



Potassium-competitive Acid Blockers in Gastroesophageal Reflux Disease and Functional Dyspepsia: A Korean Expert Review With Original Meta-analyses

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Potassium-competitive acid blockers (P-CABs) have emerged as a potent alternative to proton pump inhibitors (PPIs) for the treatment of gastroesophageal reflux disease and functional dyspepsia (FD). This narrative review incorporating original meta-analyses summarizes the latest evidence from randomized controlled trials and meta-analyses, emphasizing the efficacy, safety, and clinical applications of P-CABs such as vonoprazan, tegoprazan, fexuprazan, keverprazan, and zastaprazan. P-CABs demonstrate rapid onset, sustained acid suppression, and superior healing rates in erosive esophagitis (EE), particularly in severe EE (grade C/D). Maintenance therapy in healed EE with P-CABs also yields higher endoscopic remission rates compared to PPIs. In non-erosive reflux disease, P-CABs offer rapid and sustained symptom control compared with placebo. Their pharmacologic profiles, including flexible dosing and rapid action, support on-demand therapy, potentially enhancing patient satisfaction. In addition, P-CABs may help overcome unmet needs from suboptimal efficacy of PPIs in nocturnal heartburn and extraesophageal symptoms. Emerging economic evaluation suggests P-CABs may be cost-effective in Asian healthcare systems. In FD, tegoprazan offers effective symptom relief without delaying gastric emptying, distinguishing it from PPIs. Limited clinical and real-world data indicate that second-generation P-CABs do not exhibit significant hepatotoxicity, however, long-term hypergastrinemia and mucosal changes warrant further surveillance. This review highlights the evolving role of P-CABs in gastroesophageal reflux disease and FD and emphasizes the need for further research to refine their clinical positioning, optimize therapeutic strategies, and evaluate long-term safety outcomes.

Keywords: Dyspepsia; Gastroesophageal reflux; Potassium-competitive acid blockers

INTRODUCTION

Potassium-competitive acid blockers (P-CABs) represent a potent class of acid suppressant that reversibly inhibits the hydrogen-potassium ATPase (H⁺/K⁺-ATPase) in gastric mucosal cells, thereby providing faster, stronger, and more sustained gastric acid suppression than traditional proton pump inhibitors (PPIs). Following the clinical use of vonoprazan in Japan, other P-CABs such as tegoprazan, fexuprazan, and zastaprazan are now clinically used in Korea, while keverprazan is used in China. Beyond their pharma-

cological advantages of acid stability and minimized impact from CYP2C19 polymorphism, their convenience—allowing administration regardless of meal timing while still suppressing gastric acid secretion—makes them suitable for acid-related disorders such as gastroesophageal reflux disease (GERD), *Helicobacter pylori* infection, and peptic ulcer disease. Despite these advantages, the adoption of P-CAB varies significantly by country, due to differences in drug supply situations, insurance reimbursement policies, and cost-effectiveness considerations. In the United States, where drug prices tend to be higher than in other countries, expert guidelines

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recommend P-CAB for patients who have failed standard or double-dose PPI therapy.¹ Conversely, P-CABs have gained significant traction in actual clinical settings in Korea. This is because Korea has 3 P-CAB options, which are comparable in cost to PPIs, and offer relative advantages over PPIs for acid-related diseases. Consequently, P-CABs are frequently prescribed for *H. pylori* eradication therapy and acid-related diseases, which are different patterns than in other regions. Korean physicians are among the highest prescribers of P-CABs globally, making it important to review the clinical experience with P-CABs in Korea. Given the financial implications, the availability of various P-CABs, and the ease of access to specialists, reviewing research and sharing clinical experience in Korea is imperative. This review will provide a synopsis and comparative analysis of the efficacy and safety of P-CABs for GERD and functional dyspepsia (FD) in Korea, incorporating clinical experience compared with Western expert review.

POTASSIUM-COMPETITIVE ACID BLOCKERS IN GASTROESOPHAGEAL REFLUX DISEASE

Erosive Esophagitis

To date, a total of 11 randomized controlled trials (RCTs) comparing the healing effects of P-CABs and PPIs on erosive esophagitis (EE) have been published, including 4 vonoprazan studies, 3 tegoprazan studies, 2 fexuprazan studies, 1 keverprazan study, and 1 zastaprazan study (Table 1). Previous studies revealed that the healing rate of EE after 4-week and 8-week therapy with P-CAB was very high. In RCTs for the treatment of EE, all types of P-CABs are non-inferior to PPIs.^{2–12} Furthermore, studies investigating the 2-week healing rate showed that P-CABs demonstrated significantly higher healing rates than PPIs, and this difference was greater than the differences observed in the 4-week or 8-week healing rates.^{2,3,5,10,11} These results suggest that the healing effect of P-CABs is more potent and faster than that of PPIs. There was no difference in healing efficacy based on the timing of P-CAB administration. Regarding the timing of administration, specific clinical evidence for fexuprazan has shown that its efficacy in healing EE is not significantly affected by meal timing. A recent RCT demonstrated that post-meal administration of fexuprazan was non-inferior to pre-meal administration in terms of EE healing rates.¹³ While the pharmacological profile of P-CABs—characterized by rapid absorption and meal-independent inhibition of H⁺/K⁺-ATPase—suggests potential flexibility in dosing across the class, dedicated clinical trials for other P-CAB agents are still needed to confirm this generalizability.

A large amount of clinical data has been accumulated on this,

leading to systematic reviews and meta-analyses. A meta-analysis published in 2023 comparing vonoprazan to lansoprazole was conducted with 4 published non-inferiority RCTs mentioned above.¹⁴ At 8 weeks post-treatment, vonoprazan resulted in significantly higher rates of endoscopic healing as compared to lansoprazole (risk ratios [RR], 1.041; 95% confidence interval [CI], 1.003–1.081); however the difference was very slight. Another meta-analysis compared tegoprazan and PPI, including 4 RCTs and 963 patients. The meta-analysis showed that the healing rates between tegoprazan and PPIs were similar, with no significant differences observed at both 4 weeks and 8 weeks.¹⁵ RCTs on keverprazan, fexuprazan, and zastaprazan have also shown similar results.^{6,7,10,11}

Maintenance therapy in healed erosive esophagitis

As of now, 3 RCTs have been conducted to evaluate endoscopic remission after maintenance therapy (2 with vonoprazan and 1 with tegoprazan) (Table 2). Vonoprazan was non-inferior to lansoprazole in maintenance of healing of EE at 24 weeks, and superior to lansoprazole in maintenance of healing grade C/D esophagitis.⁸ Another study also showed that vonoprazan was not inferior to lansoprazole for maintaining endoscopic remission at 24 weeks and 12 weeks.¹⁶ Meanwhile, tegoprazan maintenance therapy also demonstrated non-inferiority to lansoprazole in terms of preventing EE recurrence at 24 weeks and 12 weeks.¹⁷

Comparison of Healing Effect for Erosive Esophagitis Between Potassium-competitive Acid Blockers

