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AGA Clinical Practice Update on Integrating Potassium-Competitive Acid Blockers Into Clinical Practice: Expert Review

Amit Patel,[1,2] Loren Laine,[3,4] Paul Moayyedi,[5] and Justin Wu[6]

[1]Division of Gastroenterology, Duke University School of Medicine, Durham, North Carolina; [2]Durham Veterans Affairs Medical Center, Durham, North Carolina; [3]Division of Gastroenterology, Yale School of Medicine, New Haven, Connecticut; [4]Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut; [5]Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; and [6]Division of Gastroenterology, Chinese University of Hong Kong, Hong Kong Special Administrative Region, The People's Republic of China

DESCRIPTION: The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update (CPU) is to summarize the available evidence and offer expert Best Practice Advice on the integration of potassium-competitive acid blockers (P-CABs) in the clinical management of foregut disorders, specifically including gastroesophageal reflux disease, *Helicobacter pylori* infection, and peptic ulcer disease. **METHODS:** This expert review was commissioned and approved by the AGA Institute Governing Board and CPU Committee to provide timely guidance on a topic of high clinical importance to the AGA membership. This CPU expert review underwent internal peer review by the CPU Committee and external peer review through the standard procedures of *Gastroenterology*. These Best Practice Advice statements were developed based on review of the published literature and expert consensus opinion. Because formal systematic reviews were not performed, these Best Practice Advice statements do not carry formal ratings of the quality of evidence or strength of the presented considerations.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: Based on nonclinical factors (including cost, greater obstacles to obtaining medication, and fewer long-term safety data), clinicians should generally not use P-CABs as initial therapy for acid-related conditions in which clinical superiority has not been shown. **BEST PRACTICE ADVICE 2:** Based on current costs in the United States, even modest clinical superiority of P-CABs over double-dose proton pump inhibitors (PPIs) may not make P-CABs cost-effective as first-line therapy. **BEST PRACTICE ADVICE 3:** Clinicians should generally not use P-CABs as first-line therapy for patients with uninvestigated heartburn symptoms or nonerosive reflux disease. Clinicians may use P-CABs in selected patients with documented acid-related reflux who fail therapy with twice-daily PPIs. **BEST PRACTICE ADVICE 4:** Although there is currently insufficient evidence for clinicians to use P-CABs as first-line on-demand therapy for patients with heartburn symptoms who have previously responded to antisecretory therapy, their rapid onset of acid inhibition raises the possibility of their utility in this population. **BEST PRACTICE ADVICE 5:** Clinicians should generally not use P-CABs as first-line therapy in patients with milder erosive esophagitis (EE) (Los Angeles classification of erosive esophagitis grade A/B EE). Clinicians may use P-CABs in selected patients with documented acid-related reflux who fail therapy with twice-daily PPIs. **BEST PRACTICE ADVICE 6:** Clinicians may use P-CABs as a therapeutic option for the healing and maintenance of healing in patients with more severe EE (Los Angeles classification of erosive esophagitis grade C/D EE). However, given the markedly higher costs of the P-CAB presently available in the United States and the lack of randomized comparisons with double-dose PPIs, it is not clear that the benefits in endoscopic outcomes over standard-dose PPIs justify the routine use of P-CABs as first-line therapy. **BEST PRACTICE ADVICE 7:** Clinicians should use P-CABs in place of PPIs in eradication regimens for most patients with *H pylori* infection. **BEST PRACTICE ADVICE 8:** Clinicians should generally not use P-CABs as first-line therapy in the treatment or prophylaxis of peptic ulcer disease. **BEST PRACTICE ADVICE 9:** Although there is currently insufficient evidence for clinicians to use P-CABs as first-line therapy in patients with bleeding gastroduodenal ulcers and high-risk stigmata, their rapid and potent acid inhibition raises the possibility of their utility in this population.

Keywords: Gastroesophageal Reflux Disease; Erosive Esophagitis; Heartburn; *Helicobacter pylori*; Peptic Ulcer Disease.

Inhibition of gastric acid secretion represents a cornerstone of treatment for a variety of common upper gastrointestinal (GI) tract conditions, including gastroesophageal reflux disease (GERD), *Helicobacter pylori* (HP) infection, peptic ulcer disease (PUD), and dyspepsia.[1–3] Histamine2-receptor antagonists and proton pump inhibitors (PPIs) are used by large proportions of the population, with a recent systematic review reporting prevalence estimates of PPI use in studies from the United States, Europe, and Australia ranging from 4% to 33%, with most data showing a pattern of increasing use over time.[4] However, limitations to PPIs (discussed below and in Table 1) have spurred interest in the development of other drugs to suppress gastric acid. Potassium-competitive acid blockers

Abbreviations used in this paper: **EE, erosive esophagitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HP, *Helicobacter pylori*; LA, Los Angeles classification of erosive esophagitis; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; PUD, peptic ulcer disease.**

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Table 1. Potassium-Competitive Acid Blocker and Proton Pump Inhibitor Class Comparison

Variable	P-CAB	PPI
Effect of gastric acid	Acid-stable	Acid-labile (note enteric coating)
Prodrug	No	Yes (converted to sulfonamide compounds in acidic environment)
Binding to proton pump	Ionic (reversible) binding (blocks access of K^+ to potassium-binding site of pump)	Binds covalently (irreversible) to cysteines on active pumps (blocks exchange of H^+ and K^+)
Half-life estimates, *h*[5–7]	6–9	1–2
Timing of administration	Independent of mealtimes (not restricted, given longer half-life)	30–60 min before meals (so presence in secretory canaliculus coincides with postprandial peak in active pumps)
Dosing range, *d*, for maximal acid suppression[5,7,8]	1	3–5
Examples	Revaprazan, vonoprazan, tegoprazan, fexuprazan, linaprazan, zastaprazan, and keverprazan	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole

(P-CABs), such as vonoprazan and tegoprazan, are a new class of antisecretory medications that may potentially provide more potent acid inhibition than PPIs, and randomized trial data evaluating the efficacy of P-CABs in a variety of upper GI conditions are increasingly available.[5,6,9] Given accumulating data and expanding regulatory approval, as well as issues around payor authorization and coverage,[10,11] this American Gastroenterological Association Clinical Practice Update expert review guides providers on how to incorporate P-CABs into clinical practice (Figure 1). These statements only apply to settings in which P-CABs represent an available option.

