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Potassium -Competitive Acid Blockers in Gastroesophageal Reflux Disease: A Narrative Review of Evolving Evidence Compared to Proton Pump Inhibitors

Abdul Malik A S[1], Naeem B[2], Sivakumar V[3]
[1]Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India-641004
[2]Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India-641004
[3]Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India-641004

Abstract—Background*: Gastroesophageal reflux disease (GERD) is a chronic condition caused by abnormal gastric acid exposure, affecting 20–30% of Western and 10–15% of Asian populations, with rising global prevalence. Acid suppression remains the cornerstone of GERD management. Proton pump inhibitors (PPIs) have been first-line therapy for over three decades; however, 30–40% of patients fail to achieve adequate symptom control due to limitations such as slow onset of action, nocturnal acid breakthrough, pharmacogenetic variability, and safety concerns, leading to the development of potassium-competitive acid blockers (P-CABs).* ***Objective****: To provide an evidence-based review of the pharmacology, clinical efficacy, safety, interindividual variability, and comparative effectiveness of PPIs and P-CABs in GERD management.* ***Methods****: This narrative review included evidence from systematic reviews, network meta-analyses, randomized controlled trials, long-term follow-up studies, pharmacokinetic and pharmacodynamic investigations, pharmacovigilance data, and clinical guidelines, with outcomes assessed including symptom relief, erosive esophagitis (EE) healing, intragastric pH control, adverse events, and predictors of treatment response.* ***Results****: PPIs achieve EE healing in 80–90% of patients; however, symptom relief in non-erosive reflux disease (NERD) is limited to 50–60%, with variability in response influenced by CYP2C19 polymorphisms. In contrast, P-CABs provide rapid acid suppression, reduced dependence on CYP2C19 metabolism, and sustained intragastric pH control above 4 for most of the 24-hour period, demonstrating improved outcomes in PPI-refractory GERD and sustained efficacy and safety in long-term studies.* ***Conclusion****: P-CABs represent a significant advancement in GERD management by addressing key limitations of PPIs and improving therapeutic outcomes, particularly in patients with refractory disease.*

Keywords— *Acid suppression; Erosive esophagitis; Fexuprazan; Gastroesophageal reflux disease, Potassium-competitive acid blockers; Proton pump inhibitors; PPI-refractory GERD; Vonoprazan.*

I. INTRODUCTION

Gastroesophageal reflux disease (GERD) is a serious global health problem that is one of the most commonly occurring chronic gastrointestinal disorders. In Western countries, it affects roughly 10 to 20% of adults, while in Asia the disease burden is around 5 to 10% [1]. The incidence of GERD is increasing globally mainly because of the aging populations, obesity, and lifestyle factors. GERD significantly impairs quality of life [17]. It is also associated with complications like erosive esophagitis (EE), Barrett's esophagus, and extraesophageal manifestations that involve the upper aero digestive tract [2].

Proton pump inhibitors (PPIs)are established as the first line pharmacological therapy in GERD [40] for more than twenty years mainly because of their unquestionable acid suppressing and mucosal healing properties. Meta analyses along with randomized controlled trials have shown that the standard dose PPIs can heal 80-90% of patients with EE [3] within 8 weeks of therapy and also lead to better symptom relief as compared to H2 receptor antagonists. Unfortunately, up to 30-40% of patients continue to experience symptoms of reflux even after using PPI therapy [3] particularly in cases of non erosive reflux disease (NERD) and refractory GERD although they are widely used. Several pharmacological and clinical factors are responsible for the suboptimal responses to PPIs. Since PPIs need acid activation and the presence of active proton pumps [4] there is a delayed onset of action and the efficacy is less when the dosing is not in line with the timing of the meal. Moreover, there is a considerable inter individual variability due to CYP2C19 genetic polymorphisms that influence drug metabolism and thus the degree of acid suppression which is insufficient in rapid metabolizers [5]. On top of that, PPIs only partially suppress nocturnal acid breakthrough which happens in as much as 70% of the patients treated with PPI twice a day and such breakthrough is significantly associated with the persistence of nighttime symptoms and sleep disturbances [6]. Besides, there have been emerging concerns regarding the dispensability of chronic PPI use. Data from extensive observational studies and meta analyses indicate that long term use of PPI therapy is likely to lead to increased incidence of enteric infections, hypomagnesemia, vitamin B deficiency, bone fractures, chronic kidney diseases, and even premalignant gastric changes [7] ,though the question of causality is still being debated. Together, ongoing symptoms and associated risks point to the fact that the current pharmacotherapy for GERD is not capable of fully satisfying the needs of patients. potassium