Meta-analyses compared the healing effects of EE according to the types of P-CABs and PPIs. One meta-analysis compared only severe esophagitis (grade C/D), and vonoprazan was most effective in the initial and maintained healing of severe esophagitis (surface under the cumulative ranking curve [SUCRA] 0.89 and 0.87, respectively).¹⁸ Another meta-analysis revealed that the maximum SUCRA value of vonoprazan 40 mg for the healing rate in EE was 90.7 in the first subgroup (vonoprazan, keverprazan, and lansoprazole) and the maximum SUCRA value of tegoprazan 50 mg was 72.1 in the second subgroup (tegoprazan, fexuprazan, and esomeprazole).¹⁹ This result suggests that standard doses of vonoprazan and tegoprazan can be very effective drugs for the healing of EE. In another meta-analysis, keverprazan showed the best results in healing rates after 8 weeks, with a SUCRA value of 84.7, and this was also true for the subgroup with severe EE at baseline.²⁰

Original Meta-analysis of Erosive Esophagitis: Potassium-competitive Acid Blocker vs Proton Pump Inhibitor

In this review, we conducted independent meta-analyses on

Table 1. Summary of Randomized Controlled Trials on the Healing Effects of Potassium-competitive Acid Blockers on Erosive Esophagitis

Year	Nation ^a	First author	Drugs	8 Weeks healing rate			4 Weeks healing rate			8 Weeks healing rate, LA-C/D		4 weeks healing rate, LA-C/D	
				ITT	FAS	PPS	ITT	FAS	PPS	FAS	PPS	FAS	PPS
2015	Japan (66)	K. Ashida	VPZ		139/144			136/144		50/50		50/50	
			20 mg		(96.5)			(94.4)		(100.0)		(100.0)	
			LPZ		126/132			123/132		43/46		40/46	
2016	Japan (39)	K. Ashida	30 mg		(95.5)			(93.2)		(93.5)		(87.0)	
			VPZ		203/205			198/205		75/75		72/75	
			20 mg		(99.0)			(96.6)		(100)		(96.0)	
2020	Asia ^b (56)	Y. Xiao	LPZ		190/199			184/199		63/72		58/72	
			30 mg		(95.5)			(92.5)		(87.5)		(80.6)	
			VPZ		220/238			203/238		63/75		55/75	
2023	USA (77), Europe (34) ^c	L. Laine	20 mg		(92.4)			(85.3)		(84.0)		(73.3)	
			LPZ		210/230			192/230		54/67		45/67	
			30 mg		(91.3)			(83.5)		(80.6)		(67.2)	
2019	South Korea (27)	KJ Lee	VPZ	478/514		462/488					162/177		
			20 mg	(92.9)		(94.7)					(91.7)		
			LPZ	431/510		410/474					125/174		
2024	China (32)	H. Zhu	30 mg	(84.6)		(86.6)					(72.0)		
			TPZ	95/99		91/92	87/99		84/92		3/3		3/3
			50 mg	(96.0)		(98.9)	(87.9)		(91.3)		(100.0)		(100.0)
2025	South Korea (20)	CM Shin	EPZ	92/99		87/88	87/99		83/88		3/3		2/3
			40 mg	(92.9)		(98.9)	(87.9)		(94.3)		(100.0)		(66.7)
			TPZ		112/123	108/117				11/11			
2022	South Korea (25)	KN Lee	50 mg		(91.1)	(92.3)				(100.0)			
			EPZ		116/125	112/118				8/10 (80)			
			40 mg		(92.8)	(94.9)							
2024	China (48)	Q. Zhuang	TPZ					98/103	95/98			8/9	
			50 mg					(95.2)	(96.9)			(88.9)	
			LPZ					94/109	92/95			7/10	
2022	China (44)	S. Chen	30 mg					(86.2)	(96.8)			(70.0)	
			FPZ		112/116	106/107		98/111	93/103		7/8		5/8
			40 mg		(96.6)	(99.1)		(88.3)	(90.3)		(87.5)		(62.5)
2024	China (48)	Q. Zhuang	EPZ		112/115	110/111		94/108	92/104		8/8		6/7
			40 mg		(97.4)	(99.1)		(87.0)	(88.5)		(100.0)		(85.7)
			FPZ		146/165	145/149		126/165	126/149	41/51	40/43	29/51	29/43
2022	China (44)	S. Chen	40 mg		(88.5)	(97.3)		(76.4)	(84.6)	(80.4)	(93.0)	(56.9)	(67.4)
			EPZ		145/163	143/146		120/163	118/146	43/47	43/45	33/47	33/45
			40 mg		(89.0)	(97.9)		(73.6)	(80.8)	(91.5)	(95.6)	(70.2)	(73.3)
2025	South Korea (29)	JH Oh	KPZ		114/119	110/111		98/119	97/111	22/24	20/21	14/24	14/21
			20 mg		(95.8)	(99.1)		(82.4)	(87.4)	(91.7)	(95.2)	(58.3)	(66.7)
			LPZ		107/119	102/110		97/119	93/110	20/25	18/23	16/25	14/23
2025	South Korea (29)	JH Oh	30 mg		(89.9)	(92.7)		(81.5)	(84.6)	(80.0)	(78.3)	(64.0)	(60.9)
			ZPZ		141/144	136/136		137/144	132/136	6/6	6/6	6/6	6/6
			20 mg		(97.9)	(100.0)		(95.1)	(97.1)	(100.0)	(100.0)	(100.0)	(100.0)
2025	South Korea (29)	JH Oh	EPZ		131/138	118/121		121/138	112/121	5/6	4/5	4/6	4/5
			40 mg		(94.9)	(97.5)		(87.7)	(92.6)	(83.3)	(80.0)	(66.7)	(80.0)

^aThe number in parentheses indicates the number of hospitals where the study was conducted.^bThe Asian countries included are China (27 sites), South Korea (12 sites), Taiwan (11 sites), and Malaysia (6 sites).^cThe European countries included are Poland, Czech Republic, Hungary, Bulgaria, and United Kingdom.

LA-C/D, Los Angeles classification C/D; ITT, intention-to-treat; FAS, full analysis set; PPS, per protocol set; VPZ, vonoprazan; LPZ, lansoprazole; EPZ, esomeprazole; TPZ, tegoprazan; FPZ, fexuprazan; KPZ, keverprazan; ZPZ, zastaprazan.

Data are presented as n (%).

Table 2. Summary of Randomized Controlled Trials on Endoscopic Remission After Maintenance Therapy With Potassium-competitive Acid Blockers on Erosive Esophagitis

Year	Nation ^a	First author	Drugs	24 Weeks endoscopic remission rate		12 Weeks endoscopic remission rate		24 Weeks endoscopic remission rate, LA-C/D
				FAS	PPS	FAS	PPS	FAS
2024	China, South Korea, and Malaysia (64)	Y. Xiao	VPZ 10 mg	157/181 (86.7)		13/18 (72.2)		28/39 (71.8)
			VPZ 20 mg	150/171 (87.7)		18/20 (90.0)		28/32 (87.5)
			LPZ 15 mg	137/184 (74.5)		13/20 (65.0)		21/36 (58.3)
2023	USA (77), Europe (34) ^b	L. Laine	VPZ 10 mg	232/293 (79.2)	231/259 (89.2)			71/95 (74.7)
			VPZ 20 mg	235/291 (80.7)	223/246 (90.7)			71/92 (77.2)
			LPZ 15 mg	211/294 (72.0)	200/251 (79.7)			59/96 (61.5)
2023	South Korea (33)	YK Cho	TPZ 25 mg	133/154 (86.4)	125/138 (90.6)	143/154 (92.9)	128/138 (92.8)	6/8 (75.0)
			LPZ 15 mg	127/151 (84.1)	111/124 (89.5)	145/151 (96.0)	119/124 (96.0)	6/10 (60.0)

^aThe number in parentheses indicates the number of hospitals where the study was conducted.