Potassium-Competitive Acid Blockers' Mechanism of Action

P-CABs are absorbed systemically and function by reversibly binding to H^+, K^+-ATPase (the "proton pump") in the gastric parietal cell, blocking potassium ion access to the potassium binding site of the proton pump, thereby

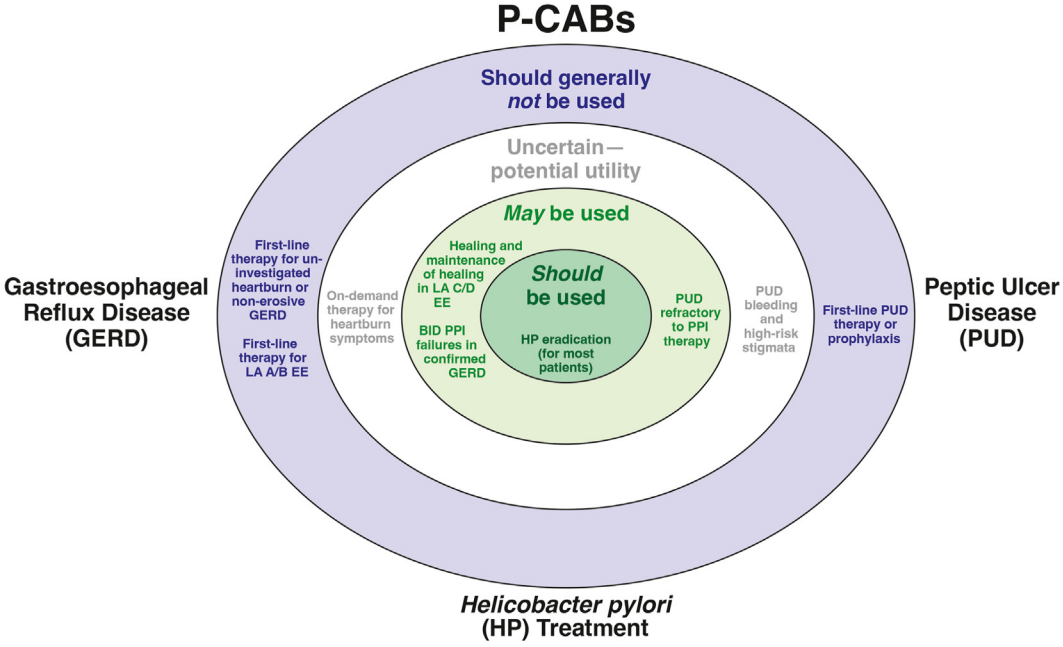

Figure 1. Best Practice Advice for the use of P-CABs in foregut disorders, focusing on GERD, HP treatment, and PUD. From the *outer circle* toward the *center*: clinical settings where P-CABs should generally not be used, may have potential utility pending further data, may be used, and should be used in most patients. BID, twice daily.

suppressing gastric acid secretion.[12] Unlike PPIs, P-CABs are acid-stable and do not require premeal dosing (Table 1). In addition, P-CABs are not prodrugs and do not require conversion to an active form to provide their pharmacologic effect, facilitating a more rapid onset of action. Given their longer half-lives, P-CABs are available to bind to proton pumps as they become active for longer periods of time, facilitating more prolonged gastric acid inhibition than PPIs. Studies have found that P-CABs can maintain target intragastric pH levels for longer proportions of a 24-hour period than PPIs.[6,13–17] Furthermore, genetic polymorphisms of CYP2C19 impact metabolism of some PPIs, leading to variability in pharmacologic and therapeutic outcomes. P-CABs, however, are not metabolized by CYP2C19 and, therefore, are impacted less by genetic polymorphisms.[18] In sum, these characteristics of P-CABs suggest they may represent effective alternatives for some patients with acid-related disorders.

Safety of Potassium-Competitive Acid Blockers

A variety of safety concerns have been raised in observational studies of PPI use, although most of these associations are probably due to the residual confounding or biases that are inherent in such studies, rather than true causal effects of PPI.[19] Nevertheless, any safety concerns related to acid inhibition with PPIs would be expected to be shared by P-CABs. Whether the more potent acid inhibition associated with P-CABs may increase any adverse effects to a greater degree than PPIs is unknown. Serum gastrin levels are raised to higher levels with P-CABs compared with PPI use. Elevations continue for the duration of P-CAB use, with levels coming down toward baseline within weeks after discontinuation.[20,21]

Randomized trial data indicate P-CABs are generally well-tolerated with short-term and medium-term safety profiles comparable with PPIs. Multiple Japanese retrospective studies suggest that although vonoprazan appears to be associated with *Clostridioides difficil*e infection, the magnitude of this association is comparable with, and not beyond, that of PPIs.[22,23] Although recently published Japanese population–based data suggest that P-CABs may be associated with increased risks of gastric cancer (compared with histamine2-receptor antagonists), the adjusted hazard ratio was <2 and rates were similar to those for PPIs.[24,25] A randomized open-label trial compared vonoprazan and lansoprazole for maintenance therapy of erosive esophagitis (EE) for 5 years and found similar proportions with adverse events, with infrequent and comparable proportions developing histologic changes of enterochromaffin-like cell hyperplasia.[26] The mean serum gastrin in the vonoprazan group was elevated at week 12 and remained at approximately the same level, consistently higher than levels in the lansoprazole group, through week 260 of the maintenance phase.[26] One case of foveolar-type adenoma was reported in the vonoprazan group and 1 case of oxyntic gland adenoma was reported in the lansoprazole group by year 4 of the study.[27,28]

