DOI: 10.4274/gulhane.galenos.2024.55822
Gulhane Med J 2025;67(1):1-7

Redefining GERD management: The emerging role of potassium-competitive acid blockers

Vania Azalia Gunawan[1,2], Titong Sugihartono[3,4]

[1]*Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia*
[2]*Department of Internal Medicine, Faculty of Medicine-Universitas Airlangga, Surabaya, Indonesia*
[3]*Division of Gastroenterology-Hepatology, Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia*
[4]*Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine-Universitas Airlangga, Surabaya, Indonesia*

Cite this article as: Gunawan VA, Sugihartono T. Redefining GERD management: the emerging role of potassium-competitive acid blockers. Gulhane Med J. 2025;67(1):1-7.

Date submitted:
28.08.2024
Date accepted:
18.12.2024
Epub:
10.01.2025
Publication Date:
20.02.2025

Corresponding Author:
Vania Azalia Gunawan, Department of Internal Medicine, Dr. Soetomo General Academic Hospital; Faculty of Medicine-Universitas Airlangga, Surabaya, Indonesia
vaniazalia9@gmail.com

ORCID:
orcid.org/0000-0002-9031-0832

Keywords: Gastroesophageal reflux, potassium-competitive acid blockers, proton pump inhibitors, reflux disease, heartburn

ABSTRACT

Gastroesophageal reflux is the regurgitation of gastric contents into the esophagus, while gastroesophageal reflux disease (GERD) denotes symptoms or mucosal damage due to recurrent reflux, manifesting as heartburn, acid regurgitation, and dysphagia. GERD's prevalence is lower in Asia (6-7%) than in Western countries (15-21%). Although not inherently dangerous, GERD can significantly reduce quality of life and cause complications, such as esophageal stricture and Barrett's esophagus. Proton pump inhibitors (PPIs) are the primary pharmacologic therapy, but approximately 40% of patients remain symptomatic. Long-term PPI use raises concerns regarding bacterial colonization, nutrient absorption, and other side effects. Potassium-competitive acid blockers emerge as a promising alternative that provides stronger acid suppression with potential benefits in refractory GERD cases and safety concerns associated with prolonged PPI use.

Introduction

Reflux of stomach contents into the esophagus is the cause of gastroesophageal reflux disease (GERD). GERD, on the other hand, is a condition in which gastric acid refluxes repeatedly into the esophagus, oropharynx, and/or respiratory tract, causing mucosal damage and/or distressing symptoms like dysphagia, acid regurgitation, and heartburn (1). GERD is generally less common in Asia than it is in Western nations. The prevalence in Western countries ranges from 15 to 21%, whereas in Asia, it is around 6-7%. GERD is frequently diagnosed by gastroenterologists, surgeons, and general practitioners (2-5).

GERD is classified into two categories: erosive esophagitis (EE), which is characterized by esophageal mucosa lesions that are visible on endoscopy, and non-erosive reflux disease (NERD), which does not have EE. Although not a serious disease, GERD can severely impair quality of life and productivity, comparable to or even lower than that of duodenal ulcers, angina pectoris, and mild heart failure (Figure 1). Untreated GERD can lead to severe consequences, such as Barrett's esophagus, ulceration, or stricture (6-8). Proton pump inhibitors (PPIs) are currently the preferred therapy for GERD. PPIs have a superior effect in resolving reflux complaints and mucosal repair compared to other medications, such as histamin-2 (H-2) blockers and mucoprotective agents. Even though PPI therapy is currently the first-line treatment for GERD, nearly 40% of patients still experience symptoms. Refractory GERD is defined as the presence of symptoms that have not improved with PPI therapy for at least 8 weeks (9). PPI use has been found to be less effective in some patients, particularly those with NERD. In addition, some publications have begun to doubt the safety of long-term use of PPI, which is known to increase the risk of bacterial colonization and infection, impaired nutrient absorption, and other non-specific side effects, such as dementia and chronic renal impairment (2,9-11).