^bThe European countries included are Poland, Czech Republic, Hungary, Bulgaria, and United Kingdom.

LA-C/D, Los Angeles classification-C/D; FAS, full analysis set; PPS, per protocol set; VPZ, vonoprazan; LPZ, lansoprazole; TPZ, tegoprazan.

the healing and maintenance for EE based on RCTs published to date. We searched the PubMed database using the keywords "vonoprazan," "tegoprazan," "fexuprazan," "keverprazan," and "zastaprazan" to identify relevant studies published until June 2025. All RCTs evaluating the clinical outcomes of P-CAB vs PPI for EE treatment were considered eligible for inclusion in the first meta-analysis. The second analysis included RCTs that compared the efficacy of P-CAB and PPI in the maintenance therapy in EE. This analysis was also conducted independently by the authors. Nine RCTs were used in the analysis of 4-week treatment for EE, 10 RCTs were used in the analysis of 8-week treatment, and 3 RCTs were used in the analysis of 24-week maintenance treatment. Statistical analyses were performed using Review Manager 5.4, employing a random-effects model to calculate pooled RRs and 95% CIs.

At 4 weeks, P-CABs demonstrated a significantly higher endoscopic healing rate than PPIs, although the difference was minimal (RR, 1.04; 95% CI, 1.01–1.06), while no statistically significant difference was observed at 8 weeks (RR, 1.02; 95% CI, 1.00–1.05) (Fig. 1). In cases of severe esophagitis (Los Angeles classification-C/D [LA-C/D]), P-CABs did not show significantly superior results compared to PPIs in endoscopic healing rates at 4 weeks after treatment (RR, 1.10; 95% CI, 0.99–1.23); however, at 8 weeks after treatment, P-CABs showed significantly higher endoscopic healing rates than PPIs (RR, 1.09; 95% CI, 1.01–1.18) (Fig. 2). The success rate of 24-week maintenance therapy with P-CABs was signifi-

cantly higher than that with PPIs, with a RR of 1.09 (95% CI, 1.02–1.18), and the difference was even greater for patients with severe esophagitis (LA-C/D) (RR, 1.22; 95% CI, 1.04–1.44) (Fig. 3).

Non-erosive Reflux Disease

Non-erosive reflux disease (NERD) is a subcategory of GERD, which is characterized by troublesome reflux symptoms with abnormally increased gastroesophageal reflux observed on 24-hour ambulatory pH-impedance monitoring in the absence of esophageal mucosal injury confirmed on endoscopy.²¹ NERD is the most common manifestation among GERD, which accounts for 60–70% in westernized countries.²² It is a persistent medical condition that markedly influences the overall quality of life of affected individuals,^{23,24} thereby requiring personalized therapeutic strategies to regulate the manifestation of symptoms. Despite its prevalence, management of NERD with conventional PPI therapy has been challenging, previous studies showed that the PPI efficacy for symptom control is much less for NERD than erosive esophagitis.^{25,26}

In a Japanese RCT with NERD in 2016, vonoprazan did not demonstrate superiority over placebo, however, the study design excluded patients whose heartburn symptoms improved with antacids during a 1-week run-in phase.²⁷ As a result, the study may not have included suitable patients with acid-induced symptoms, potentially limiting the assessment of treatment efficacy.²⁷ A study conducted in South Korea showed that once-daily tegoprazan (50 mg

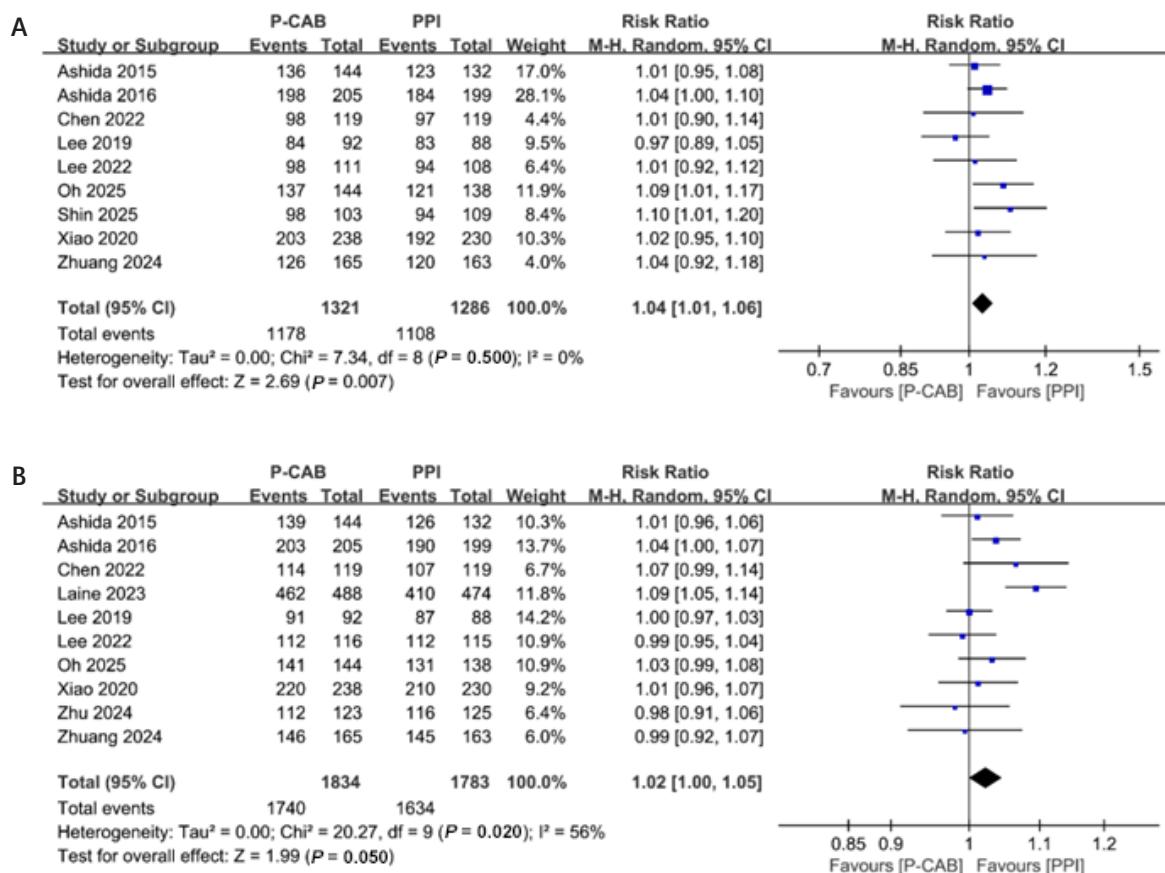


Figure 1. Forest plots of endoscopic healing rates of erosive esophagitis for potassium-competitive acid blocker (P-CAB) versus proton pump inhibitor (PPI) in 4-week (A) and 8-week (B) after treatment. M-H, Mantel-Haenszel; CI, confidence interval.

or 100 mg) was significantly more effective than placebo in resolving heartburn symptoms and, notably, regurgitation as well.²⁸ In the meta-analysis of 3 RCTs evaluating the efficacy of P-CABs—specifically vonoprazan (10 mg and 20 mg) and tegoprazan (50 mg and 100 mg)—in patients with NERD, the number of symptom-free days over a 4-week period was compared between P-CABs and placebo.²⁹ The pooled analysis showed that P-CABs resulted in a mean increase of 7.94 symptom-free days compared to placebo (95% CI, 3.80–12.08).²⁹ Sensitivity analyses, which combined various P-CAB types and doses across the 3 NERD studies, confirmed a statistically significant benefit of P-CABs over placebo, with no evidence of heterogeneity.²⁹ A recent trial in the United States showed that vonoprazan demonstrated a rapid onset of action, alleviating heartburn symptoms as early as day 1.³⁰ This treatment effect was maintained consistently over the 20-week extension period.³⁰ Therefore, in NERD patients with clearly acid-related symptoms, P-CABs may offer advantages over PPIs in terms of more rapid and sustained symptom relief.