Because of their potent acid suppression, PPI or P-CAB use may also be associated with clinically relevant infection risks. PPIs appear to be associated with increased risks of enteric infections based on observational and randomized trial data[19]; similar associations would be expected for P-CABs. Vonoprazan use has also been associated with microbiota changes that may decrease defense against enteric infections.[29] Although safety data are limited for P-CABs in pregnant and lactating populations, no maternal or developmental toxicity was observed with vonoprazan exposure in an animal study.[30] Although present evidence does not identify clear-cut safety signals with P-CABs, it will be important to continue to assess emerging long-term safety data to evaluate for any potential impact of the more potent acid inhibition and elevated gastrin levels seen with P-CABs compared with PPIs.

Foregut Acid-Related Disorders

Best Practice Advice 1: Based on nonclinical factors (including cost, greater obstacles to obtaining medication, and fewer long-term safety data), clinicians should generally not use P-CABs as initial therapy for acid-related conditions in which clinical superiority has not been shown.

Best Practice Advice 2: Based on current costs in the United States, even modest clinical superiority of P-CABs over double-dose PPIs may not make P-CABs cost-effective as first-line therapy.

The inhibition of gastric acid secretion by P-CABs is as potent or more potent than the inhibition by PPIs, varying by specific agent and dose. Therefore, P-CABs generally have clinical efficacy at least similar to PPIs for acid-related disorders. Based on pharmacodynamic studies, some doses of P-CABs used in clinical trials (eg, zastaprazan 10 mg,[15] fexuprazan 40 mg,[16] tegoprazan 50–100 mg,[31] and vonoprazan 20 mg[18]) may have intragastric acid inhibition similar to that of standard PPI doses rather than more potent acid inhibition.

However, compared with PPIs, P-CABs are likely to be associated with higher costs, less availability (PPIs are sold over-the-counter), higher likelihood of requiring insurer's prior authorization, and less-robust long-term safety data. Although more potent acid inhibition is not necessarily associated with superior outcomes across all foregut disorders (eg, heartburn,[32] prevention of nonsteroidal anti-inflammatory drug–associated ulcers[33,34]), P-CABs may play a role in patients with acid-related disorders who fail PPI therapy. As the cost of the P-CAB currently available in the United States is markedly higher than that of standard-dose and double-dose PPIs, evidence that standard-dose P-CABs are superior not only to standard-dose PPIs but also double-dose PPIs will be important in making decisions on medication choice in the United States and other countries with these large cost differentials. Overall, factors such as medication costs, obstacles to obtaining P-CABs, and less long-term safety data may outweigh potential advantages related to acid inhibition and P-CAB characteristics, particularly if superiority in clinical efficacy is not documented.

Gastroesophageal Reflux Disease

Nonerosive Reflux Disease

Best Practice Advice 3: Clinicians should generally not use P-CABs as first-line therapy for patients with uninvestigated heartburn symptoms or nonerosive reflux disease. Clinicians may use P-CABs in selected patients with documented acid-related reflux who fail therapy with twice-daily PPIs.

Compared with EE, there is less robust evidence for P-CABs in the management of nonerosive GERD (Table 2). Two randomized trials from Japan compared vonoprazan with placebo in patients with nonerosive GERD. The first trial, which found similarly low median proportions of heartburn-free days between vonoprazan and placebo (10%–12% vs 7%), excluded patients responsive to antacids during a 1-week run-in period. This exclusion may have enriched the study population with functional heartburn patients, potentially explaining the poor results in all study groups.[35] In contrast, the second trial found a trend toward higher median proportions of heartburn-free days for vonoprazan (72% vs 62%; $P = .06$).[36] A Korean trial demonstrated higher rates of complete heartburn resolution for tegoprazan 50–100 mg compared with placebo (42%–49% vs 24%; $P = .006$ and $P = .0004$) with proportions of heartburn-free days approximately 10% higher with tegoprazan (67%–68%) than placebo (57%).[37] A recent randomized trial of US patients with heartburn without EE randomized to vonoprazan 10–20 mg or placebo for 4 weeks demonstrated higher percentages of heartburn-free days in the vonoprazan group compared with placebo (44%–45% vs 28%; $P < .0001$), beginning as early as the first day of therapy.[38]

Interpretation of these findings for clinical application should acknowledge that the persistence of suspected reflux symptoms despite PPI or P-CAB therapy may not necessarily be associated with ongoing acid reflux, but instead the presence of other processes in which increasing acid inhibition further is unlikely to be associated with symptomatic benefit.[32,49] As PPIs are typically more available (including over-the-counter) and less costly than P-CABs (based on current US prices), with more associated long-term safety data in the setting of unclear clinical superiority of P-CABs, it is difficult to justify the recommendation of P-CABs as initial empiric therapy for uninvestigated heartburn symptoms or first-line therapy for nonerosive GERD at this time.

Best Practice Advice 4: Although there is currently insufficient evidence for clinicians to use P-CABs as first-line on-demand therapy for patients with heartburn symptoms who have previously responded to antisecretory therapy, their rapid onset of acid inhibition raises the possibility of their utility in this population.

The pharmacodynamic characteristics (more rapid acid suppression) of P-CABs raise the possibility that they can represent an effective option for on-demand use of reflux symptoms. Furthermore, if they are used infrequently, cost may not represent as significant an issue as for other indications. A North American randomized controlled trial randomly assigned 207 patients with GERD without EE (with heartburn that resolved during the final week of a 4-week, open-label, run-in period of once-daily vonoprazan 20 mg) to on-demand vonoprazan or placebo.[39] The proportions of evaluable heartburn episodes with complete relief within 3 hours and sustained for 24 hours were higher for vonoprazan (56%–70% vs 27%), with differences present within 1 hour of on-demand use.[39] Although these placebo-controlled data suggest the efficacy of P-CABs as on-demand therapy, clinical trials comparing P-CABs with PPIs and histamine2-receptor antagonists would be helpful to better understand their utility in this context.