The GERD consensus recommends a new gastric acid suppression drug that acts as a potassium blocker. Potassium-competitive acid blockers (P-CAB) work by inhibiting proton pump activity in the cytoplasmic tubulovesicle and secretory canaliculus, providing a more potent suppressive effect than PPIs (9).

Physiology of gastric acid secretion

Gastric acid is secreted by parietal cells located in the fundus and corpus of the stomach. Gastric acid is secreted to form acidic conditions in the gastric lumen (pH <2), and serves to kill bacteria, facilitate digestion, and absorb minerals such as phosphate, calcium, and iron. Food digestion is aided by the equilibrium of parietal cell secretion activators and inhibitors that protect the gastric and duodenal mucosa. Excessive gastric acid secretion can disrupt gastric mucosal integrity. Activators of the gastric acid secretion process include vagus nerve/ acetylcholine, gastrin, histamine, and ghrelin, whereas inhibitors include somatostatin and glucagon-like peptide 1 (12,13).

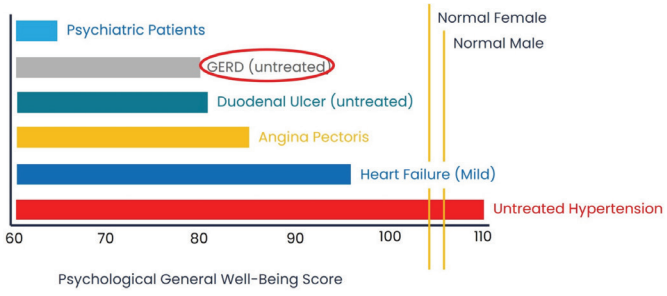

Figure 1. The impact of different medical conditions on quality of life (8)
GERD: Gastroesophageal reflux disease

The activator stimulates the fusion of tubulovesicles containing H^+/K^+ ATPase with the apical secretory canaliculi. The proton pump H^+/K^+ ATPase induces secretion by transporting H^+ ions to the gastric lumen to bind with Cl^- ions and form gastric acid. The entry of K^+ ions from the extracellular space into the cytoplasm of parietal cells occurs concurrently with the entry of H^+ ions into the gastric lumen. This mechanism, along with the sites targeted by acid-suppressing drugs, is illustrated in Figure 2. PPIs and P-CAB are two types of medications that target the H^+/K^+ ATPase pump. PPI acts on gastric parietal cells, covalently binding to the active H^+/K^+ ATPase and inhibiting the secretion of gastric acid, meanwhile, P-CAB works by competitively blocking potassium ions from binding to the H^+/K^+ ATPase, thereby preventing gastric acid secretion in a reversible manner (12,13).

Gastroesophageal reflux disease

GERD is a type of mucosal damage caused by the reflux of stomach contents into the esophagus, oropharynx, or respiratory tract (3,5). It leads to uncomfortable symptoms or complications such as heartburn, acid regurgitation, and dysphagia (3,5).

Etiology and pathophysiology

Esophageal reflux is a physiological condition that can occur in healthy individuals. The pathophysiology of GERD is associated with an imbalance between offensive and defensive factors of the esophageal defense system and gastric reflux material. This imbalance leads to pathologically recurrent

