABs in overcoming HP management challenges.[43] The Maastricht VI/Florence 2021 Consensus Report had 100% agreement that P-CAB–based treatment regimens are superior—or at least not inferior—to conventional PPI-based triple therapies for first- and second-line treatment of HP, and superior for antimicrobial-resistant infections.[44]

In this setting, substantial evidence supports the clinical use of P-CABs in the primary management of HP infection, which has contributed to the regulatory approval of vonoprazan-based treatment regimens in the United States. Although HP treatment has typically included PPIs, multiple studies have identified that the rates of successful HP eradication are higher with triple therapy that utilizes vonoprazan (in combination with amoxicillin and clarithromycin) than with PPIs.[17,45,46] A meta-analysis incorporating randomized controlled trial (RCT) and retrospective cohort data favored vonoprazan-based triple therapy over PPI-based triple therapy with an odds ratio (OR) of 1.19 (95% CI, 1.15-1.24), with all but 1 study demonstrating a statistically significant benefit.[17,47] Importantly, pooled adverse-event rates were similar between the vonoprazan-based and PPI-based triple therapy groups.

More recent investigation has continued to build the case for the efficacy and role of vonoprazan-based triple therapy as a first-line treatment option for HP infection. A large trial of 1688 patients demonstrated HP eradication rates of 91% following vonoprazan-based triple therapy, representing a significant improvement over eradication rates of 68% to 78% with PPI-based triple therapy.[48] A subsequent meta-analysis of RCTs published in 2019 revealed a combined HP eradication rate of 91% using vonoprazan-based triple therapy compared with 75% with PPI-based triple therapy.[49] Differing from prior suggestions of similar side-effect profiles, the authors found that vonoprazan-based therapy led to fewer adverse events than PPI-based triple therapy (OR, 0.71) in this analysis. A recent network meta-analysis of indirect treatment comparisons including 12,773 patients across 42 trials found that vonoprazan-based triple therapies led to higher odds of HP eradication than each compared PPI-based triple therapy.[50]

Given increased macrolide resistance rates globally, the role of P-CABs in regimens beyond standard triple therapy has also been evaluated.[51] The studies discussed thus far involved varying dosages of clarithromycin, with eradication rates not differing significantly based on clarithromycin dosage. In fact, additional RCT data have demonstrated similar efficacy of first-line vonoprazan and amoxicillin dual therapy and vonoprazan-based triple therapy.[52-54] A prospective study of 335 randomized Japanese patients demonstrated higher eradication rates for clarithromycin-resistant HP strains treated with vonoprazan-based dual therapy than with vonoprazan-based triple therapy (92% vs 76%).[52] Among a non-Asian population, a recent study of 1046 treatment-naive American and European adults with HP infection assessed open-label vonoprazan-based dual therapy (with amoxicillin) or double-blind triple therapy (vonoprazan or lansoprazole, with amoxicillin and clarithromycin) for 14 days.[55] HP eradication rates were superior for vonoprazan-based triple and dual therapy (81% and 77%, respectively) compared with lansoprazole-based triple therapy (69%), driven primarily by differences in clarithromycin-resistant strains (66% and 70%, respectively, vs 32%). These study findings corroborate similar data from Asian populations and suggest a potential global role for P-CABs in HP treatment, particularly in the setting of high rates of clarithromycin resistance.

Overall, the investigation of P-CABs in HP eradication regimens has produced a growing body of evidence supporting the role of P-CAB–based first-line treatments.

Although vonoprazan is the most extensively studied P-CAB in this setting, the benefits of P-CAB inclusion in HP treatment regimens are likely to extend to the entire class, as shown by a recent RCT of 350 patients comparing tegoprazan-based triple therapy with PPI-based triple therapy.[56] Integration of P-CABs into HP treatment regimens may also facilitate the use of shorter treatment durations, as suggested by an RCT from Singapore that showed comparable efficacy between vonoprazan-based triple therapy for 1 week and PPI-based triple therapy for 2 weeks for first-line HP eradication (per protocol analysis, 96% vs 94%).[57] Furthermore, given that bismuth-based quadruple therapies are associated with higher pill burden and more complex dosing schedules, P-CAB–based dual therapy may offer a simplified but effective treatment course in the context of evolving HP antibiotic resistance. Overall, additional data comparing the efficacy of various P-CAB–based HP therapies, including dual therapy, with other PPI-based treatment regimens across diverse populations, treatment durations, and antibiotic resistance settings (including the most appropriate roles for susceptibility testing) are warranted.