Erosive Esophagitis

Best Practice Advice 5: Clinicians should generally not use P-CABs as first-line therapy in patients with milder EE (Los Angeles classification of erosive esophagitis [LA] grade A/B EE). Clinicians may use P-CABs in selected patients with documented acid-related reflux who fail therapy with twice-daily PPIs.

For the healing of EE, randomized trials for P-CABs have generally been noninferiority comparisons with PPIs. A systematic review of P-CABs vs PPI in EE identified 4 trials evaluating 2208 participants, 67% with LA grade A/B EE, with a relative risk of healing with vonoprazan vs PPI of 1.10 (95% CI, 1.003–1.081).[50] The slight benefit of P-CABs in healing overall EE likely relates to healing of severe EE; for milder EE the medication classes have similar efficacy (Table 2).

For analyses focusing on the healing of LA grade A/B EE, 8-week randomized trials have demonstrated the similarity of healing rates for P-CABs compared with PPIs (tegoprazan, 95%–96% vs 93% in a trial with 96% LA grade A/B[42]), vonoprazan (92%–99% vs 96%–100%[40,41,43]), keverprazan (97% vs 93%[44]), and fexuprazan (92% vs 88%,[46] 99% vs 99% in a trial with 93% LA grade A/B[45]) in Asian populations. A single trial from the United States and Europe has been published evaluating P-CAB therapy for EE, with similar healing rates for vonoprazan 20 mg vs lansoprazole 30 mg by 8 weeks in LA grade A/B EE (94% vs 91%).[20] Overall, this evidence base has established the relatively similar efficacy of P-CABs compared with PPIs for the healing of LA grade A/B EE.

For maintenance of healing of LA grade A/B EE over 24 weeks, randomized trial data from South Korea demonstrated similar results for tegoprazan 25 mg vs lansoprazole 15 mg (87% vs 86%),[48] although a randomized trial from Japan showed results for vonoprazan 10–20 mg tended to be somewhat better than lansoprazole 15 mg (97%–99% vs 89%).[47] The randomized trial from the United States and Europe compared vonoprazan 10 or 20 mg with lansoprazole 15 mg daily, and found maintenance of healing at 24 weeks for those with LA grade A/B EE of 81%–82% with vonoprazan vs 77% with lansoprazole.[20]

Given the present greater cost (based on current US prices) and more limited availability of P-CABs, they are unlikely to be appropriate for first-line therapy in LA grade A/B EE. However, P-CABs can be considered in PPI

Table 2. Summary of Selected Randomized Controlled Trials Evaluating Potassium-Competitive Acid Blockers in Gastroesophageal Reflux Disease

Condition	First author, year	P-CAB	Comparator	Patients	Duration, *wk*	Outcome	Result (P-CAB vs comparator), %
Nonerosive GERD	Kinoshita, 2016[35]	Vonoprazan 10–20 mg daily	Placebo	827	4	Median proportion of days without heartburn	10–1 vs 7
	Kinoshita, 2019[36]	Vonoprazan 10 mg daily	Placebo	483	4	Median proportion of days without heartburn	72 vs 62
	Kim, 2021[37]	Tegoprazan 50 mg or 100 mg daily	Placebo	324	4	Heartburn resolution	42–49 vs 24
	Laine, 2024[38]	Vonoprazan 10–20 mg	Placebo	772	4	Percentage of days without heartburn	44.4–44.8 vs 27.7
Heartburn (endoscopy without EE, with resolution on wk 4 of vonoprazan 20 mg daily)	Fass, 2023[39]	On-demand vonoprazan 10–40 mg	Placebo	207	6	Proportions of heartburn episodes with complete relief within 3 hours and sustained for 24 hours	56–70 vs 27
Healing of EE	Ashida, 2015[40]	Vonoprazan 5–40 mg daily	Lansoprazole 30 mg daily	732 (60% with LA grade A/B)	4	Healing of EE	92–97 vs 93 (LA grade A/B: 92–98 vs 97, LA grade C/D: 87–100 vs 87)
	Ashida, 2016[41]	Vonoprazan 20 mg	Lansoprazole 30 mg daily	409 (63% with LA grade A/B)	8	Healing of EE	99 vs 96 (LA grade A/B: 99 vs 100, LA grade C/D: 99 vs 88)
	Lee, 2019[42]	Tegoprazan 50–100 mg daily	Esomeprazole 40 mg	302 (96% with LA grade A/B)	8	Healing of EE	95–96 vs 93
	Xiao, 2020[43]	Vonoprazan 20 mg daily	Lansoprazole 30 mg daily	481 (70% with LA grade A/B)	8	Healing of EE	92 vs 91 (LA grade A/B: 96 vs 96, LA grade C/D: 84 vs 81)
	Chen, 2022[44]	Keverprazan 20 mg daily	Lansoprazole 30 mg daily	238 (79% with LA grade A/B)	8	Healing of EE	96 vs 90 (LA grade A/B: 97 vs 93, LA grade C/D: 92 vs 80)
	Lee, 2022[45]	Fexuprazan 40 mg daily	Esomeprazole 40 mg daily	231 (93% with LA grade A/B)	8	Healing of EE	99 vs 99