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competitive acid blockers (P-CABs) represent a novel class of acid suppressive therapy that has been introduced to address some of the drawbacks of proton pump inhibitors PPIs.

Unlike PPIs, these drugs inhibit the gastric H^+/K^+ATPase enzyme by reversible blocking by competing with potassium at the luminal binding site thus leading to rapid, strong and lasting acid suppression that is not dependent on acid activation or meal timing [9].

Pharmacodynamics studies show that P-CABs from the very first dose are able to keep higher intragastric pH levels [10] and thus they achieve more reliable acid suppression over 24 hours than the standard PPIs. Clinical studies and meta analyses have demonstrated that P-CABs especially vonoprazan [11] achieve at least equal or superior healing rates in EE [12] provide better symptom relief in PPI refractory and NERD patients [13] and offer significantly improved control of nocturnal reflux symptoms [14]. 5 year long term extension studies results suggest that efficacy is maintained and safety is acceptable, though pharmacovigilance should still be continued [15].

This paper synthesizes the latest knowledge of the pharmacological mechanisms, clinical effectiveness and safety aspects of PPIs and P-CABs with a special emphasis on refractory and non erosive GERD. It also looks at the changing role of P- CABs as either substitutes or complements to PPIs and deliberates on the opportunity for tailor made acid suppression strategies guided by disease phenotype, genetic variability, and treatment response [16].

Pathophysiology of GERD and the Rationale for Acid Suppression

GERD is a complex condition where several factors contribute to failure of the normal anti reflux mechanisms. This failure allows gastric contents to move backward into the esophagus [17]. Among various mechanisms, transient lower esophageal sphincter relaxations (TLESRs) are the main cause of reflux in the case of both erosive and non erosive GERD. According to high resolution manometry (HRM) studies TLESRs are responsible for as much as 90% of reflux episodes in patients who don't have severe baseline lower Esophageal Sphincter (LES) hypotension [17].

Structural problems, such as a hiatal hernia which is found in about 40-60% of patients with severe GERD, further weaken the LES by changing the gastroesophageal pressure gradient and disrupting the diaphragmatic pinch cock mechanism. Dysfunctional esophageal clearance is also very important in the development of the disease[17].

Ambulatory 24-hour pH impedance monitoring studies show that increased acid exposure time (AET >6%) is strongly associated with symptom severity [20,42].

Continuous and strong acid suppression are therefore necessary not only in symptom control but also in mucosal healing and prevention of long term complications [21]. Nevertheless, standard treatments often do not secure a lasting 24 hour acid inhibition especially during the night and in those with highly acid-producing stomachs or who metabolize drugs quickly.

Proton pump inhibitor in GERD Management

PPIs are a class of drugs that decrease stomach acid production [4] through permanent inhibition of the H^+/K^+-ATPase enzyme on gastric parietal cell surfaces. PPIs should be taken before meals so their timing coincides with the maximal proton pump activation [4] Otherwise acid suppression is lessened. Pharmacodynamics studies indicate that PPIs once daily only repress 60-70% of 24 hour gastric acid secretion and therefore in a sizeable number of patients there is still leftover acid overnight and after meals.