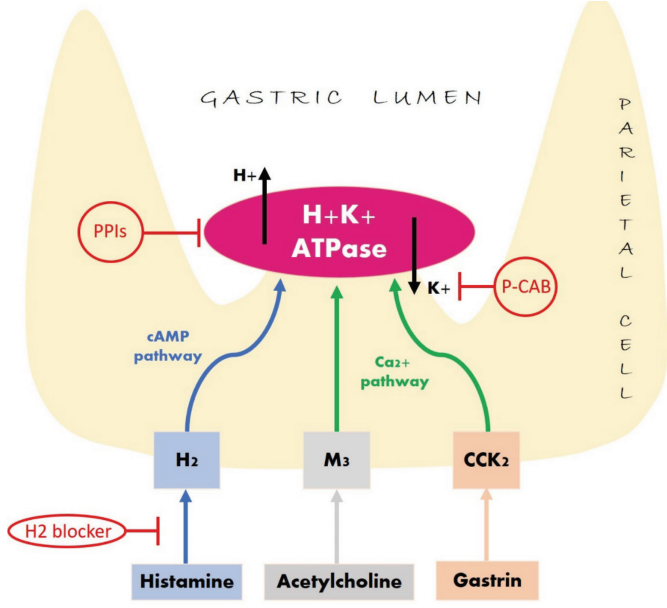

Figure 2. Mechanisms of action of gastric acid-suppressing agents (12,13)
PPIs: Proton pump inhibitors, P-CAB: Potassium-competitive acid blockers, cAMP: Cyclic adenosine monophosphate, Ca^{2+}: Calcium ions, M_3: M_3 muscarinic ACh receptor, H_2: Histamine H_2 receptor, CCK_2: Cholecystokinin receptor

esophageal reflux and causes esophageal mucosal damage. Gastric acid, pepsin, bile acids, and trypsin are considered offensive factors, whereas the lower esophageal sphincter (LES), esophageal clearance mechanisms, and epithelium are considered defensive factors (14,15).

The LES is an anatomical structure composed of smooth muscle cells of the esophagogastric junction (EGJ), separating the esophagus and stomach. Under normal conditions, the LES is in a state of contraction, maintaining high pressure in the zone above the stomach to prevent the migration of gastric reflux material into the esophagus. Physiologically, the LES undergoes transient relaxation during swallowing. In GERD, there is a weakness of the LES, and relaxation occurs without swallowing stimulation, causing gastric contents to flow into the esophagus. This mechanism is the most common cause (90%) explaining the incidence of GERD. Drug use, diet, hormone intake, and structural anomalies are among other factors that can impair LES function (14,15).

The mechanism of esophageal clearance involves the ability of the esophagus to rid itself of gastric reflux material, including bicarbonate in saliva, esophageal peristalsis, gravity, and salivary clearance. Under normal conditions, acidic gastric reflux material is cleared by esophageal peristalsis and neutralized by salivary bicarbonate. Saliva also contains growth factors, such as epidermal growth factor, which promote mucosal repair. Saliva's ability to neutralize stomach acid is compromised in GERD due to a disturbance in the mechanism of esophageal clearance, which allows stomach acid particles to come into contact with the esophagus. Repeated occurrences may cause esophagitis (14,15). The esophageal epithelium consists of cell membranes, intercellular junctions that limit the diffusion of H^+ ions into the esophageal tissue, and esophageal blood flow that supplies nutrients (oxygen and bicarbonate) and excretes H^+ ions and CO_2. Acidic gastric acid and pepsin contents, as well as alkaline duodenal contents of bile salts and pancreatic enzymes, can disrupt defensive mechanisms. Both of these cause damage to the gastric mucosa (15).

Risk factors

Several risk factors are significantly associated with GERD incidence. A family history of heartburn or GERD shows an increased risk as much as 3 times higher. Risk also increases with age, which is related to decreased LES tone. Anatomical abnormalities, such as hiatal hernia, may reduce the competence of the EGJ, increasing the risk of reflux and impairing the clearance of the esophageal refluxate. Obesity is a major risk factor for the emergence and progression of GERD. A decrease in body mass index by 3.5 points can reduce the frequency of GERD symptoms by as much as 40%. In addition to causing an increase in intra-abdominal pressure, increased progesterone hormone has a relaxing effect on the LES (3,16,17).