Table 2. Continued

Condition	First author, year	P-CAB	Comparator	Patients	Duration, *wk*	Outcome	Result (P-CAB vs comparator), %
	Laine, 2023[20]	Vonoprazan 20 mg daily	Lansoprazole 30 mg daily	1024 (66% with LA grade A/B)	8	Healing of EE	93 vs 85 (LA grade A/B: 94 vs 91, LA grade C/D: 92 vs 72)
	Zhuang, 2024[46]	Fexuprazan 40 mg daily	Esomeprazole 40 mg daily	328 (68% with LA grade A/B)	8	Healing of EE	89 vs 89 (LA grade A/B: 92 vs 88, LA grade C/D: 80 vs 91)
Maintenance of healing of EE	Ashida, 2018[47]	Vonoprazan 10–20 mg daily	Lansoprazole 15 mg daily	607 (80% with LA grade A/B)	24	Recurrence of EE	2–5 vs 17 (LA grade A/B: 1–3 vs 11, LA grade C/D: 5–13 vs 39)
	Cho, 2023[48]	Tegoprazan 25 mg daily	Lansoprazole 15 mg daily	305 (95% with LA grade A/B)	24	Maintenance of healing	91 vs 90 (LA grade A/B: 87 vs 86, LA grade C/D: 75 vs 60)
	Laine, 2023[20]	Vonoprazan 10–20 mg daily	Lansoprazole 15 mg daily	878 (68% with LA grade A/B)	24	Maintenance of healing	79–81 vs 72 (LA grade A/B: 81–82 vs 77, LA grade C/D, 75–77 vs 62)

treatment failures (eg, refractory esophagitis) when confirmatory GERD evidence is present (LA grade B or greater EE, biopsy-proven Barrett's esophagus, peptic stricture, or ambulatory reflux monitoring with distal esophageal acid exposure times >6%).[32,51–53]

Best Practice Advice 6: Clinicians may use P-CABs as a therapeutic option for the healing and maintenance of healing in patients with more severe EE (LA grade C/D EE). However, given the markedly higher costs of the P-CAB presently available in the United States and the lack of randomized comparisons with double-dose PPIs, it is not clear that the benefits in endoscopic outcomes over standard-dose PPIs justify the routine use of P-CABs as first-line therapy.

Analysis of patients with LA grade C/D EE from randomized trials suggest that P-CABs may be superior to PPIs for healing and maintenance of healing of more severe EE and may be associated with more rapid healing (Table 2). However, PPIs may vary in potency based on the specific medication and dosing, and the trials showing these differences were performed with the PPI lansoprazole (30 mg for healing, 15 mg for maintenance). In the randomized trial from the United States and Europe, vonoprazan 20 mg appeared superior for the healing of LA grade C/D EE at 2 weeks (70% vs 53%) and 8 weeks (92% vs 72%).[20] Among Asian randomized trials, which included smaller numbers of patients with LA grade C/D EE, vonoprazan 20 mg tended to have higher rates of EE healing for LA grade C/D EE than lansoprazole 30 mg by 8 weeks in 2 of 3 studies (100% vs 87%, 99% vs 88%, and 84% vs 81%),[40,41,43] as did keverprazan 20 mg vs lansoprazole 30 mg (92% vs 80%),[44] but not fexuprazan 40 mg vs esomeprazole 40 mg (80% vs 91%).[46]

There is also evidence supporting the efficacy of P-CABs for the maintenance of healing of severe EE in comparison with PPI therapy (Table 2). The maintenance phase of the randomized trial from the United States and Europe demonstrated the superiority of vonoprazan 10 mg and 20 mg over lansoprazole 15 mg for maintenance of healing among those with LA grade C/D EE (75%–77% vs 62%).[20] For those patients with LA grade C/D EE in a Japanese randomized trial of maintenance of healed EE, recurrence rates were lower for vonoprazan 10 mg and 20 mg than lansoprazole 15 mg (5%–13% vs 39%).[47] P-CABs should be employed if PPIs are used as initial therapy and fail to maintain healing.

Management of *Helicobacter pylori*

Best Practice Advice 7: Clinicians should use P-CABs in place of PPIs in eradication regimens for most patients with HP infection.

P-CABs have been studied extensively in HP treatment regimens, primarily among Asian populations.[54] A systematic review of 7 Asian randomized trials revealed significantly higher pooled eradication rates in first-line HP treatment for vonoprazan vs PPI (92% vs 80%).[55] It is important to note that at some of the doses studied in this context, P-CABs may not be more effective than PPIs. For example, 2 recently published studies suggested that triple therapy with tegoprazan 50 mg twice daily was not significantly more effective for HP eradication than regimens with esomeprazole 40 mg twice daily (with sodium bicarbonate)[56] or rabeprazole 20 mg twice daily.[57]

A duration of 14 days is generally advised for HP regimens, and US approval for vonoprazan-based regimens was for 14 days.[58] However, P-CABs have also demonstrated efficacy as part of more streamlined treatment regimens with less medication burden and/or shorter treatment durations. A Japanese trial with 335 patients found relatively similar HP eradication rates with vonoprazan 20 mg plus amoxicillin 750 mg twice daily dual therapy for 7 days compared with vonoprazan-based triple therapy (85% vs 89%).[59] A Singaporean trial with 244 patients compared 1 week of vonoprazan 20 mg twice daily–based triple therapy with 2 weeks of PPI-based triple therapy (omeprazole or esomeprazole or rabeprazole 20 mg twice daily) found similar rates of HP eradication (87% vs 88%).[60]

When sub-populations of patients with clarithromycin-resistant HP strains within randomized trials are assessed, P-CABs given twice daily had an even greater incremental benefit over PPI-based regimens, presumably because the increased acid inhibition that can result with the P-CAB doses used improves the efficacy of other antibiotics, such as amoxicillin. The Japanese trial cited above showed superior eradication rates for 1 week of vonoprazan dual therapy compared with vonoprazan-based triple therapy among patients with clarithromycin-resistant strains (92% vs 76%).[59] A trial including 1046 treatment-naïve American and European adults assessed open-label dual therapy (with vonoprazan 20 mg twice daily and 1 g amoxicillin thrice daily) or double-blind triple therapy (with vonoprazan 20 mg twice daily or lansoprazole 30 mg twice daily) for 14 days.[61] Among all study patients, HP eradication rates were superior for both vonoprazan triple therapy (81%) and dual therapy (77%) compared with lansoprazole triple therapy (69%).[61] In particular, the vonoprazan-based regimens demonstrated markedly larger differences vs lansoprazole-based regimens in eradication rates for patients with clarithromycin-resistant infections (66%–70% vs 32%).[61] Notably, eradication rates in all arms of the trial were <90%, a threshold advised by some for eradication therapy. Regarding utility as second-line treatment, a meta-analysis of 16 Japanese studies (15 of which were retrospective) evaluating second-line HP eradication found that vonoprazan-based regimens were superior to PPI-based regimens (odds ratio, 1.5; 95% CI, 1.3–1.8).[62]