Second-Line Therapy

Given the described rises in antibiotic resistance among HP strains, failure of first-line treatment regimens has become increasingly common and resulted in more frequent utilization of second- and third-line therapy regimen options.[51] In an open-label study of 50 patients with a history of gastric or duodenal ulcer who had failed vonoprazan- or lansoprazole-based triple therapy, treatment with vonoprazan, amoxicillin, and metronidazole as second-line therapy achieved an HP eradication rate of 98%.[58] Later studies have suggested comparable but not quite as lofty HP eradication rates. For example, the efficacy of vonoprazan-based second-line therapy for 23 patients failing vonoprazan-based triple therapy was reported in a Japanese cohort as 87%.[59] A recent meta-analysis of 6664 patients across 16 studies found that vonoprazan-based regimens were superior to PPI-based regimens for overall second-line HP infection eradication success (OR, 1.51), with similar adverse-event rates.[60] These findings differed from those reported in an older meta-analysis of Japanese populations, wherein vonoprazan did not show superiority to PPIs as part of second-line triple therapies (intention-to-treat analysis, 83% vs 82%).[16] Given the increasing complexities associated with HP treatment, there are also available data on vonoprazan-based third-line therapies. An RCT of 7-day triple therapy regimens with sitafloxacin and amoxicillin showed vonoprazan-based therapy to be more effective than PPI-based triple therapy (per-protocol analysis, 83% vs 57%).[61]

Potassium-Competitive Acid Blockers for Peptic Ulcer Disease

Healing of Gastric and Duodenal Ulcers

Although the evaluation of HP status (with treatment as appropriate) along with assessment for offending medications (such as nonsteroidal anti-inflammatory drugs [NSAIDs]) represent important clinical aspects in the management of ulcers, acid-suppressive therapy (traditionally with PPIs) is typically utilized in the pharmacologic management of peptic ulcer disease (PUD).[62] However, the rapid and potent acid-suppressive actions of P-CABs have raised interest in their role in the treatment and prophylaxis of PUD. A Japanese trial randomized patients with gastric or duodenal ulcers to vonoprazan 20 mg once daily or lansoprazole 30 mg once daily, demonstrating the similar efficacy of vonoprazan and lansoprazole for the primary endpoint of endoscopically confirmed ulcer healing after 6 to 8 weeks of therapy (healing rates of 93%-94% for gastric ulcers and 96%-98% for duodenal ulcers).[63] Notably, the study protocol involved medication administration once daily after eating breakfast; differences owing to medication administration timing may have influenced results based on the known pharmacokinetics of each medication.[64] Similar results were found in a subsequent RCT comparing tegoprazan 50 mg or 100 mg once daily with lansoprazole 30 mg once daily in 306 patients with gastric ulcer disease, in which endoscopically confirmed healing rates after 8 weeks of therapy were 95% for tegoprazan 50 mg, 95% for tegoprazan 100 mg, and 96% for lansoprazole 30 mg.[25]

Although the overall rates of peptic ulcer healing were impressive in these trials, response rates may differ based upon ulcer etiology. A multicenter observational analysis of 162 patients reported gastric and duodenal ulcer healing rates after vonoprazan 20 mg once daily based upon the presence of HP infection and NSAID use.[65] The authors found that the healing rates of idiopathic peptic ulcers were marginally lower than those of HP-associated ulcers (81% vs 94%). Furthermore, the healing rates of NSAID-related ulcers were significantly lower than those of HP-associated ulcers. Overall, the healing rates for HP-associated ulcer disease with P-CABs approximated the rates described in the aforementioned trials, corroborating their effectiveness across multiple populations and P-CAB formulations. However, further attention to the significance of different etiologies of peptic ulcers, as well as potential incremental benefits in the setting of peptic ulcer–associated gastrointestinal bleeding (with or without endoscopic hemostasis), is warranted to better characterize P-CAB therapy in this clinical context.