On-demand Therapy

In the long-term management of GERD, effective symptom con-

trol is the primary goal. Both the US and Korean guidelines recommend on-demand or intermittent therapy as appropriate treatment strategies in patients with NERD.^{21,31} On-demand therapy, in which medication is taken at the onset of symptoms, is particularly effective when using agents with a rapid onset and sustained duration of action. However, PPIs are less appropriate for on-demand therapy because of their relatively slow onset of action and the need to be converted into an active form in an acidic environment, which may delay symptom relief.³² These limitations of PPI have been recognized as an unmet need in the treatment of GERD,³² and P-CABs have emerged as a promising alternative treatment option in on-demand therapy due to their rapid onset of action and flexible dosing that are not dependent on meal timing.

A North American randomized controlled trial in patients with NERD showed that on-demand vonoprazan significantly improved heartburn relief compared to placebo, with a higher proportion of episodes completely resolved within 3 hours and sustained relief lasting 24 hours.³³ Notably, a statistically significant difference was observed as early as 1 hour after administration.³³ A recent RCT compared the efficacy of on-demand tegoprazan 50 mg versus esomeprazole 20 mg in GERD patients who had previously respond-

ed to acid-suppressive therapy.³⁴ Among 69 patients completing 8 weeks of on-demand treatment, patient satisfaction scores were comparable between groups, however, tegoprazan led to signifi-

cantly faster symptom relief, with 26.2% of episodes improving within 30 minutes versus 16.1% in the esomeprazole group.³⁴ Another single-center prospective cohort study involving 31 GERD

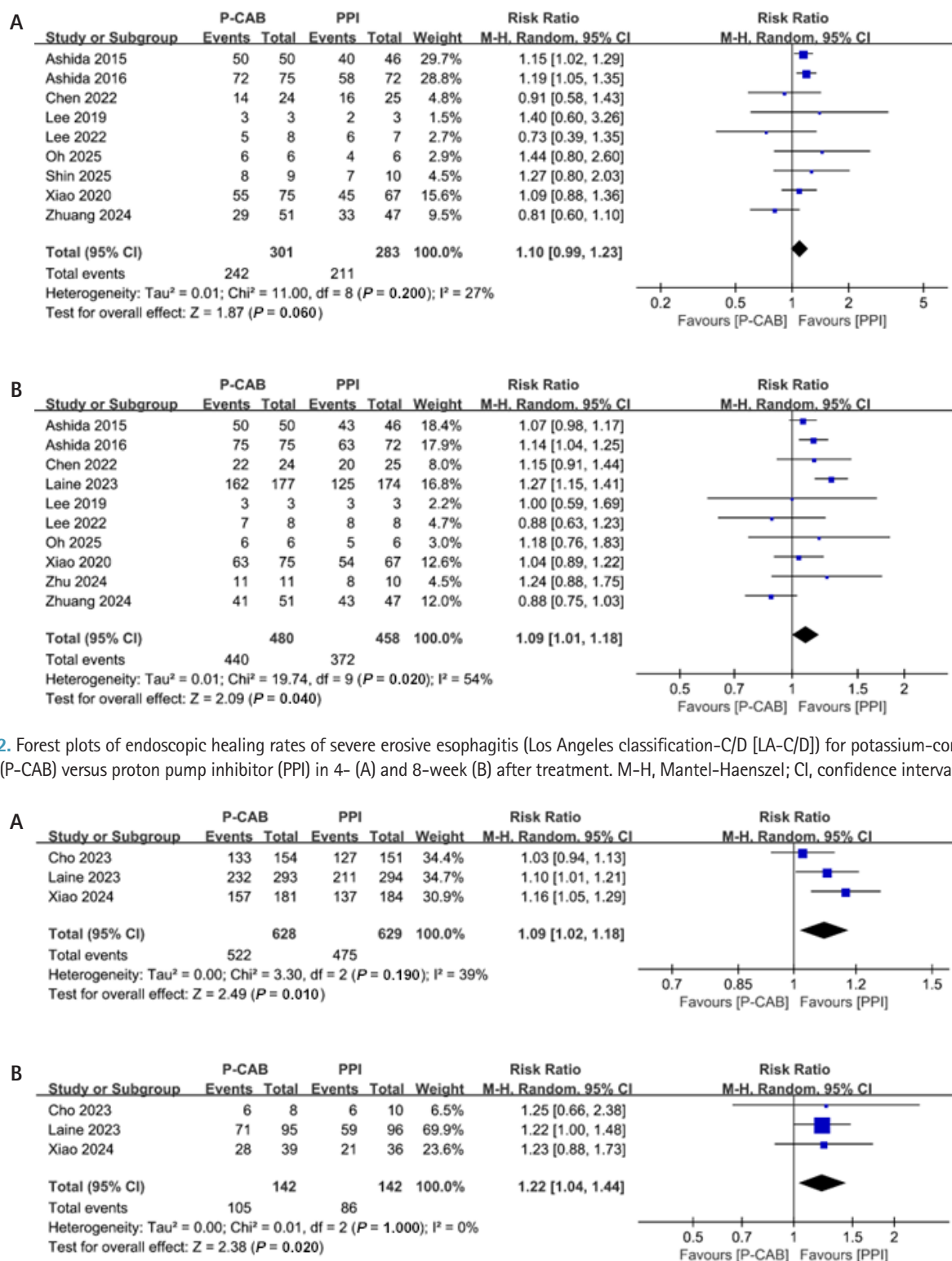


Figure 2. Forest plots of endoscopic healing rates of severe erosive esophagitis (Los Angeles classification-C/D [LA-C/D]) for potassium-competitive acid blocker (P-CAB) versus proton pump inhibitor (PPI) in 4- (A) and 8-week (B) after treatment. M-H, Mantel-Haenszel; CI, confidence interval.

Figure 3. Forest plots of success rates of 24-week maintenance therapy for potassium-competitive acid blocker (P-CAB) versus proton pump inhibitor (PPI) in erosive esophagitis (A) and severe erosive esophagitis (Los Angeles classification-C/D [LA-C/D]) (B). M-H, Mantel-Haenszel; CI, confidence interval.

patients demonstrated that fexuprazan was effective for both the initial 4-week treatment and subsequent 4-week maintenance phase.³⁵ Approximately 68% of patients preferred on-demand therapy, which provided symptom control comparable to that of continuous therapy.³⁵ These findings suggest that P-CABs, compared to PPIs, may serve as a more effective, faster-acting, and patient-preferred option for on-demand management of GERD.