Some anti-hypertensive drugs, such as nitrates and calcium canal blockers, can decrease the LES tone. Alpha-and beta-adrenergic receptor agonists, theophylline and anti-cholinergics show similar actions. The use of non-steroidal anti-inflammatory drugs does not cause reflux but significantly increases the risk of esophagitis and stricture. Psychological stress can cause impaired esophagus motility. Alcohol consumption and smoking decrease LES tone. Some high-fat diets and soft drinks cause gastric distension, decreased LES, mucosal irritation, and slow gastric emptying (3,16).

Diagnosis

GERD is diagnosed based on clinical symptoms, response to acid suppression drugs, and objective examination, which includes endoscopy and pH monitoring of the esophagus. The symptoms of GERD are highly variable and are classified as typical, atypical, and extraesophageal. Typical symptoms are often observed after meals, aggravated by the recumbent position and improved by the administration of acid-suppressive medications (2,5).

Typical symptoms of GERD include heartburn and regurgitation. Heartburn is a substernal burning sensation that can radiate from the epigastrium to the upper neck, typically occurring after eating or in a lying position. Regurgitation is the return of gastric contents to the mouth, accompanied by a sour or bitter taste. Heartburn and regurgitation are GERD-specific symptoms with a specificity of up to 95%. These two symptoms can be the basis of a presumptive diagnosis and the cornerstone for starting empirical therapy (2,5,14).

Atypical symptoms of GERD include epigastric pain, dyspepsia, nausea, bloating, and burping. These symptoms are not specific and may be caused by other diseases, such as gastric ulcer and achalasia. The extraesophageal symptoms include chronic cough, asthma, laryngitis, and dental erosion. This may be due to the microaspiration of reflux material (2,5,14,15).

GERD is considered when heartburn and regurgitation symptoms are present. Additional objective examination may be considered in elderly patients who are unresponsive/refractory to acid suppression therapy, have a history of malignancy, have warning signs, and have a suspicion of Barret's esophagus. Some of the warning signs include dysphagia, odynophagia, anemia, hematemesis, and weight loss (5,14,18). An endoscopic examination of the upper gastrointestinal tract can be performed to assess the presence of lesions and the degree of complications. Most (75%) of the cases had no lesions on endoscopic examination, with 20-25% having EE and as many as 5-7% having Barret's esophagus (18). In patients with normal endoscopy, ambulatory reflux monitoring can provide confirming evidence. pH-impedance identifies all reflux, irrespective of acidity levels, and is widely regarded as the gold standard of

GERD diagnosis, as outlined in the Lyon Consensus. However, this test is generally not easily accessible, and interpretation is time-consuming (19).

Management

Chronic GERD necessitates long-term treatment, which includes lifestyle modification, medication, and surgery. Lifestyle modification includes weight loss in overweight and obese people, sleeping with a higher pillow, avoiding food consumption <3 hours before sleep, and eliminating stimulating foods, such as chocolate, caffeine, and alcohol (2,5,14,18).

In patients who do not improve with lifestyle changes, pharmacological therapy is recommended. The main drugs used to manage GERD are neutralizing or reducing stomach acid. PPIs are considered the most beneficial for both erosive and non-erosive GERD. PPIs are started once daily before meals and may be increased to twice daily if an inadequate response is observed. Night-time treatment may be considered to manage symptoms that occur at night. The addition of H-2 blockers may be considered when nighttime symptom control is not optimal with maximal PPI administration. There is limited data on the effects of prokinetic agents like metoclopramide and domperidone in GERD treatment (2,5,14,18,20).

Refractory gastroesophageal reflux disease

GERD that does not improve after at least 8 weeks of PPI therapy, supported by objective evidence, is referred to as refractory GERD. There are several causes of refractory GERD. Poor compliance and improper use of PPI medication should be evaluated in patients with suspected refractory GERD. PPI is a prodrug that requires gastric acid activation and should be taken 30-60 minutes before meals. A previous study stated that almost 100% of patients did not take the drug at the correct time, but rather more than 1 hour before a meal, during a meal, or before bedtime (17,21).