Peptic Ulcer Prophylaxis in the Setting of Nonsteroidal Anti-Inflammatory Drug Use

Beyond the treatment of PUD, antisecretory therapy is utilized for the prevention of adverse gastrointestinal effects, such as peptic ulcers, in the setting of NSAID use for high-risk patients. P-CABs have also demonstrated utility for such prophylaxis indications. Among 621 Japanese patients with a history of peptic ulcers receiving low-dose aspirin randomized to vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg once daily for 24 weeks, recurrence rates of peptic ulcers were similar at 0.5%, 1.5%, and 2.8%, respectively.[19] An extension study lasting up to 2 years and including 439 patients demonstrated significantly lower peptic ulcer recurrence rates with vonoprazan 10 mg once daily compared with lansoprazole 15 mg once daily.[19] Similarly, among 642 Japanese patients at risk of peptic ulcer recurrence receiving long-term NSAID therapy randomized to vonoprazan 10 mg or vonoprazan 20 mg once daily or lansoprazole 15 mg once daily for 24 weeks, vonoprazan was noninferior, with rates of recurrent peptic ulcer at 3%, 3%, and 5% to 6% for vonoprazan 10 mg, vonoprazan 20 mg, and lansoprazole 15 mg, respectively.[18] The noninferiority of vonoprazan prophylaxis extended into the follow-up period, wherein cumulative incidence rates of peptic ulcer recurrence over 2 years were reported as 4%, 6%, and 7% to 8% for vonoprazan 10 mg, vonoprazan 20 mg, and lansoprazole 15 mg, respectively. Although treatment should be individualized and tailored to risk factors and clinical scenarios, these data overall suggest that P-CABs represent a viable alternative to PPI therapy for the pharmacologic prophylaxis of PUD.

Conclusions and the Future

P-CABs have strong potential utility in clinical practice across the spectrum of acid peptic disorders. Specifically, the characteristics that distinguish P-CABs from PPI formulations should facilitate their inclusion in the armamentarium for the management of patients who have disorders such as GERD (particularly for the treatment of severe EE), HP infection (first- or second-line regimens), and PUD (for healing and prophylaxis). With further study, P-CABs may also demonstrate utility for additional indications such as nonvariceal gastrointestinal bleeding, EoE, Barrett esophagus, and dyspepsia. Further data, especially in populations beyond Asia,[66] in the setting of pregnancy and lactation, for novel and expanding indications, on the safety of long-term use, and around costs and antibiotic stewardship, will be crucial, particularly for expanding regulatory approval and indications in clinical practice.

Disclosures

The authors have no relevant conflicts of interest to disclose.