Safety of PPIs in GERD Management

PPIs are used globally on a large scale and the short term safety profile of PPIs in treating GERD is very good. Clinical trials and Cochrane systematic reviews indicate that that PPIs have the safety profile that the side effect occurrence is not significantly different from the placebo during the short term use (48 weeks) [16] and the side effects are mostly mild and the most common ones are headache, diarrhea, nausea, and abdominal discomfort that occur in only <5-10% of patients.

Long Term Safety concerns

Since GERD is a chronic and relapsing condition, many patients need to be on PPI treatment for a long time. This has led to an extensive study of the side effects of prolonged acid suppression [6,7,16]. During the last decade, large observational studies and meta analyses have identified potential safety signals associated with prolonged PPI therapy; however, causality remains debated and evidence from randomized trials is limited [7, 21].

Micronutrient malabsorption

Long - term low stomach acid may lead to deficient uptake of some micronutrients. Meta analyses show a correlation between long term use of PPI and vitamin B_{12} deficiency [24] especially beyond 2-3 years of continuous use with odds ratios between 1.3 and 1.7. Besides, PPIs have been associated with hypomagnesemia [24] very rare but potentially severe side effect that usually manifests itself after prolonged use and in some cases the discontinuation of the medication becomes necessary.

Enteric and Respiratory Infections

Meta analyses indicate that the prolonged use of PPIs may result in 1.5-2.0 times higher risk of Clostridioides difficile infection [25] especially in hospitalized or elderly patients. This association is biologically plausible because gastric acid acts as a natural barrier against ingested pathogens, and suppression of acid secretion may increase susceptibility to enteric infections [45].

Gastric Mucosal changes and malignancy risk

One recent systematic review and Meta analysis found that there is a link between long term PPI use and the emergence of premalignant gastric lesions [26] particularly in patients who had been infected with Helicobacter pylori previously. However, no definite causal connection to gastric cancer has been demonstrated in randomized trials.

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Renal Outcomes

According to cohort studies the relative risk of developing Chronic Kidney Disease (CKD) for the first time is 20-50% higher in PPI users who have taken these drugs for a long time compared to users of H2 receptor antagonists [7], although the possibility of residual confounding cannot be ruled out. Acute interstitial nephritis, although being an uncommon complication is still considered as one of the recognized idiosyncratic reactions.

Bone Health and Fracture Risk

Major population based meta analyses demonstrated that there is a slight but measurable elevation in the likelihood of hip, spine, and wrist fractures [46] among chronic PPI users especially at high doses or durations over one year (relative risk about 1.2-1.4). Definitely, the risk of fracture at the absolute level is still low and the factor of age and other diseases that exist together are significant in explaining the confounding.

Clinical efficacy of PPIs

Symptom relief in GERD

Meta analyses show that standard dose PPIs are capable of completely resolving symptoms in around 55-70% of patients [21] with typical GERD symptoms within 48 weeks of therapy as compared to 30-40% of those who took H2 receptor antagonists and fewer than 25% of those on placebo.

Healing of erosive esophagitis

Several large Randomized Controlled Trials (RCTs) and systemic reviews have demonstrated that after 8 weeks [3] of once daily PPI therapy the endoscopic healing rates are 80-90% and patients with mild to moderate esophagitis (Los Angeles grades A-B) can achieve healing rates of over 90%. On the other hand, patients with severe esophagitis (grades C-D) are more likely to achieve healing after treatment at higher doses or longer durations while at standard doses the healing rate is 65-80%. These results are highly consistent with the mechanism of PPIs that is, their ability to keep intragastric pH above 4 for a long time.

Maintenance of remission and relapse prevention

In patients with non-erosive reflux disease or mild erosive esophagitis, on-demand or maintenance PPI therapy can maintain remission in approximately 70–85% over 6–12 months [28]. On demand PPI regimens have proven especially effective in patients with NERD and mild erosive disease by reducing overall drug exposure while maintaining symptom control.

In NERD

Research studies suggest that standard dose PPIs can help only 45-55% of NERD patients get complete symptom relief [5] which is due to the fact that this condition is characterized by a diverse pathophysiology including among other factors weakly acidic reflux, visceral hypersensitivity, and functional heartburn.