A syndrome with esophageal symptoms but no underlying structural, metabolic, or infectious cause is called functional esophageal abnormality. These disorders may be caused by increased mucosal sensitivity to mechanical and chemical stimulation. Functional esophageal abnormalities, weak acid reflux, and acid residues are the most common mechanisms of refractory GERD. Weak acid reflux causes a minimal decrease in pH, but reflux in large volumes may cause esophageal dilatation and induce reflux-related symptoms. Continued reflux may interfere with the healing process of the esophagus (21).

Potassium-competitive acid blocker

P-CABs are a relatively new category of acid-suppression drugs. The H^+/K^+ ATPase enzyme is in the final stage of gastric acid secretion and is the target of several anti-acid secretion drugs. P-CAB is one of the drugs that work by inhibiting the action of this enzyme by selectively acting as a competitive inhibitor of K^+ ions The binding of P-CAB is reversible (7,22,23).

P-CABs are available in tablets orally. The administration of food without or with food does not affect the bioavailability of the drug. The alkaline nature of these drugs causes them to accumulate at higher concentrations in the acidic gastric parietal cell canaliculi than in the plasma. There are several types of P-CABs, including vonoprazan, tegoprazan, and keverprazan, each with distinct pharmacokinetic characteristics. Vonoprazan binds to plasma proteins by 85-88% and is primarily metabolized in the liver to inactive metabolites and is excreted mostly (67%) through urine, whereas the rest is excreted through feces. In contrast, tegoprazan is minimally excreted through urine, accounting for less than 6%. Meanwhile, keverprazan is excreted in 36.3% of cases through urine and 7.33% through feces (23-25).

Efficacy of potassium-competitive acid blocker in gastroesophageal reflux disease

Patients with NERD were found to be less sensitive to PPI therapy; however, although P-CABs have proven effective for gastric acid suppression and show clear benefits in treating EE, their advantages for patients with NERD remain less certain. A study by Niikura et al. (9) found that 12 weeks of vonoprazan therapy can significantly improve the symptoms of NERD. Results from a South Korean trial involving 324 patients with NERD showed that the tegoprazan group achieved higher rates of complete heartburn resolution at 4 weeks than the placebo group (43-49% vs. 24%) (26). Esophageal mucosal lesions that are detectable during endoscopy are the hallmarks of EE. PPI medications have traditionally been the primary treatment for mucosal healing in EE. Although the American College of Gastroenterology does not specifically address the use of P-CABs in GERD, they acknowledge these medications as promising new treatment options. Some studies have indicated that vonoprazan is at least as effective as PPIs for healing EE, with some even showing superior efficacy. Additionally, other P-CABs, such as tegoprazan in Korean patients and keverprazan in Chinese patients, are non-inferior to PPI formulations for initial EE healing. This may be because P-CAB has a longer-lasting and more effective suppressive effect than PPI. As many as 99% of patients with EE achieved mucosal healing after 8 weeks of vonoprazan therapy (6,9,26). P-CAB is also known to reduce the frequency of symptoms in patients resistant to PPIs. The therapeutic effect of vonoprazan 20 mg was better than that of rabeprazole 20 mg, with a duration of therapy of 8 weeks (7).

Safety

Some studies have suggested that P-CAB is relatively safe. The majority of P-CAB safety data is gathered from vonoprazan studies, which reported excellent safety equivalent to anti-

secretory PPI formulations. The most common side effect is diarrhea. Other side effects that have been reported include nasopharyngitis, dyspepsia, headache, nausea, vomiting, and mild to moderate abdominal pain. Skin rash and erythema multiformity have been reported, but the incidences are rare. To date, there have been no reports of life-threatening side effects (22,27). In addition to vonoprazan, another type of P-CAB, tegoprazan, showed no significant difference from placebo regarding treatment-emergent side events in a 4-week trial on NERD (26). Another meta-analysis by Dong et al. (28) found that the tolerability of P-CABs, including vonoprazan, tegoprazan, and keverprazan, was comparable to that of lansoprazole. Although the study reported a slightly higher incidence of serious adverse events with P-CABs than with lansoprazole (P-CABs: 9.6% vs. lansoprazole: 9.3%), it is important to note that such events were rare.