In light of this accumulating data, the 2022 Maastricht VI/Florence Consensus featured 100% expert agreement that P-CAB–based treatment regimens for HP are "superior, or not inferior to, conventional PPI-based triple therapies . . . and superior in patients with evidence of antimicrobial resistant infections."[58] Furthermore, in contrast to most of the other indications discussed in this Clinical Practice Update, the short-term durations of HP eradication regimens reduced potential concerns about P-CAB costs and safety in this setting. Nevertheless, further data on the optimal utility of P-CABs in HP treatment, particularly among diverse and

non-Asian populations, with better understanding of the roles of susceptibility testing, antibiotic selection, and treatment dosing and durations, will be crucial for clinical guidance.

Peptic Ulcer Disease

Best Practice Advice 8: Clinicians should generally not use P-CABs as first-line therapy in the treatment or prophylaxis of PUD.

The acid inhibition properties of P-CABs have prompted their evaluation in the management of PUD, for both treatment and prophylaxis. A Japanese randomized trial demonstrated the noninferiority of vonoprazan 20 mg compared with lansoprazole 30 mg once daily after breakfast for gastric ulcer healing (8 weeks, 94% vs 94%) and duodenal ulcers (6 weeks, 96% vs 98%).[63] Similarly, a Korean randomized trial demonstrated the noninferiority of tegoprazan 50–100 mg to lansoprazole 30 mg for gastric ulcer healing at 8 weeks (95% vs 96%).[21] Ulcer etiology may affect treatment success; multicenter observational data of Japanese patients with gastric or duodenal ulcers treated with vonoprazan 20 mg for 6–8 weeks found higher rates of healing for HP-associated ulcers compared with idiopathic or nonsteroidal anti-inflammatory drug–related ulcers.[64] Overall, given the present higher costs (based on current US prices) and more limited availability of P-CABs, P-CABs may not represent the most appropriate first-line therapy for patients with PUD. However, P-CABs may be useful in PPI treatment failures of ulcers, assuming such ulcers are not secondary to processes that can cause ulcers even without acid (eg, cancer, opportunistic infections, vasculitis, and ischemia). Furthermore, the use of P-CABs to treat Zollinger-Ellison syndrome, in which very high-dose PPI use is generally advised to reduce ulcers and ulcer complications, represents a potential indication, but supporting evidence is presently scant.[65]

Beyond the treatment of PUD, P-CABs have also been studied for secondary ulcer prophylaxis in patients at risk for ulcer recurrence. A Japanese double-blind trial randomized patients with a PUD history who required long-term low-dose aspirin to vonoprazan 10–20 mg or lansoprazole 15 mg, demonstrating the noninferiority of vonoprazan for 24-week ulcer recurrence (0.5%–1.5% vs 2.8%).[66] Furthermore, the cumulative incidence of gastroduodenal bleeding was 0% vs 3% for the 24-week treatment period, and rates remained low over the subsequent 6 months during a single-blind extension period.[66] Another Japanese trial randomized patients with a PUD history requiring long-term nonsteroidal anti-inflammatory drug therapy to vonoprazan 10–20 mg or lansoprazole 15 mg.[67] At 24 weeks, vonoprazan was noninferior for ulcer recurrence (3% vs 6%); single-blind extension to 104 weeks showed similar results on comparison of vonoprazan and lansoprazole for ulcer recurrence (4%–6% vs 8%).[67] Although further data are needed among additional populations, and decisions around ulcer prophylaxis should be tailored to individual patients in the setting of risk factors and clinical considerations, these data suggest that P-CABs are noninferior to PPIs for secondary peptic ulcer prophylaxis, but do not support their routine use as first-line prophylactic therapy.

Best Practice Advice 9: Although there is currently insufficient evidence for clinicians to use P-CABs as first-line therapy in patients with bleeding gastroduodenal ulcers and high-risk stigmata, their rapid and potent acid inhibition raises the possibility of their utility in this population.

In combination with their pharmacodynamic properties, emerging data suggest the potential benefit of P-CABs for ulcer bleeding. After endoscopic hemostasis for high-risk stigmata ulcer bleeding, 194 patients across 6 centers in Thailand were randomized to oral vonoprazan (20 mg twice daily for 3 days, then 20 mg once daily for 28 days) or high-dose PPI (pantoprazole intravenous infusion 8 mg/h for 3 days, then omeprazole 20 mg twice daily for 28 days).[68] The vonoprazan regimen was noninferior to PPI for rebleeding at 3 days, 7 days, and 30 days (7.1% vs 10.4%, risk difference, 3.3%; 95% CI, −11.2% to 4.7%).[68] Higher doses of P-CABs for short periods, for prophylaxis against high-risk upper GI ulcer rebleeding, warrant further study.