Economic perspectives on Potassium-competitive Acid Blockers vs Proton Pump Inhibitors

In the United States, the use of P-CABs in first-line treatment of uninvestigated heartburn symptoms or NERD is not recommended by cost-effectiveness concerns due to their higher price compared to PPIs, which are widely available as over-the-counter medications.¹ P-CABs are currently available only as branded prescription medications, whereas several PPIs are widely accessible as low-cost generic or over-the-counter formulations. As a result, the acquisition cost of P-CABs is substantially higher than that of PPIs in the US healthcare setting.³⁶ Reflecting these considerations, a recent AGA Clinical Practice Update noted that, at current US pricing, the modest clinical advantages of P-CABs over standard- or double-dose PPIs may not be sufficient to justify their routine use as first-line therapy from a cost-effectiveness perspective.¹

In contrast, the economic landscape differs considerably in East Asian countries. PPIs are not readily available over the counter in Asian countries, and the cost gap between P-CABs and PPIs is relatively modest compared to that observed in the United States. In East Asian countries including Japan, Korea, and China, various P-CABs are commercially available with broader insurance coverage, and the narrower price differential between P-CABs and PPIs creates a more favorable economic environment for their clinical adoption.^{37,38}

Recent economic evaluations have demonstrated that P-CABs, particularly vonoprazan, are a cost-effective option for GERD management. Intermittent P-CAB therapy showed superior cost-effectiveness compared to maintenance PPI therapy, with fewer medication days and clinic visits, and high patient acceptability.³⁹ A vonoprazan-first strategy also provided greater QALYs at lower costs than PPI-based step-up approaches.⁴⁰ These findings were consistent across GERD severity levels, supporting the early use of P-CABs as a clinically effective and economically efficient option for long-term management.⁴⁰ A cost-effectiveness analysis in China similarly concluded that vonoprazan generates incremental QALYs at lower costs compared with PPIs, demonstrating its dominant cost-effectiveness profile in Asian healthcare settings.⁴¹

Accordingly, in Asian countries, P-CABs—despite being slightly more expensive than PPIs—may be preferred from an economic

perspective due to their superior efficacy and cost-effectiveness profile. However, these favorable economic profiles in Asian countries may not be generalizable to Western settings. Future economic evaluations will be needed to assess the cost-effectiveness of individual P-CAB considering current market prices and regional healthcare system characteristics.

Extraesophageal Symptoms

P-CABs have emerged as potential therapeutic alternatives to PPIs for the management of GERD, particularly in patients with extraesophageal symptoms (EES) such as chronic cough, hoarseness, and globus sensation. These symptoms are often refractory to PPI therapy, likely due to limitations such as delayed onset, short plasma half-life, and inadequate nocturnal acid suppression.⁴² In contrast, P-CABs offer rapid onset, potent and sustained acid inhibition, and acid-independent activation, making them theoretically more effective in EES management. However, it should be noted that EES are often weakly associated with esophageal acid exposure and are frequently driven by non-acid reflux, hypersensitivity, or functional and central mechanisms, which may limit the clinical relevance of intensified acid suppression in this population.⁴³

Four randomized controlled trials have been conducted to investigate the efficacy of P-CABs in patients with EES. A preliminary, double-blind, randomized, placebo-controlled trial involving 35 patients with laryngopharyngeal reflux disease (LPRD) demonstrated that tegoprazan (50 mg daily) administration improved LPRD symptoms and signs, however, did not show superiority over placebo.⁴⁴ Kim et al⁴⁵ performed an 8-week randomized, double-blind study that compared fexuprazan with esomeprazole in treating LPRD patients, and both fexuprazan and esomeprazole significantly reduced the total reflux symptom index (RSI) and reflux finding score. Notably, in patients with severe LPRD (RSI > 18), fexuprazan led to significantly greater RSI improvement than esomeprazole after 4 weeks, especially in chronic cough and hoarseness symptoms. In the GERD-related cough, both vonoprazan and esomeprazole significantly reduced cough severity scores; however, vonoprazan was not superior to esomeprazole.⁴⁶ A recent 8-week randomized, double-blind study comparing fexuprazan with esomeprazole in GERD patients with chronic cough demonstrated that both treatments provided comparable efficacy in improving cough-related quality of life, however, fexuprazan led to significantly greater improvement in typical reflux symptoms based on RDQ scores.⁴⁷

The current evidence on the role of P-CABs in EES remains limited by small sample sizes and short durations. Given the multifactorial etiology of EES and the uncertain role of acid suppression

in their pathogenesis, P-CABs cannot be routinely recommended over PPIs for EES. However, P-CABs may be considered on an individual basis in selected patients with documented acid-related EES refractory to optimized PPI therapy. Thus, large-scale, placebo-controlled randomized trials with validated EES assessment tools are warranted to determine the definitive role of P-CABs in the treatment of extraesophageal GERD.

Nighttime Heartburn

Nighttime heartburn symptoms are commonly observed in individuals with frequent GERD complaints and are associated with greater impairment in health-related quality of life.⁴⁸ These symptoms are often more severe and less responsive to PPIs due to impaired acid clearance during sleep.³² As a result, management of nocturnal GERD remains an important unmet need, with growing interest in alternative therapies with a faster onset and longer duration of acid suppression, such as P-CABs. Two randomized controlled trials have evaluated the effect of P-CABs on night-time heartburn. In one study, tegoprazan 50 mg demonstrated a shorter time to first night-time heartburn-free day (1.5 days vs 3.0 days with PPI), although the difference was not statistically significant.⁴⁹ In another trial, vonoprazan 20 mg provided significantly higher complete relief of night-time heartburn compared to lansoprazole during the first 7 days of treatment ($P < 0.01$), suggesting a more rapid symptom resolution in patients with nocturnal reflux.⁵⁰ Based on these findings, P-CABs may be preferred in GERD patients with night-time symptoms to improve sleep quality and overall quality of life.

POTASSIUM-COMPETITIVE ACID BLOCKERS IN FUNCTIONAL DYSPESIA

FD is a common gastrointestinal disorder whose pathophysiology is known to involve gastric acid. As a result, most clinical guidelines recommend the use of antisecretory agents, particularly PPIs. Consequently, P-CABs may have a mechanistic rationale for alleviating FD symptoms. However, evidence on P-CABs in FD remains limited. A recent prospective, multicenter, single-arm study evaluated tegoprazan (50 mg once daily for 8 weeks) in patients with FD according to Rome IV criteria. Results demonstrated satisfactory symptom relief rates of 74.6% at 4 weeks and 86.7% at 8 weeks, with significant improvement in Nepean Dyspepsia Index-Korean and GERD-Health-Related Quality of Life scores, irrespective of FD subtype or *H. pylori* status.⁵¹ If future RCTs comparing P-CABs with PPIs or placebo in FD demonstrate efficacy, P-CABs may be considered for inclusion in future FD guidelines.