PPI Refractory GERD

As many as 30-40% of GERD patients report persistent symptoms [37], even though they have been treated with once daily PPI therapy [20] and around 10-20% still complain of symptoms after twice daily dosing. Additionally, gender-based differences in symptom persistence and partial response to PPI therapy have been observed, suggesting that individualized treatment approaches may be necessary in certain subgroups [29]. Refractory symptoms can arise from inadequate acid suppression, nocturnal acid breakthrough, rapid drug metabolism (e.g., CYP2C19 polymorphisms), non acid reflux or the presence of other diagnoses. Expert consensus updates now recommend consideration of P-CAB therapy as an appropriate step-up strategy in patients with persistent symptoms despite optimized PPI treatment [27].

Nocturnal acid control

Ambulatory pH monitoring studies have revealed that nocturnal acid breakthrough is noted in 60-70% of patients on twice daily PPI therapy [6] which is linked to the persistence of nighttime symptoms and disturbances in sleep quality. This limitation in pharmacodynamics significantly impacts patients with nighttime GERD symptoms and those having extra esophageal manifestations of the disease.

Impact on GERD Related complications

With PPIs decreasing acid exposure the risk of reflux related complications such as peptic strictures and ulcerative esophagitis is also reduced. Data from long term observational studies further indicate that PPIs lessen the symptoms and inflammatory activity of Barrett's esophagus [21]. However, their effect in preventing the development of esophageal adenocarcinoma is still unclear.

Summary of clinical efficacy

Generally, the PPIs continue being the first choice in the treatment of acid related issues in GERD [21,36] as they have shown great results in controlling symptoms, healing the mucosa, and preventing relapse. On the other hand, there are still cases of NERD, refractory GERD, and nocturnal acid breakthrough where the symptoms are not completely eliminated and this indicates that there are still some therapeutic gaps that need to be addressed.

Mechanism of action and pharmacological properties of P-CABs

P-CABs are a group of new acid suppressive agents that have been designed to address the pharmacological limitations of PPIs [8]. Both P-CABs and PPIs inhibit the gastric H^+/K^+ ATPase but P-CABs differ in molecular binding characteristics have faster onset of action and are able to suppress acid in a more stable manner. These features of P-CABs have a significant impact on the clinical outcome of the management of GERD [19].

Molecular mechanism of action

P-CABs inhibit gastric acid secretion by reversibly and competitively blocking the potassium binding site [9] of the H^+/K^+ ATPase on the luminal surface of parietal cells. Preventing potassium exchange P-CABs therefore stop proton translocation into the gastric lumen directly which leads to an immediate suppression of acid secretion. Unlike PPIs, P-CABs do not need acid dependent activation and they are not dependent on the presence of actively secreting proton pumps thus they can work irrespective of meal timing or circadian acid secretion patterns.

Pharmacodynamics properties

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Rapid acid suppression is one of the most clinically relevant features of P-CABs.

In intragastric pH monitoring studies P-CABs have been shown to inhibit acid effectively by the first dose [33] while PPIs usually need a period of 35 days of repeated dosing to reach their full effect. Ambulatory pH studies have also shown that P-CABs enable almost total suppression of nocturnal acid secretion [23] which is a widely known limitation of PPIs. Meta analyses have established that P-CAB treatment significantly lowers nocturnal acid breakthrough and compared to twice daily PPI regimens results in better nighttime GERD symptoms.

Pharmacokinetic characteristics

P-CABs have properties that allow for stable pharmacokinetics [33] which in turn lead to stable and consistent therapeutic effects. They quickly enter the bloodstream and their plasma concentration peaks within 12 hours. Besides they show relatively predictable drug exposure in different patient populations. Most notably the metabolism of P-CABs is unlike PPIs less influenced by CYP2C19 polymorphisms [34] which is why there is less inter individual variability in acid suppression. Furthermore, population pharmacokinetic analyses reveal only minor if any, age, sex, or ethnicity, based differences in drug exposure [35].