Future Directions

Overall, P-CABs show promise for the management of common upper GI disorders, including GERD, HP, and PUD. However, it is imperative to better understand the clinical implications of the benefits of P-CABs vs PPIs (eg, more rapid onset with initial dosing, no premeal dosing requirement, less variability in pharmacodynamic effects related to CYP2C19 status, and longer duration of effects) compared with their potentially higher costs, more limited availability, and less robust long-term safety data. Furthermore, the doses of P-CABs used in clinical trials and approved for use likely influence clinical outcomes. Emerging data will allow refinements in the populations and clinical settings for which P-CABs at various doses may be considered and advised, and may reveal more clinical scenarios in which they can provide meaningful benefit. Further investigations, including additional populations and novel indications, as well as evaluating long-term safety data and cost-effectiveness,[69] are warranted, as P-CABs are incorporated more broadly into clinical practice worldwide.

References

1. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63:871–880.
2. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2021. Gastroenterology 2022;162:621–644.
3. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. Gastroenterology 2017;153:420–429.

4. Shanika LGT, Reynolds A, Pattison S, et al. Proton pump inhibitor use: systematic review of global trends and practices. Eur J Clin Pharmacol 2023;79:1159–1172.
5. Wong N, Reddy A, Patel A. Potassium-competitive acid blockers: present and potential utility in the armamentarium for acid peptic disorders. Gastroenterol Hepatol (N Y) 2022;18:693–700.
6. Abdel-Aziz Y, Metz DC, Howden CW. Review article: potassium-competitive acid blockers for the treatment of acid-related disorders. Aliment Pharmacol Ther 2021; 53:794–809.
7. 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;63:302–311.
8. Oshima T, Miwa H. Potent potassium-competitive acid blockers: a new era for the treatment of acid-related diseases. J Neurogastroenterol Motil 2018;24:334–344.
9. Graham DY, Dore MP. Update on the use of vonoprazan: a competitive acid blocker. Gastroenterology 2018; 154:462–466.
10. Patel A, Jacobson BC, Mathew L, et al. American Gastroenterological Association membership policy priorities: building the American Gastroenterological Association advocacy agenda. Gastroenterology 2023; 164:847–850.
11. Shah ED, Amann ST, Hobley J, et al. 2021 National survey on prior authorization burden and its impact on gastroenterology practice. Am J Gastroenterol 2022; 117:802–805.
12. Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. Aliment Pharmacol Ther 2015;42:719–730.
13. 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; 117:1158–1161.
14. Ghim JL, Chin MC, Jung J, et al. Pharmacokinetics and pharmacodynamics of tegoprazan coadministered with amoxicillin and clarithromycin in healthy subjects. J Clin Pharmacol 2021;61:913–922.
15. Hwang I, Ji SC, Oh J, et al. Randomised clinical trial: safety, tolerability, pharmacodynamics and pharmacokinetics of zastaprazan (JP-1366), a novel potassium-competitive acid blocker, in healthy subjects. Aliment Pharmacol Ther 2023;57:763–772.
16. Sunwoo J, Oh J, Moon SJ, et al. Safety, tolerability, pharmacodynamics and pharmacokinetics of DWP14012, a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 2018; 48:206–218.
17. Han S, Choi HY, Kim YH, et al. Comparison of pharmacodynamics between tegoprazan and dexlansoprazole regarding nocturnal acid breakthrough: a randomized crossover study. Gut Liver 2023;17:92–99.
18. 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;43:1048–1059.
19. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology 2019;157:682–691.e2.
20. Laine L, DeVault K, Katz P, et al. Vonoprazan versus lansoprazole for healing and maintenance of healing of erosive esophagitis: a randomized trial. Gastroenterology 2023;164:61–71.
21. 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;52:789–797.
22. Watanabe K, Shimodaira Y, Takahashi S, et al. Potent acid suppression with vonoprazan vs proton pump inhibitors does not have higher association with *Clostridioides difficile* infection. Am J Gastroenterol 2021; 116:1632–1637.
23. Saruta Y, Watanabe K, Tsuji T, et al. Vonoprazan poses no additional risk of developing *Clostridioides difficile* infection compared to proton pump inhibitors. J Gastroenterol Hepatol 2023;38:940–947.
24. Arai J, Miyawaki A, Aoki T, et al. Association between vonoprazan and the risk of gastric cancer after *Helicobacter pylori* eradication. Clin Gastroenterol Hepatol 2024;22:1217–1225.e6.
25. Howden CW, Chey WD, Shah SC. Re-evaluating the proposed association between vonoprazan and gastric cancer following eradication of *H. pylori* infection [published online ahead of print May 8, 2024]. Clin Gastroenterol Hepatol https://doi.org/10.1016/j.cgh.2024.04.015.
26. Kinoshita Y, Haruma K, Yao T, et al. EP54 Final observation results of vision trial: a randomized, open-label study to evaluate the long-term safety of vonoprazan as maintenance treatment in patients with erosive esophagitis. Gastroenterology 2023;164:S–S1202.
27. Shinozaki S, Osawa H, Miura Y, et al. Long-term changes in serum gastrin levels during standard dose vonoprazan therapy. Scand J Gastroenterol 2022; 57:1412–1416.
28. Kushima R, Uemura N, Kinoshita Y, et al. EP1118: 4-year interim analysis results of vision trial: a randomized, open-label study to evaluate the long-term safety of vonoprazan as maintenance treatment in patients with erosive esophagitis. Gastroenterology 2022;162:S-1066–S-1067.
29. 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;66:1723–1725.
30. Li T, Qiao H, Yue P, et al. Embryo-fetal toxicity assessment of vonoprazan in rats and rabbits. J Appl Toxicol 2018;38:987–995.
31. 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; 50:751–759.