Several P-CAB-type drugs have been developed since 1990, but many are not widely used because of their hepatotoxicity. Unlike the first generation, vonoprazan was found safer for the liver. One study stated that 4-8 weeks of vonoprazan treatment did not significantly induce abnormalities in aspartate aminotransferase and alanine aminotransferase. However, there are currently not many studies on this. Liver function should be monitored when using P-CAB (22,27).

P-CAB increases serum gastrin, pepsinogen 1, and pepsinogen 2 as feedback mechanisms for hypoadditivity. One study compared median gastrin levels 7 days after administering vonoprazan 20 mg twice daily and esomeprazole 20 mg twice daily. The median gastrin level was 529 pg/mL for vonoprazan, compared to 258 pg/mL for esomeprazole (25). Another study reported that the consumption of vonoprazan for 8 weeks did not have a significant effect on gastrin levels compared with the PPI group. Hypergastrinemia stimulates hyperplasia of parietal cells and ECL, causing hypersecretion of gastric acid and allowing the return of symptoms when the drug is discontinued (22). However, gastrin levels typically stabilize and return to normal immediately after therapy cessation. Although P-CABs exhibit nearly equivalent anti-secretory effects, they appear to cause varying degrees of hypergastrinemia, with vonoprazan producing higher levels than tegoprazan, furazan, and zestaprazan. The precise causes of this discrepancy remain unknown, and long-term studies are needed (29).

Proton pump inhibitors vs. potassium-competitive acid blockers

PPIs are currently the first-line therapy of choice for gastroesophageal reflux. However, the therapeutic efficacy of PPI is currently limited. PPI is unstable in an acidic atmosphere and requires an enteric-coated formulation to overcome this. P-CABs have better solubility and stability under acidic conditions, so they do not require enteric coating and can dissolve rapidly. This favors a rapid onset of action and maintains the inhibitory effect even in acidic environments. In addition, the effectiveness of PPI is altered by food intake, which is why it is recommended to take PPI 30-60 minutes before meals, whereas the action of P-CAB is not affected by food intake (7,13,22).

PPIs are activated in the acidic environment of the stomach, where they inhibit gastric acid production by forming a disulfide bond with the H^+/K^+ ATPase. However, the active form is unstable and easily degraded in such conditions. The half-life of PPI is also short at around 1-2 hours, whereas the half-life of P-CAB is longer at approximately 7 hours. As much as 25% of H^+/K^+ ATPase is synthesized daily and stimulated by the feeding process. This explains why multiple doses of PPI are required to achieve an adequate suppressive effect. Unlike PPI, P-CAB binds non-covalently to the H^+/K^+ ATPase, does not require activation, and can quickly suppress gastric acid in a single dose. It is also stable in acidic environments. In healthy male participants, tegoprazan showed greater efficacy and longer-lasting intragastric acid suppression than esomeprazole. Likewise, vonoprazan accumulates and resides in the stomach for a duration of >24 hours. The slow dissociation of vonoprazan gives a longer suppressive effect than that of PPI. Table 1 highlights the pharmacokinetic differences between several PPIs and P-CABs (7,13,22,26).