Stability in acidic environment

Unlike PPIs that are acid labile and need to be coated with a substance that resists the stomach acid to avoid their breakdown, P- CABs are acid stable compounds [19]. This stability allows direct luminal access to the proton pump and accounts for their quick onset of action. Not needing an enteric formulation also increases the ease and reliability of dosing.

Clinical implications of pharmacological properties

The synchronized pharmacological properties of P-CABs are fast initiation of action, strong and long-lasting acid suppression, minimized variation in patient responses [8, 35] and good control of nighttime acid production [23] offer solutions to several aspects of GERD treatment that still lack effective response. These benefits are especially significant in PPI resistant GERD cases, patients with non-erosive reflux disease, severe erosive esophagitis and those experiencing nocturnal symptoms situations in which conventional acid suppressive therapy frequently does not provide satisfactory control [5,20]. Beyond GERD management, vonoprazan has also demonstrated established efficacy in Helicobacter pylori eradication regimens, supporting its broader therapeutic role in acid-related disorders [30].

Safety of P-CABs

All in all, the existing proof features P- CABs exhibiting a very safe and predictable safety profile [18] broadly comparable to and in some areas different from that of PPIs when used for GERD and other acid related disorders.

Short-Term safety and Tolerability

Throughout phase II-III randomized double blind clinical trials in patients with erosive esophagitis, non-erosive reflux disease (NERD) and PPI refractory GERD, P-CABs were generally well tolerated. Adverse event rates overall were from 20-35% which is comparable with those reported with PPIs and placebo. The most frequently treatment emergent adverse events reported by patients were headache, diarrhea, constipation, nausea, and abdominal discomfort. Each of these occurred in <5-10% of the patients and were predominantly mild to moderate in severity. There were very few times when patients discontinued the treatment because of adverse events, it was usually in less than 35% of the cases [18] suggesting good short-term tolerability.

Long-Term Safety data

Long term studies as well as open label extension studies give reassuring data for continuous P-CAB exposure. 5 year randomized open label trial investigating vonoprazan as maintenance therapy for erosive esophagitis. It showed continuous efficacy and no unexpected safety issues. Serious adverse events were rare. At the same time follow-up studies lasting up to 96 weeks [41] in patients refractory to PPI have revealed stable laboratory parameters, low discontinuation rates, and no cumulative toxicity with continued P-CAB use.

1) Hypergastrinemia and Gastric Mucosal Effects

Potent and sustained acid suppression with P-CABs causes a dose dependent hypergastrinemia [18] which is generally more intense than that with PPIs. In the clinical studies, the mean fasting serum gastrin has been reported to increase by 24 times over the baseline especially during long term treatment. Histological examinations revealed reversible enterochromaffin like cell (ECL) hyperplasia in some patients however, there has not been any definite proof of dysplasia or neuroendocrine tumor formation in clinical trials so far. There have been reports of fundic gland polyps yet the frequency of their occurrence seems not to surpass that observed with chronic PPI therapy and no cases of malignant transformation have been documented.

Hepatic and Renal Safety

P-CABs are metabolized in the liver mostly through CYP3A4 however, clinical trials along with pooled safety analyses demonstrate that clinically significant liver enzyme elevations occur at very low rates. Transient elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been recorded in <23% of patients generally without symptoms and the enzymes return to normal without stopping the medication. In contrast to PPIs, P-CABs have not been closely associated with acute interstitial nephritis or chronic kidney disease based on clinical trials [18].

Infection Risk

By producing profound acid suppression, P-CABs theoretically share the infection related risks associated with PPIs. However, there is some evidence that the risk of enteric infections and pneumonia with P- CABs is low and similar to that of PPIs in the randomized controlled trials [18]. It has not been possible to find any indication of increased Clostridioides difficile infection so far but post marketing surveillance is still running [31].