References

1. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2022;117(1):27-56.
2. Gyawali CP, Carlson DA, Chen JW, Patel A, Wong RJ, Yadlapati RH. ACG clinical guidelines: clinical use of esophageal physiologic testing. *Am J Gastroenterol*. 2020;115(9):1412-1428.
3. Patel A, Yadlapati R. Diagnosis and management of refractory gastroesophageal reflux disease. *Gastroenterol Hepatol (N Y)*. 2021;17(7):305-315.
4. Abdel-Aziz Y, Metz DC, Howden CW. Review article: potassium-competitive acid blockers for the treatment of acid-related disorders. *Aliment Pharmacol Ther*. 2021;53(7):794-809.
5. Oshima T, Miwa H. Potent potassium-competitive acid blockers: a new era for the treatment of acid-related diseases. *J Neurogastroenterol Motil*. 2018;24(3):334-344.
6. Yang X, Li Y, Sun Y, et al. Vonoprazan: a novel and potent alternative in the treatment of acid-related diseases. *Dig Dis Sci*. 2018;63(2):302-311.
7. Graham DY, Dore MP. Update on the use of vonoprazan: a competitive acid blocker. *Gastroenterology*. 2018;154(3):462-466.
8. Phathom Pharmaceuticals. Phathom Pharmaceuticals announces FDA approval of Voquezna™ Triple Pak™ (vonoprazan, amoxicillin, clarithromycin) and Voquezna™ Dual Pak™ (vonoprazan, amoxicillin) for the treatment of H. pylori infection in adults. https://investors.phathompharma.com/news-releases/news-release-details/phathom-pharmaceuticals-announces-fda-approval-voqueznatm-triple. Published May 3, 2022.
9. Phathom Pharmaceuticals. Phathom Pharmaceuticals announces FDA acceptance for filing of vonoprazan NDA for the treatment of erosive esophagitis. https://investors.phathompharma.com/news-releases/news-release-details/phathom-pharmaceuticals-announces-fda-acceptance-filing. Published May 25, 2022.
10. Han S, Choi HY, Kim YH, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple oral doses of tegoprazan (CJ-12420), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther*. 2019;50(7):751-759.
11. Laine L, Sharma P, Mulford DJ, et al. Pharmacodynamics and pharmacokinetics of the potassium-competitive acid blocker vonoprazan and the proton pump inhibitor lansoprazole in US subjects. *Am J Gastroenterol*. 2022;117(7):1158-1161.
12. Yamasaki H, Kawaguchi N, Nonaka M, et al. In vitro metabolism of TAK-438, vonoprazan fumarate, a novel potassium-competitive acid blocker. *Xenobiotica*. 2017;47(12):1027-1034.
13. Kagami T, Sahara S, Ichikawa H, et al. Potent acid inhibition by vonoprazan in comparison with esomeprazole, with reference to CYP2C19 genotype. *Aliment Pharmacol Ther*. 2016;43(10):1048-1059.
14. Ashida K, Iwakiri K, Hiramatsu N, et al. Maintenance for healed erosive esophagitis: phase III comparison of vonoprazan with lansoprazole. *World J Gastroenterol*. 2018;24(14):1550-1561.
15. Cheng Y, Liu J, Tan X, et al. Direct comparison of the efficacy and safety of vonoprazan versus proton-pump inhibitors for gastroesophageal reflux disease: a systematic review and meta-analysis. *Dig Dis Sci*. 2021;66(1):19-28.
16. Dong SQ, Singh TP, Wei X, Yao H, Wang HL. Review: a Japanese population-based meta-analysis of vonoprazan versus PPI for Helicobacter pylori eradication therapy: is superiority an illusion? *Helicobacter*. 2017;22(6).
17. Jung YS, Kim EH, Park CH. Systematic review with meta-analysis: the efficacy of vonoprazan-based triple therapy on Helicobacter pylori eradication. *Aliment Pharmacol Ther*. 2017;46(2):106-114.
18. Mizokami Y, Oda K, Funao N, et al. Vonoprazan prevents ulcer recurrence during long-term NSAID therapy: randomised, lansoprazole-controlled non-inferiority and single-blind extension study. *Gut*. 2018;67(6):1042-1051.
19. Kawai T, Oda K, Funao N, et al. Vonoprazan prevents low-dose aspirin-associated ulcer recurrence: randomised phase 3 study. *Gut*. 2018;67(6):1033-1041.
20. Lee KJ, Son BK, Kim GH, et al. Randomised phase 3 trial: tegoprazan, a novel potassium-competitive acid blocker, vs. esomeprazole in patients with erosive oesophagitis. *Aliment Pharmacol Ther*. 2019;49(7):864-872.
21. He J, Cao G, Yu J, et al. Safety, tolerability and pharmacokinetics of single ascending and multiple oral doses of tegoprazan in healthy Chinese subjects. *Clin Drug Investig*. 2021;41(1):89-97.
22. Kim SH, Cho KB, Chun HJ, et al. Randomised clinical trial: comparison