Genetic polymorphisms of the cytochrome P450 CYP2C19 cause differences in the efficacy of PPIs in some patients and are

Table 1. Comparison of the pharmacokinetic properties of PPIs and P-CABs (25,26,30,31)

	Esomeprazole	Pantoprazole	Vonoprazan	Tegoprazan
Prodrug	Yes, acid needed		No activation is needed, rapid onset of action	
Acid stability	No (enteric-coated)		Yes	
Dosage (mg)	20 mg, 40 mg	20 mg, 40 mg	10 mg, 20 mg	50 mg
Time to plasma concentration peak	1.5 hours	2-3 hours	2 hours	0.5-1.5 hours
Maximum inhibition of acid secretion	Multiple doses (3-5 days)		A single dose (faster with a higher dose)	
Plasma half-life	1-1.5 hours	1-1.9 hours	6-8.8 hours	3.7-5.4 hours
Liver metabolism	CYP2C19	CYP2C19, CYP3A4	Primarily CYP3A4	

PPIs: Proton pump inhibitors, P-CABs: Potassium-competitive acid blockers, mg: milligram

one of the causes of PPI resistance. In patients with extensive CYP2C19 metabolizer activity, PPI concentrations are lower, whereas drug levels are higher in patients with poor metabolizers because of low metabolic activity. The therapeutic effect was found to be higher in patients with poor metabolizers (84.6% compared to 45.8% in patients with extensive metabolizers). According to a study conducted in Indonesia, the most common types of metabolizers were intermediates (41.6%), followed by rapid (38.5%) and poor (19.9%) (32). CYP3A4 and non-oxidative enzymes (sulfotransferases) are among the enzymes that break down P-CAB. The metabolism of this drug is not influenced by CYP2C19, as shown in Table 1, so it is not influenced by genetic polymorphism and provides the same inhibitory effect on each individual (7,13,22).

Conclusion

GERD is one of the most prevalent conditions encountered by gastroenterologists, surgeons, and general practitioners. The condition is caused by the reflux of gastric contents into the esophagus. Although it is not a deadly disease, it can severely impair the quality of life and productivity. The first-line treatment for GERD is currently PPIs; however, in certain cases, especially NERD, the results are frequently inadequate. P-CAB, a new type of gastric acid suppression drug, is expected to provide a more potent effect than PPIs and can become one of the drugs of choice for GERD therapy.