Drug–Drug Interactions and Pharmacogenomics Considerations

P-CABs depend less on CYP2C19 metabolism than PPIs so the risk of variability due to genetic polymorphisms is lower. Although caution should be exercised when taking strong CYP3A4 inhibitors or inducers drug drug interaction

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studies have shown that there are no significant clinically relevant interactions with most commonly used medications [32].

Clinical Efficacy of P-CABs

Symptom Relief in GERD

Clinical trials reveal that heartburn and regurgitation symptoms are notably lessened already on the first day of treatment when using P-CABs whereas PPIs typically have to be taken for several days before maximal acid suppression is achieved. P-CABs in GERD patients with symptoms were able to eliminate symptoms in around 65-80% of the patients within 4-8 weeks [22] thus exceeding the effects of standard dose PPIs particularly in patients with persistent or severe symptoms. Network meta-analyses in acid-related disorders further support the superior or comparable efficacy of P-CABs compared with PPIs across multiple clinical endpoints, including ulcer healing outcomes [38].

Healing of EE

Several phase III trials and meta analyses have shown that P- CABs are at least as effective if not more than PPIs in achieving endoscopic healing [13] Including patients with severe esophagitis (Los Angeles grades C-D) healing rates with P-CABs have been shown to be 90-95% after 8 weeks of treatment [39] where healing rates following P-CAB therapy have consistently been higher than that of standard dose PPI therapy.

Efficacy in NERD

Clinical trials indicate that P-CABs are more effective than PPIs in NERD symptom control especially in acid sensitive phenotypes of patients. Research on NERD that is resistant to PPI treatment shows that there is a very considerable drop in symptom scores and reflux episodes after the therapy with P-CABs [22] with response rates of 60 to 70% versus around 45 to 55% when using PPI therapy**.**

PPI-Refractory GERD

According to clinical studies changing the medication to a P-CAB provides a substantial relief of symptoms for 60-75% of patients that have not responded to once or twice daily PPI therapy [41]. Furthermore, studies at the cellular level reveal that P-CABs efficiently counteract PPI limitations associated with their delayed activation at the cellular level, nocturnal acid breakthrough and CYP2C19 related variations, all being contributing factors to refractory disease.

Control of Nocturnal Acid and Nighttime Symptoms

Ambulatory pH testing together with meta analyses have shown that P-CABs offer better overnight acid control than PPIs [23]. Besides, P-CAB treatment lowers nocturnal acid breakthrough to a great extent and thus relieves nighttime heartburn and sleep disturbance.

Maintenance Therapy and Relapse Prevention

Long term studies have demonstrated that P-CABs are extremely effective in maintaining remission in GERD [44]. In maintenance studies lasting up to 5 years, the remission rate was over 85-90% with symptom control continued and relapse rate being very low. These results were even achieved at lower maintenance doses thus indicating that long term therapy is a viable option.

TABLE I: Clinical Efficacy Outcomes of PPIs and P-CABs in GERD [12,13,22,44]

Outcome	PPIs	P-CABs
Symptom relief (overall GERD)	55–70%	65–80%
Symptom relief in NERD	45–55%	60–70%
Response in PPI-refractory GERD	10–20% (dose escalation/switch)	60–75% (after switch)
Onset of action	Delayed (3–5 days)	Rapid (day 1)
Nocturnal symptom control	Incomplete in many patients	Significantly improved
Maintenance of remission (6–12 months)	70–85%	85–90%

This table summarizes the key comparative efficacy data for PPIs and P-CABs in GERD management.