32. Patel A, Yadlapati R. Diagnosis and management of refractory gastroesophageal reflux disease. Gastroenterol Hepatol (N Y) 2021;17:305–315.
33. Agrawal NM, Campbell DR, Safdi MA, et al. Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multicenter study. NSAID-Associated Gastric Ulcer Study Group. Arch Intern Med 2000;160:1455–1461.
34. Hawkey CJ, Karrasch JA, Szczepañski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole Versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998; 338:727–734.
35. Kinoshita Y, Sakurai Y, Shiino M, et al. Evaluation of the efficacy and safety of vonoprazan in patients with non-erosive gastroesophageal reflux disease: a phase III, randomized, double-blind, placebo-controlled, multicenter study. Curr Ther Res Clin Exp 2016;81–82:1–7.
36. 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:e00101.
37. 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; 54:402–411.
38. Laine L, Spechler S, Yadlapati R, et al. Vonoprazan is efficacious for treatment of heartburn in non-erosive reflux disease: a randomized trial [published online ahead of print May 14, 2024]. Clin Gastroenterol Hepatol https://doi.org/10.1016/j.cgh.2024.05.004.
39. Fass R, Vaezi M, Sharma P, et al. Randomised clinical trial: efficacy and safety of on-demand vonoprazan versus placebo for non-erosive reflux disease. Aliment Pharmacol Ther 2023;58:1016–1027.
40. Ashida K, Sakurai Y, Nishimura A, et al. Randomised clinical trial: a dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs lansoprazole for the treatment of erosive oesophagitis. Aliment Pharmacol Ther 2015;42:685–695.
41. 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;43:240–251.
42. 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: 864–872.
43. 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; 69:224–230.
44. 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;55:1524–1533.
45. Lee KN, Lee OY, Chun HJ, et al. Randomized controlled trial to evaluate the efficacy and safety of fexuprazan compared with esomeprazole in erosive esophagitis. World J Gastroenterol 2022;28:6294–6309.
46. Zhuang Q, Liao A, He Q, et al. The efficacy and safety of fexuprazan in treating erosive esophagitis: a phase III, randomized, double-blind, multicenter study. J Gastroenterol Hepatol 2024;39:658–666.
47. Ashida K, Iwakiri K, Hiramatsu N, et al. Maintenance for healed erosive esophagitis: phase III comparison of vonoprazan with lansoprazole. World J Gastroenterol 2018;24:1550–1561.
48. Cho YK, Kim JH, Kim HS, et al. Randomised clinical trial: comparison of tegoprazan and lansoprazole as maintenance therapy for healed mild erosive oesophagitis. Aliment Pharmacol Ther 2023;57:72–80.
49. Patel A, Gyawali CP. Gastroesophageal reflux monitoring. J Am Med Assoc 2018;319:1271.
50. Chandan S, Deliwala S, Mohan BP, et al. Vonoprazan versus lansoprazole in erosive esophagitis - a systematic review and meta-analysis of randomized controlled trials. Indian J Gastroenterol 2023;42:475–484.
51. Katzka DA, Kahrilas PJ. Potassium-competitive acid blocker suppression of gastric acid in erosive esophagitis: is stronger and longer better? Gastroenterology 2023;164:14–15.
52. Gyawali CP, Yadlapati R, Fass R, et al. Updates to the modern diagnosis of GERD: Lyon Consensus 2.0. Gut 2024;73:361–371.
53. Gyawali CP, Carlson DA, Chen JW, et al. ACG clinical guidelines: clinical use of esophageal physiologic testing. Am J Gastroenterol 2020;115:1412–1428.
54. Fallone CA. The current role of vonoprazan in *Helicobacter pylori* treatment. Gastroenterology 2022; 163:572–574.
55. Simadibrata DM, Syam AF, Lee YY. A comparison of efficacy and safety of potassium-competitive acid blocker and proton pump inhibitor in gastric acid-related diseases: a systematic review and meta-analysis. J Gastroenterol Hepatol 2022;37:2217–2228.
56. Park CH, Park JH, Jung YS. Comparative efficacy of tegoprazan vs esomeprazole/sodium bicarbonate for the treatment of *Helicobacter pylori* infection. Clin Transl Gastroenterol 2023;14:e00632.
57. Jung YS, Kim S, Kim HY, et al. Efficacy and tolerability of 14-day tegoprazan- versus rabeprazole-based triple therapy for eradication of *Helicobacter pylori:* a real-world evidence study. Gut Liver 2023;17:711–721.
58. Malfertheiner P, Megraud F, Rokkas T, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/ Florence Consensus report. Gut 2022 Aug 8. gutjnl-2022-327745.
59. 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;69:1019–1026.
60. 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;56:436–449.

61. Chey WD, Mégraud F, Laine L, et al. Vonoprazan triple and dual therapy for *Helicobacter pylori* infection in the United States and Europe: randomized clinical trial. Gastroenterology 2022;163:608–619.
62. 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; 102:319–325.
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;45:240–252.
64. 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;54:963–971.
65. Imagawa N, Sato T, Tanaka K, et al. A case of severe esophagoduodenal ulcers associating Zollinger-Ellison syndrome successfully treated by vonoprazan fumarate, a novel potassium-competitive acid blocker. Endosc Forum Dig Dis 2015;31:135–140.
66. Kawai T, Oda K, Funao N, et al. Vonoprazan prevents low-dose aspirin-associated ulcer recurrence: randomised phase 3 study. Gut 2018;67:1033–1041.
67. 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;67:1042–1051.
68. Geeratragool T, Kaosombatwattana U, Boonchote A, et al. Comparison of vonoprazan vs intravenous proton pump inhibitor for prevention of high-risk peptic ulcers rebleeding after successful endoscopic hemostasis: a multicenter randomized noninferiority trial. Gastroenterology 2024;167:778–787.e3.
69. Shah ED, Curley MA, Patel A, et al. Heartburn relief is the major unmet need for drug development in gastroesophageal reflux disease: threshold value analysis [published online ahead of print February 16, 2024]. Clin Gastroenterol Hepatol https://doi.org/10.1016/j.cgh.2024.01.049.

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Correspondence
Address correspondence to: Amit Patel, MD, AGAF, Division of Gastroenterology, Duke University School of Medicine and the Durham Veterans Affairs Medical Center, DUMC Box 3913, Durham, North Carolina 27710. e-mail: Amit.patel@duke.edu.

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