of tegoprazan and placebo in non-erosive reflux disease. *Aliment Pharmacol Ther*. 2021;54(4):402-411.
23. Ashida K, Sakurai Y, Hori T, et al. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. *Aliment Pharmacol Ther*. 2016;43(2):240-251.
24. Uemura N, Kinoshita Y, Haruma K, Yao T, Kushima R, Kanoo T. Rationale and design of the VISION study: a randomized, open-label study to evaluate the long-term safety of vonoprazan as maintenance treatment in patients with erosive esophagitis. *Clin Exp Gastroenterol*. 2018;11:51-56.
25. Cho YK, Choi MG, Choi SC, et al. Randomised clinical trial: tegoprazan, a novel potassium-competitive acid blocker, or lansoprazole in the treatment of gastric ulcer. *Aliment Pharmacol Ther*. 2020;52(5):789-797.
26. Otsuka T, Sugimoto M, Inoue R, et al. Influence of potassium-competitive acid blocker on the gut microbiome of *Helicobacter pylori*-negative healthy individuals. *Gut*. 2017;66(9):1723-1725.
27. Li T, Qiao H, Yue P, Cai M, He X. Embryo-fetal toxicity assessment of vonoprazan in rats and rabbits. *J Appl Toxicol*. 2018;38(7):987-995.
28. Kinoshita Y, Sakurai Y, Takabayashi N, et al. Efficacy and safety of vonoprazan in patients with nonerosive gastroesophageal reflux disease: a randomized, placebo-controlled, phase 3 study. *Clin Transl Gastroenterol*. 2019;10(11):e00101.
29. Iwakiri K, Fujiwara Y, Manabe N, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021. *J Gastroenterol*. 2022;57(4):267-285.
30. Niikura R, Yamada A, Hirata Y, et al. Efficacy of vonoprazan for gastroesophageal reflux symptoms in patients with proton pump inhibitor-resistant non-erosive reflux disease. *Intern Med*. 2018;57(17):2443-2450.
31. Abe Y, Koike T, Saito M, et al. The ameliorating effect of switching to vonoprazan: a novel potassium-competitive acid blocker in patients with proton pump inhibitor refractory non-erosive reflux disease. *Digestion*. 2021;102(3):480-488.
32. Xiao Y, Zhang S, Dai N, et al. Phase III, randomised, double-blind, multicentre study to evaluate the efficacy and safety of vonoprazan compared with lansoprazole in Asian patients with erosive oesophagitis. *Gut*. 2020;69(2):224-230.
33. Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and management of Barrett's esophagus: an updated ACG guideline. *Am J Gastroenterol*. 2022;117(4):559-587.
34. Chen S, Liu D, Chen H, et al. The efficacy and safety of keverprazan, a novel potassium-competitive acid blocker, in treating erosive oesophagitis: a phase III, randomised, double-blind multicentre study. *Aliment Pharmacol Ther*. 2022;55(12):1524-1533.
35. Hoshino S, Kawami N, Takenouchi N, et al. Efficacy of vonoprazan for proton pump inhibitor-resistant reflux esophagitis. *Digestion*. 2017;95(2):156-161.
36. Oshima T, Arai E, Taki M, et al. Randomised clinical trial: vonoprazan versus lansoprazole for the initial relief of heartburn in patients with erosive oesophagitis. *Aliment Pharmacol Ther*. 2019;49(2):140-146.
37. Laine L, Devault KR, Katz PO, et al. 883: Double-blind randomized trial of the potassium-competitive acid blocker vonoprazan vs. the proton pump inhibitor lansoprazole in U.S. and European patients with erosive esophagitis. *Gastroenterology*. 2022;162(7)(suppl):S-214.
38. Hirano I, Chan ES, Rank MA, et al; AGA Institute Clinical Guidelines Committee; Joint Task Force on Allergy-Immunology Practice Parameters. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters clinical guidelines for the management of eosinophilic esophagitis. *Gastroenterology*. 2020;158(6):1776-1786.
39. Posner S, Boyd A, Patel A. Dysphagia in a 34-year-old woman. *JAMA*. 2020;323(7):660-661.
40. Ishimura N, Ishihara S, Kinoshita Y. Sustained acid suppression by potassium-competitive acid blocker (P-CAB) may be an attractive treatment candidate for patients with eosinophilic esophagitis. *Am J Gastroenterol*. 2016;111(8):1203-1204.
41. Kuzumoto T, Tanaka F, Sawada A, et al. Vonoprazan shows efficacy similar to that of proton pump inhibitors with respect to symptomatic, endoscopic, and histological responses in patients with eosinophilic esophagitis. *Esophagus*. 2021;18(2):372-379.
42. Laserna-Mendieta EJ, Casabona S, Guagnozzi D, et al; EUREOS EoE CONNECT Research group. Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry. *Aliment Pharmacol Ther*. 2020;52(5):798-807.
43. Fallone CA. The current role of vonoprazan in Helicobacter pylori treatment. *Gastroenterology*. 2022;163(3):572-574.
44. Malfertheiner P, Megraud F, Rokkas T, et al; European Helicobacter and Microbiota Study group. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report [published online August 8, 2022]. *Gut*. doi:10.1136/gutjnl-2022-327745.
45. Suzuki S, Gotoda T, Kusano C, Iwatsuka K, Moriyama M. The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-day PPI-based low-dose clarithromycin triple therapy. *Am J Gastroenterol*. 2016;111(7):949-956.