TABLE II: Endoscopic Healing of EE [43]

Disease Severity	PPIs (8 weeks)	P-CABs (8 weeks)
Overall EE	80–90%	90–95%
LA Grade A–B	>90%	>95%
LA Grade C–D	65–80%	85–90%

LA- los Angeles Classification

TABLE III: Long-Term Maintenance Outcomes [44]

Parameter	PPIs	P-CABs
Maximum reported follow-up	>10–20 years (observational)	Up to 5 years (RCTs)
Maintenance remission rate	70–85%	85–90%
Dose escalation needed	Common in refractory cases	Less frequent
Symptom relapse after withdrawal	High	Lower during maintenance

TABLE IV: Comparative Safety Findings [18]

Safety Aspect	PPIs	P-CABs
Overall tolerability	Good	Good
Serious adverse events	Rare	Rare
Hypergastrinemia	Mild–moderate	Moderate (monitoring required)
Infection risk	Increased (observational)	No consistent signal
Renal/bone effects	Reported (observational)	Not clearly observed
Long-term trial safety	Limited RCT data	Favorable up to 5 years

Future Directions in GERD Pharmacotherapy

Despite effective acid suppression with PPIs 30–40% of GERD patients remain symptomatic, highlighting unmet therapeutic needs. Future GERD pharmacotherapy is moving toward more potent, consistent, and personalized acid suppression**.** Potassium-competitive acid blockers (P-CABs) represent the most immediate advance demonstrating faster onset, superior nocturnal acid control, and higher healing rates, particularly in severe erosive and PPI-refractory GERD. Long-term studies (up to 5 years) support their sustained efficacy and acceptable safety suggesting a potential role as earlier-line therapy. Emerging strategies emphasize personalized treatment integrating GERD phenotype, acid burden, and pharmacogenomics variability to guide drug selection. Combination therapies targeting non-acid reflux, esophageal hypersensitivity, and motility disorders are also

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being explored to improve outcomes in non-erosive and refractory disease. Overall, GERD management is transitioning from a PPI-centered approach **to a** precision-based, mechanism-driven strategy, aiming to optimize efficacy while minimizing long-term risks.

II. CONCLUSION

The incorporation of P-CABs into GERD therapy represents an important step toward more efficient and personalized acid suppression. Although PPIs achieve mucosal healing in 80–90% of patients, persistent symptoms occur in up to 30–40% particularly in non-erosive and refractory GERD. P-CABs provide rapid, meal-independent and sustained acid suppression resulting in higher healing rates (≈90–95%), faster symptom relief, and improved nocturnal acid control. Long-term studies up to 5 years demonstrate durable efficacy with an acceptable safety profile. Collectively current evidence supports P-CABs as a valuable addition that enables phenotype-driven, individualized GERD management, enabling personalized treatment strategies.