Footnotes

Authorship Contributions

Concept: V.A.G., T.S., Design: V.A.G., Literature Search: V.A.G., T.S., Writing: V.A.G., T.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Leiman DA, Metz DC. Clinical gastrointestinal endoscopy, Elsevier, Amsterdam, 2019:268-278.e3. Available from: https://www.sciencedirect.com/science/article/abs/pii/B9780323415095000244
2. 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.
3. Makmun D, Fauzi A, Maulahela H, et al. Konsensus Nasional Penatalaksanaan Penyakit Refluks Gastroesofageal (Gastroesophageal Reflux Disease/GERD) di Indonesia. Revisi 2022. Jakarta, Indonesia: Perkumpulan Gastroenterologi Indonesia (PGI); 2022. Available from: https://pbpgigastro.com/wp-content/uploads/2024/07/Konsensus-Nasional-Penatalaksanaan-GERD-di-Indonesia-Revisi-2022.pdf
4. Saputera MD, Budianto W. Diagnosis of tatalaksana gastroesophageal cancer reflux disease (gerd) di pusat pelayanan kesehatan primer. CDK-252. 2019;44:329-332.
5. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. World J Gastrointest Pharmacol Ther. 2014;5:105-112.
6. Cheng Y, Liu J, Tan X, et al. Direct comparison of the efficacy and safety of vonoprazan versus proton-pump inhibitors for gastroesophageal reflux disease: a systematic review and meta-analysis. Dig Dis Sci. 2021;66:19-28.
7. Miyazaki H, Igarashi A, Takeuchi T, et al. Vonoprazan versus proton-pump inhibitors for healing gastroesophageal reflux disease: a systematic review. J Gastroenterol Hepatol. 2019;34:1316-1328.
8. Dimenäs E. Methodological aspects of evaluation of quality of life in upper gastrointestinal diseases. Scand J Gastroenterol Suppl. 1993;199:18-21.
9. Niikura R, Yamada A, Hirata Y, et al. Efficacy of vonoprazan for gastroesophageal reflux symptoms in patients with proton pump inhibitor-resistant non-erosive reflux disease. Intern Med. 2018;57:2443-2450.
10. Song TJ, Kim J. Risk of post-stroke pneumonia with proton pump inhibitors, H2 receptor antagonists and mucoprotective agents: a retrospective nationwide cohort study. PLoS One. 2019;14:e0216750.
11. Haastrup PF, Thompson W, Søndergaard J, Jarbøl DE. Side effects of long-term proton pump inhibitor use: a review. Basic Clin Pharmacol Toxicol. 2018;123:114-121.
12. Engevik AC, Kaji I, Goldenring JR. The physiology of the gastric parietal Cell. Physiol Rev. 2020;100:573-602.
13. Otake K, Sakurai Y, Nishida H, et al. Characteristics of the novel potassium-competitive acid blocker vonoprazan fumarate (TAK-438). Adv Ther. 2016;33:1140-1157.
14. Antunes C, Aleem A, Curtis SA. Gastroesophageal reflux disease. Treasure Island, FL: StatPearls Publishing; 2023. Available from: https://pubmed.ncbi.nlm.nih.gov/28722967/
15. Tack J, Pandolfino JE. Pathophysiology of gastroesophageal reflux disease. Gastroenterology. 2018;154:277-288.
16. Torlutter M, Onwukwe SC, Pretorius D, Mpangula NM, Omole OB. Dyspepsia: literature review and evidence for management in primary care. S Afr Fam Pract. *2018;*60:25-32.
17. Sandhu DS, Fass R. Current trends in the management of gastroesophageal reflux disease. Gut Liver. 2018;12:7-16.
18. Ribolsi M, Giordano A, Guarino MPL, Tullio A, Cicala M. New classifications of gastroesophageal reflux disease: an improvement for patient management? Expert Rev Gastroenterol Hepatol. 2019;13:761-769.
19. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the lyon consensus. Gut. 2018;67:1351-1362.
20. Ahmed A, Clarke JO. Proton pump inhibitors (PPI). 2023 may 1. In: statpearls [Internet]. treasure island (FL): statpearls publishing; 2024 Jan.
21. Mermelstein J, Chait Mermelstein A, Chait MM. Proton pump inhibitor-refractory gastroesophageal reflux disease: challenges and solutions. Clin Exp Gastroenterol. 2018;11:119-134.

22. Akazawa Y, Fukuda D, Fukuda Y. Vonoprazan-based therapy for Helicobacter pylori eradication: experience and clinical evidence. Therap Adv Gastroenterol. 2016;9:845-852.

23. Echizen H. The first-in-class potassium-competitive acid blocker, vonoprazan fumarate: pharmacokinetic and pharmacodynamic considerations. Clin Pharmacokinet. 2016;55:409-418.

24. Scott DR, Marcus EA, Sachs G. Vonoprazan: MarKed competition for PPIs? Dig Dis Sci. 2016;61:1783-1784.

25. 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.

26. 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.

27. 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.

28. Dong Y, Xu H, Zhang Z, Zhou Z, Zhang Q. Comparative efficiency and safety of potassium competitive acid blockers versus lansoprazole in peptic ulcer: a systematic review and meta-analysis. Front Pharmacol. 2024;14:1304552.

29. Scarpignato C, Hunt RH. Potassium-competitive acid blockers: current clinical use and future developments. Curr Gastroenterol Rep. 2024;26:273-293.

30. Yoon DY, Lee S, Jang IJ, et al. Prediction of drug-drug interaction potential of tegoprazan using physiologically based pharmacokinetic modeling and simulation. Pharmaceutics. 2021;13:1489.

31. Strand DS, Kim D, Peura DA. 25 Years of proton pump inhibitors: a comprehensive review. Gut Liver. 2017;11:27-37.

32. Miftahussurur M, Doohan D, Syam AF, et al. CYP2C19 Polymorphisms in indonesia: comparison among ethnicities and the association with clinical outcomes. Biology (Basel). 2021;10:300.