PPIs have been associated with delayed gastric emptying. A systematic review reported consistent delays in gastric emptying of solid meals due to impaired peptic hydrolysis under acid suppression.⁵² Clinical studies further support this finding. For example, omeprazole increased gastric half-emptying time by approximately 17 minutes,⁵³ and Benini et al⁵⁴ observed an increase from ~199.6 to 230.9 minutes after four days of omeprazole pretreatment. In contrast, in an in vivo canine model, tegoprazan administration at pharmacologically active doses induced phase III-like contractions of the migrating motor complex in the stomach. These contractile patterns are associated with enhanced gastric clearance, suggesting a potential prokinetic effect beyond acid suppression.⁵⁵ Recently, a randomized, double-blind, placebo-controlled study in healthy adults showed that tegoprazan (50 mg) did not significantly alter gastric half-emptying time or gastric retention at 4 hours compared to placebo.⁵⁶ A contemporary commentary emphasizes that, unlike PPIs, tegoprazan offers potent, rapid acid suppression without delaying gastric emptying.⁵⁷

Taken together, P-CABs like tegoprazan exhibit promising symptom relief in FD without adversely affecting gastric emptying, unlike PPIs. This suggests that P-CABs may offer therapeutic advantages in FD management. Nonetheless, larger RCTs comparing P-CABs with PPIs and placebo in FD populations are needed. Further studies should also explore long-term effects on gastric motility, gut microbiota, and overall symptomatology.

SHORT-TERM AND LONG-TERM SAFETY ISSUES IN POTASSIUM-COMPETITIVE ACID BLOCKERS

PPIs have been widely prescribed for the treatment and prevention of a broad spectrum of acid-related disorders (GERD, peptic ulcer disease, nonsteroidal anti-inflammatory drug-related ulcer prevention, *H. pylori* eradication, etc), and a substantial proportion of patients receive these agents on a long-term basis. Population-based studies and narrative reviews have repeatedly documented high rates of chronic and often inappropriate PPI use.⁵⁸ Concerns about the safety of prolonged PPI therapy have accumulated over the last decade and include associations—typically observed in observational studies and meta-analyses—with pneumonia, *Clostridioides difficile* infection, acute and chronic kidney disease, hypomagnesaemia, vitamin B12 deficiency, bone fracture risk, and other outcomes; these signals have driven calls for regular re-evaluation and deprescribing when appropriate.⁵⁹

P-CABs are a newer class of antisecretory agents that achieve rapid, potent and sustained acid suppression by reversible

K⁺-competitive inhibition of the gastric H⁺/K⁺ ATPase. Early developmental compounds in the P-CAB class (historical prototypes such as SCH28080 and other imidazopyridine derivatives) were associated with hepatotoxicity in preclinical and early clinical work, which slowed their development and raised safety concerns for the class.⁶⁰ Subsequent, clinically used P-CABs—including vonoprazan, tegoprazan, fexuprazan, keverprazan, and zastaprazan—have undergone more extensive clinical testing and postmarketing surveillance. Overall, the contemporary clinical and real-world evidence indicates that these later-generation P-CABs have not demonstrated a consistently higher risk of clinically significant hepatotoxicity compared with PPIs. For example, a nationwide Korean claims-database cohort study reported no increase in hepatotoxicity with tegoprazan relative to 6 common PPIs (and in some analyses lower hepatotoxicity risk with tegoprazan).⁶¹ Clinical trials and early postmarketing evaluations of fexuprazan and zastaprazan have likewise reported no clinically meaningful liver-safety signal to date, although vigilance continues.⁶²

A biologically plausible adverse effect of very potent and sustained acid suppression is hypergastrinemia. Vonoprazan—the most extensively used P-CAB worldwide—has been repeatedly shown to raise fasting serum gastrin to a greater extent than conventional PPIs (in a dose- and duration-dependent manner). Long-term vonoprazan therapy has been associated with significant gastrin increases and gastric mucosal changes, including parietal-cell and foveolar hyperplasia as well as fundic gland polyps in some cohorts.⁶³ Observational data have raised further concern: recent epidemiologic analyses have reported an association between P-CAB exposure (primarily vonoprazan in Japan) and an increased risk of gastric cancer among populations previously treated for *H. pylori*.⁶⁴ However, the observational nature of these studies precludes causal inference, and independent replication is warranted.

By contrast, available data for other P-CABs are more heterogeneous. Tegoprazan and fexuprazan have generally produced smaller gastrin elevations that are similar to those seen with PPIs in short- to medium-term studies, suggesting that not all P-CABs produce the same degree of hypergastrinemia as vonoprazan. Nevertheless, long-term comparative data on gastrin dynamics and related histologic change remain limited.⁵⁶

Evidence on systemic long-term harms associated specifically with chronic P-CAB use (eg, osteoporosis/fracture risk, community-acquired pneumonia, renal disease, or other PPI-linked outcomes) is currently sparse. The VISION long-term maintenance program for vonoprazan (a randomized, multicenter open-label trial with maintenance follow-up) and its interim reports (3-year and 5-year data) found no clear excess of clinically important systemic complications compared with lansoprazole over the trial period, although

they did confirm higher gastrin levels and gastric mucosal changes with vonoprazan and emphasize the need for ongoing surveillance and longer follow-up.⁶⁵ Larger, population-based studies with longer follow-up are needed to determine whether class-level differences exist for these systemic endpoints.³⁸

Until longer-term, well-powered comparative safety studies are available, clinicians should apply the same stewardship principles to P-CAB therapy as are recommended for PPIs: regularly re-assess the indication for ongoing antisecretory treatment, limit duration to the minimum necessary, down-titrate to the lowest effective dose when possible and avoid unnecessary chronic use. Recent expert guidance (AGA clinical practice updates and AGA technical reviews on integrating P-CABs into practice) explicitly recommends routine re-evaluation of ongoing antisecretory therapy and suggests that deprescribing strategies and “lowest-effective-dose” approaches that were developed for PPIs are applicable to P-CABs as well.⁶⁶

In summary, early P-CAB prototypes raised hepatotoxicity concerns, but second-generation P-CABs (vonoprazan, tegoprazan, fexuprazan, keverprazan, zastaprazan) have not shown a consistent hepatic safety signal compared with PPIs in available clinical trials and real-world cohorts; nevertheless, potent acid suppression by some agents (notably vonoprazan) leads to greater hypergastrinemia and mucosal changes, and isolated observational reports have suggested a possible association with gastric neoplasia in specific contexts (eg, after *H. pylori* eradication), although causality remains unestablished. Given the current evidence gaps regarding long-term systemic risks, clinicians should minimize unnecessary P-CAB exposure by adopting evidence-based deprescribing and monitoring strategies, as established for PPIs. Continued long-term comparative safety studies and post-marketing surveillance are mandatory to define the true risk-benefit profile of each P-CAB. A summary of evidence-based recommendations for P-CAB use in GERD and FD is presented in Table 3.