46. Maruyama M, Tanaka N, Kubota D, et al. Vonoprazan-based regimen is more useful than PPI-based one as a first-line *Helicobacter pylori* eradication: a randomized controlled trial. *Can J Gastroenterol Hepatol*. 2017;2017:4385161.
47. Kajihara Y, Shimoyama T, Mizuki I. Analysis of the cost-effectiveness of using vonoprazan-amoxicillin-clarithromycin triple therapy for first-line Helicobacter pylori eradication. *Scand J Gastroenterol*. 2017;52(2):238-241.
48. Ozaki H, Harada S, Takeuchi T, et al. Vonoprazan, a novel potassium-competitive acid blocker, should be used for the Helicobacter pylori eradication therapy as first choice: a large sample study of vonoprazan in real world compared with our randomized control trial using second-generation proton pump inhibitors for Helicobacter pylori eradication therapy. *Digestion*. 2018;97(3):212-218.
49. Lyu QJ, Pu QH, Zhong XF, Zhang J. Efficacy and safety of vonoprazan-based versus proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: a meta-analysis of randomized clinical trials. *BioMed Res Int*. 2019;2019:9781212.
50. Malfertheiner P, Moss SF, Daniele P, et al. Potassium-competitive acid blocker and proton pump inhibitor-based regimens for first-line *Helicobacter pylori* eradication: a network meta-analysis. *Gastro Hep Adv*. 2022;1(5):824-834.
51. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in Helicobacter pylori: a systematic review and meta-analysis in World Health Organization regions. *Gastroenterology*. 2018;155(5):1372-1382.e17.
52. Suzuki S, Gotoda T, Kusano C, et al. Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line *Helicobacter pylori* treatment: a multicentre randomised trial in Japan. *Gut*. 2020;69(6):1019-1026.
53. Gotoda T, Kusano C, Suzuki S, Horii T, Ichijima R, Ikehara H. Clinical impact of vonoprazan-based dual therapy with amoxicillin for H. pylori infection in a treatment-naïve cohort of junior high school students in Japan. *J Gastroenterol*. 2020;55(10):969-976.
54. Furuta T, Yamade M, Kagami T, et al. Dual therapy with vonoprazan and amoxicillin is as effective as triple therapy with vonoprazan, amoxicillin and clarithromycin for eradication of Helicobacter pylori. *Digestion*. 2020;101(6):743-751.
55. Chey WD, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW. Vonoprazan triple and dual therapy for Helicobacter pylori infection in the United States and Europe: randomized clinical trial. *Gastroenterology*. 2022;163(3):608-619.
56. Choi YJ, Lee YC, Kim JM, et al. Triple therapy-based on tegoprazan, a new potassium-competitive acid blocker, for first-line treatment of Helicobacter pylori infection: a randomized, double-blind, phase III, clinical trial. *Gut Liver*. 2022;16(4):535-546.
57. Ang D, Koo SH, Chan YH, et al. Clinical trial: seven-day vonoprazan- versus 14-day proton pump inhibitor-based triple therapy for first-line Helicobacter pylori eradication. *Aliment Pharmacol Ther*. 2022;56(3):436-449.
58. Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study. *Gut*. 2016;65(9):1439-1446.
59. Katayama Y, Toyoda K, Kusano Y, et al. Efficacy of vonoprazan-based second-line *Helicobacter pylori* eradication therapy in patients for whom vonoprazan-based first-line treatment failed. *Gut*. 2017;66(4):752-753.
60. Shinozaki S, Kobayashi Y, Osawa H, et al. Effectiveness and safety of vonoprazan versus proton pump inhibitors for second-line Helicobacter pylori eradication therapy: systematic review and meta-analysis. *Digestion*. 2021;102(3):319-325.
61. Sue S, Shibata W, Sasaki T, et al. Randomized trial of vonoprazan-based versus proton-pump inhibitor-based third-line triple therapy with sitafloxacin for Helicobacter pylori. *J Gastroenterol Hepatol*. 2019;34(4):686-692.
62. NIH Consensus Conference. Helicobacter pylori in peptic ulcer disease. NIH Consensus Development Panel on Helicobacter pylori in peptic ulcer disease. *JAMA*. 1994;272(1):65-69.
63. Miwa H, Uedo N, Watari J, et al. Randomised clinical trial: efficacy and safety of vonoprazan vs. lansoprazole in patients with gastric or duodenal ulcers—results from two phase 3, non-inferiority randomised controlled trials. *Aliment Pharmacol Ther*. 2017;45(2):240-252.
64. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology*. 2000;118(2)(suppl 1):S9-S31.
65. Sugawara K, Koizumi S, Horikawa Y, et al. Is the new potent acid-inhibitory drug vonoprazan effective for healing idiopathic peptic ulcers? A multicenter observational study in Akita Prefecture, Japan. *J Gastroenterol*. 2019;54(11):963-971.
66. Scarpignato C, Leifke E, Smith N, et al. A population pharmacokinetic model of vonoprazan: evaluating the effects of race, disease status, and other covariates on exposure. *J Clin Pharmacol*. 2022;62(6):801-811.