CONCLUSION

P-CABs represent a significant advancement in acid suppression therapy, offering clinical benefits that address limitations of conventional PPIs. Their rapid onset, potent acid inhibition, and flexible dosing make them particularly suitable for diverse GERD phenotypes, including EE, NERD, and extraesophageal manifestations. Evidence supports their superior efficacy in healing and maintenance of EE, and their utility in on-demand therapy enhances patient-centered care. In FD, P-CABs like tegoprazan show encouraging results without impairing gastric motility, suggesting

Table 3. Summary Recommendation of Potassium-competitive Acid Blockers in Gastroesophageal Reflux Disease and Functional Dyspepsia

Clinical phenotype	Evidence	Suggestion
GERD		
Initial treatment of EE	RCTs show non-inferiority or superiority of P-CABs over PPIs in the healing of EE, more rapid healing of EE, and superiority in the healing of severe EE.	P-CABs can be considered as a treatment option for healing patients with EE, especially those with severe EE.
Maintenance of healed EE	RCTs demonstrate that P-CABs (vonoprazan and tegoprazan) are superior to PPIs in the maintenance of healed EE.	P-CABs are recommended for use in maintaining the healing of EE.
Initial treatment of NERD	RCTs show that P-CABs (vonoprazan and tegoprazan) provide significantly more symptom-free days than placebo in NERD.	P-CABs can be used as an initial treatment for NERD in patients with clearly acid-related symptoms.
On-demand therapy	RCT evidence directly comparing P-CABs with PPIs is limited.	P-CABs, with their rapid onset of action and flexible dosing, may be more suitable than PPIs for on-demand therapy.
Extraesophageal symptoms	Limited evidence shows tegoprazan and fexuprazan improve RSI/RFS and chronic cough scores; vonoprazan comparable to PPI.	P-CABs may be considered over PPIs in patients with severe extraesophageal symptoms refractory to PPIs, however, routine use over PPIs is not recommended without objective evidence of pathologic reflux.
Nighttime heartburn	Small RCTs show P-CABs (vonoprazan and tegoprazan) provide faster relief of nocturnal reflux compared to PPIs.	P-CABs may be preferred in GERD patients with nighttime symptoms to improve sleep quality and overall quality of life.
FD		
Functional dyspepsia	Evidence is sparse. Confirmation from large RCTs is essential.	P-CABs such as tegoprazan may be considered for FD, as they offer effective symptom relief without impairing gastric emptying.
Safety issue		
Long-term safety	Limited clinical and real-world data suggest no consistent increase in hepatotoxicity with second-generation P-CABs compared with PPIs.	Long-term comparative safety studies are still needed.

GERD, gastroesophageal reflux disease; EE, erosive esophagitis; NERD, non-erosive reflux disease; FD, functional dyspepsia; RCT, randomized controlled trial; P-CABs, potassium-competitive acid blockers; PPIs, proton pump inhibitors; RSI, reflux symptom index; RFS, reflux finding score.

broader therapeutic potential. Safety profiles of newer P-CABs appear favorable, though vigilance is necessary regarding hypergastrinemia and long-term mucosal changes. Economic analyses further support their adoption in Asian contexts, where cost-effectiveness aligns with clinical performance. With the increasing use of P-CABs, future studies should focus on comparative effectiveness, long-term safety, and personalized treatment algorithms. In summary, P-CABs represent a significant therapeutic advancement for GERD and FD, overcoming efficacy gaps of PPIs and expected to play a key role in future management.

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Study concept and design: Seung In Seo, Sang Pyo Lee, Cheol Min Shin, and Moo In Park; literature search and study selection: Seung In Seo, Sang Pyo Lee, and Cheol Min Shin; data extraction and meta-analysis: Sang Pyo Lee; drafting of the manuscript: Seung In Seo, Sang Pyo Lee, and Cheol Min Shin; critical revision of the manuscript for important intellectual content: Yu Kyung Cho, Jeong Hwan Kim, Jung-Hwan Oh, and Moo In Park; and supervision: Moo In Park. All authors reviewed and approved the final version of the manuscript.

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REFERENCES

- Patel A, Laine L, Moayyedi P, Wu J. AGA clinical practice update on integrating potassium-competitive acid blockers into clinical practice: expert review. *Gastroenterology* 2024;167:1228–1238.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- Zhu H, Xue Q, Song Y, et al. Efficacy and safety of tegoprazan (LXI-15028) vs. esomeprazole in patients with erosive esophagitis: a multicenter, randomized, double-blind, non-inferiority phase III trial. *Chin Med J (Engl)* 2025;138:2464–2471.
- 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.
- Oh JH, Kim HS, Cheung DY, et al. Randomized, double-blind, active-controlled phase 3 study to evaluate efficacy and safety of zastaprazan compared with esomeprazole in erosive esophagitis. *Am J Gastroenterol* 2025;120:353–361.
- Shin CM, Choi SC, Cho JW, et al. Comparison of tegoprazan and lansoprazole in patients with erosive esophagitis up to 4 weeks: a multi-center, randomized, double-blind, active-comparator phase 4 trial. *Neurogastroenterol Motil* 2025;37:e14969.
- Lee SP, Sung IK, Lee OY, et al. Randomized multicenter study to evaluate the efficacy and safety of fexuprazan according to the timing of dosing in patients with erosive esophagitis. *J Neurogastroenterol Motil* 2025;31:86–94.
- 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.
- Hussaini H, Kebede TM, Afework TS, et al. Comparative efficacy and safety of tegoprazan versus proton pump inhibitors for erosive esophagitis: a systematic review and meta-analysis. *Cureus* 2025;17:e83302.
- Xiao Y, Qian J, Zhang S, et al. Vonoprazan 10 mg or 20 mg vs. lansoprazole 15 mg as maintenance therapy in Asian patients with healed erosive esophagitis: a randomized controlled trial. *Chin Med J (Engl)* 2024;137:962–971.
- 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.
- Zhuang Q, Chen S, Zhou X, et al. Comparative efficacy of P-CAB vs proton pump inhibitors for grade C/D esophagitis: a systematic review and network meta-analysis. *Am J Gastroenterol* 2024;119:803–813.
- Wang Y, Dai X, Zhang X. Network meta-analysis of comparing different dosages of potassium-competitive acid blocker with proton-pump inhibitor in acid-related disorders. *Clin Transl Gastroenterol* 2024;15:e00776.
- Liu Y, Gao Z, Hou X. Potassium-competitive acid blockers and proton-pump inhibitors for healing of erosive esophagitis: a systematic review and network meta-analysis. *Ther Adv Gastroenterol* 2024;17:17562848241251567.
- Jung HK, Tae CH, Song KH, et al. 2020 Seoul consensus on the diagnosis and management of gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2021;27:453–481.
- Fass R, Boeckstaens GE, El-Serag H, Rosen R, Sifrim D, Vaezi MF. Gastro-oesophageal reflux disease. *Nat Rev Dis Primers* 2021;7:55.
- Quigley EM, Hungin AP. Review article: quality-of-life issues in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005;22(Suppl 1):41–47.
- El-Serag HB. Epidemiology of non-erosive reflux disease. *Digestion* 2008;78(Suppl 1):6–10.
- Dean BB, Gano AD Jr, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004;2:656–664.
- Bytzer P, van Zanten SV, Mattsson H, Wernersson B. Partial symptom-response to proton pump inhibitors in patients with non-erosive reflux disease or reflux oesophagitis – a post hoc analysis of 5796 patients. *Aliment Pharmacol Ther* 2012;36:635–643.
- Kinoshita Y, Sakurai Y, Shiino M, et al. Evaluation of the efficacy and safety of vonoprazan in patients with nonerosive gastroesophageal reflux disease: a phase III, randomized, double-blind, placebo-controlled, multicenter study. *Curr Ther Res Clin Exp* 2016;81:82:1–7.
- 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.
- Seo S, Jung HK, Gyawali CP, et al. Treatment response with potassium-competitive acid blockers based on clinical phenotypes of gastroesophageal reflux disease: a systematic literature review

- and meta-analysis. *J Neurogastroenterol Motil* 2024;30:259-271.
30. Laine L, Spechler S, Yadlapati R, et al. Vonoprazan is efficacious for treatment of heartburn in non-erosive reflux disease: a randomized trial. *Clin Gastroenterol Hepatol* 2024;22:2211-2220, e10.
31. 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;117:27-56.
32. Dickman R, Maradey-Romero C, Gingold-Belfer R, Fass R. Unmet needs in the treatment of gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2015;21:309-319.
33. 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.
34. Kang SH, Moon HS, Sung JK, et al. Assessment of the efficacy of on-demand tegoprazan therapy in gastroesophageal reflux disease through a randomized controlled trial. *Sci Rep* 2025;15:168.
35. Jung BW, Park CH, Eun CS. Preference for on-demand fexuprazan therapy in gastroesophageal reflux disease: a prospective cohort study. *J Pers Med* 2025;15:19.
36. The Medical Letter. Vonoprazan (Voquezna) for erosive esophagitis. *Med Lett Drugs Ther* 2023;65:203-205.
37. Ishii M, Kawai T, Tsujita K, et al. Cost-effectiveness of vonoprazan compared with proton pump inhibitors in patients taking low-dose aspirin for secondary prevention of cardiovascular events in Japan. *Circ J* 2023;87:348-359.
38. Scarpignato C, Hunt RH. Potassium-competitive acid blockers: current clinical use and future developments. *Curr Gastroenterol Rep* 2024;26:273-293.
39. Habu Y, Hamasaki R, Maruo M, Nakagawa T, Aono Y, Hachimine D. Treatment strategies for reflux esophagitis including a potassium-competitive acid blocker: a cost-effectiveness analysis in Japan. *J Gen Fam Med* 2021;22:237-245.
40. Yokoya Y, Igarashi A, Uda A, Deguchi H, Takeuchi T, Higuchi K. Cost-utility analysis of a 'vonoprazan-first' strategy versus 'esomeprazole- or rabeprazole-first' strategy in GERD. *J Gastroenterol* 2019;54:1083-1095.
41. Wang Z, Sun R, Sheng Y, Qu S, Dong L, Wu B. Cost-effectiveness analysis of vonoprazan versus proton pump inhibitors in the treatment of reflux esophagitis in China. *Ann Transl Med* 2022;10:480.
42. Kim GH, Fass R. Potassium-competitive acid blockers for treatment of extraesophageal symptoms and signs. *J Neurogastroenterol Motil* 2025;31:170-177.
43. Chen JW, Vela MF, Peterson KA, Carlson DA. AGA clinical practice update on the diagnosis and management of extraesophageal gastroesophageal reflux disease: expert review. *Clin Gastroenterol Hepatol* 2023;21:1414-1421, e3.
44. Jeon HK, Kim GH, Cheon YI, Shin SC, Lee BJ. Efficacy of tegoprazan in patients with laryngopharyngeal reflux disease: a preliminary feasibility study. *J Clin Med* 2023;12:6116.
45. Kim SI, Lee YC, Cha W, et al. Efficacy and safety of fexuprazan in patients with symptoms and signs of laryngopharyngeal reflux disease: a randomized clinical trial. *Eur Arch Otorhinolaryngol* 2024;281:5873-5883.
46. Zhong S, Zhong M, Fang L, et al. Potassium-competitive acid blocker versus proton pump inhibitor: a pilot study on comparable efficacy in the treatment of gastroesophageal reflux-related cough. *Allergy Asthma Immunol Res* 2024;16:191-201.
47. Kang N, Kang MG, Lee SE, et al. Efficacy and safety of fexuprazan versus esomeprazole for gastroesophageal reflux disease-related chronic cough: a randomized, double-blind, active-controlled exploratory trial. *Lung* 2025;203:59.
48. Farup C, Kleinman L, Sloan S, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. *Arch Intern Med* 2001;161:45-52.
49. Kim JS, Seo SI, Kang SH, et al. Effects of tegoprazan versus esomeprazole on nighttime heartburn and sleep quality in gastroesophageal reflux disease: a multicenter double-blind randomized controlled trial. *J Neurogastroenterol Motil* 2023;29:58-64.
50. 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;49:140-146.
51. Huh CW, Youn YH, Jung DH, et al. Efficacy of tegoprazan in patients with functional dyspepsia: a prospective, multicenter, single-arm study. *J Neurogastroenterol Motil* 2024;30:313-321.
52. Sanaka M, Yamamoto T, Kuyama Y. Effects of proton pump inhibitors on gastric emptying: a systematic review. *Dig Dis Sci* 2010;55:2431-2440.
53. Tougas G, Earnest DL, Chen Y, Vanderkoy C, Rojavin M. Omeprazole delays gastric emptying in healthy volunteers: an effect prevented by tegaserod. *Aliment Pharmacol Ther* 2005;22:59-65.
54. Benini L, Castellani G, Bardelli E, et al. Omeprazole causes delay in gastric emptying of digestible meals. *Dig Dis Sci* 1996;41:469-474.
55. Takahashi N, Take Y. Tegoprazan, a novel potassium-competitive acid blocker to control gastric acid secretion and motility. *J Pharmacol Exp Ther* 2018;364:275-286.
56. Lim HS, Yoon HJ, Jung HK, Hong JT, Yoo MY, Jeong ES. Effects of tegoprazan, potassium-competitive acid blocker, on the gastric emptying and postprandial symptoms in healthy humans. *Dig Dis Sci* 2025;70:1091-1098.
57. Remes-Troche JM. PPIs have it: does tegoprazan affect gastric emptying and produce dyspeptic symptoms? *Dig Dis Sci* 2025;70:1283-1285.
58. Torres-Bondia F, de Batlle J, Galván L, Buti M, Barbé F, Piñol-Ripoll G. Evolution of the consumption trend of proton pump inhibitors in the Lleida Health Region between 2002 and 2015. *BMC Public Health* 2022;22:818.
59. Jaynes M, Kumar AB. The risks of long-term use of proton pump inhibitors: a critical review. *Ther Adv Drug Saf* 2018;10:2042098618809927.
60. Inatomi N, Matsukawa J, Sakurai Y, Otake K. Potassium-competitive acid blockers: advanced therapeutic option for acid-related diseases. *Pharmacol Ther* 2016;168:12-22.
61. Kim MG, Im YJ, Lee JH, Kim EY, Yeom SW, Kim JS. Comparison of hepatotoxicity of tegoprazan, a novel potassium-competitive acid blocker, with proton pump inhibitors using real-world data: a na-

- tionwide cohort study. *Front Med (Lausanne)* 2023;9:1076356.
62. 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.
63. Kojima Y, Takeuchi T, Sanomura M, et al. Does the novel potassium-competitive acid blocker vonoprazan cause more hypergastrinemia than conventional proton pump inhibitors? A multicenter prospective cross-sectional study. *Digestion* 2018;97:70–75.
64. 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.
65. Haruma K, Kinoshita Y, Yao T, et al. Randomised clinical trial: 3-year interim analysis results of the VISION trial to evaluate the long-term safety of vonoprazan as maintenance treatment in patients with erosive oesophagitis. *BMC Gastroenterol* 2023;23:139.
66. Targownik LE, Fisher DA, Saini SD. AGA clinical practice update on de-prescribing of proton pump inhibitors: expert review. *Gastroenterology* 2022;162:1334–1342.