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REFERENCES

[1]. Gupta AK. Gastroesophageal reflux disease: comprehensive review from medical to surgical management. International Journal of Surgery. 2025 Nov 13:10-97. DOI: 10.1097/JS9.0000000000004035
[2]. Ciorba A, Bianchini C, Zuolo M, Feo CV. Upper aerodigestive tract disorders and gastro-oesophageal reflux disease. World Journal of Clinical Cases: WJCC. 2015 Feb 16;3(2):102. DOI:10.12998/wjcc.v3.i2.102
[3]. Youssef MM, Watson AC, Profitt SA, Allaway M, Ongso Y, Sivakumar J, Kamal AN, Shimamura Y, Thompson SK, Watson DI, Duong CP. Current pharmacological and procedural treatments for gastro-oesophageal reflux disease: comprehensive review. BJS open. 2025 Dec;9(6):zraf115. DOI:10.1093/bjsopen/zraf115
[4]. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Current gastroenterology reports. 2008 Dec;10(6):528-34. DOI: 10.1007/s11894-008-0098-4
[5]. Rettura F, Bronzini F, Campigotto M, Lambiase C, Pancetti A, Berti G, Marchi S, de Bortoli N, Zerbib F, Savarino E, Bellini M. Refractory gastroesophageal reflux disease: a management update. Frontiers in medicine. 2021 Nov 1;8:76506. DOI:10.3389/fmed.2021.765061
[6]. 6. Lehault LW, Hughes DM. Review of the long-term effects of proton pump inhibitors. Federal Practitioner. 2017 Feb;34(2):19.
[7]. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gastroenterology. 2017 Mar 1;152(4):706-15. DOI: 10.1053/j.gastro.2017.01.031
[8]. Scarpignato C, Hunt RH. Potassium-competitive acid blockers: current clinical use and future developments. Current gastroenterology reports. 2024 Nov;26(11):273-93. DOI:10.1007/s11894-024-00939-3
[9]. St. Onge E, Phillips B. Vonoprazan: a new potassium-competitive acid blocker. Journal of Pharmacy Technology. 2023 Jun;39(3):139-46. DOI:10.1177/87551225231166531
[10]. Niikura R, Yamada A, Hirata Y, Hayakawa Y, Takahashi A, Shinozaki T, Takeuchi Y, Fujishiro M, Koike K. Efficacy of vonoprazan for gastroesophageal reflux symptoms in patients with proton pump inhibitor-resistant non-erosive reflux disease. Internal Medicine. 2018 Sep 1;57(17):2443-50. DOI:10.2169/internalmedicine.0492-17
[11]. Oshima T, Miwa H. Potent potassium-competitive acid blockers: a new era for the treatment of acid-related diseases. Journal of neurogastroenterology and motility. 2018 Jul 1;24(3):334. DOI:10.5056/jnm18029
[12]. Savarino V, Marabotto E, Zentilin P, Demarzo MG, de Bortoli N, Savarino E. Pharmacological management of gastro-esophageal reflux disease: an update of the state-of-the-art. Drug design, development and therapy. 2021 Apr 19:1609-21.
[13]. Raza H, Singla B, Singla S, Kumawat S, Malhans JS, Kaur J, Usman M, Fatima I, Salman R, SINGLA B. Comparative Efficacy of Potassium-Competitive Acid Blockers (P-CABs) Versus Proton Pump Inhibitors (PPIs) in the Management of Erosive Esophagitis: A Systematic Review. Cureus. 2025 Nov 15;17(11). DOI:10.7759/cureus.96916
[14]. Shang H, Mao H, Wang J, Tian X, Zheng K, Wang J. Optimizing acid-related disease management: insights into potassium-competitive acid blockers and proton pump inhibitors. European Journal of Clinical Pharmacology. 2025 Dec;81(12):1773-86 . DOI:10.1007/s00228-025-03912-9
[15]. Scarpignato C, Hunt RH. Acid suppressant therapy: a step forward with potassium-competitive acid blockers. Current Treatment Options in Gastroenterology. 2021 Mar;19(1):94-132.
[16]. Thomson AB, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. World journal of gastroenterology: WJG. 2010 May 21;16(19):2323. DOI:10.3748/wjg.v16.i19.2323
[17]. Savarino V, Marabotto E, Zentilin P, Furnari M, Bodini G, De Maria C, Tolone S, De Bortoli N, Frazzoni M, Savarino E. Pathophysiology, diagnosis, and pharmacological treatment of gastro-esophageal reflux disease. Expert review of clinical pharmacology. 2020 Apr 2;13(4):437-449. DOI: 10.1080/17512433.2020.1752664
[18]. Jang Y, Park J, Kang D, Kim JH, Choi HS, Jeon HL, Lee H. Safety of Potassium-Competitive Acid Blockers Compared With Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease and Peptic Ulcer Disease: A Systematic Review and Meta-Analysis. Journal of Gastroenterology and Hepatology. 2026 Jan;41(1):28-40. DOI:. 10.1111/jgh.70178
[19]. Antequera CM, Orleck K, Jacob R, Kenneally A, Wright WL. Potassium-competitive acid blockers: rethinking acid suppression for gastroesophageal reflux disease and Helicobacter pylori. Postgraduate Medicine. 2024 Feb 17;136(2):131-40. DOI:10.1080/00325481.2024.2320081
[20]. Yadlapati R, DeLay K. PPI refractory gastroesophageal reflux disease. The Medical clinics of North America. 2018 Nov 1;103(1):15. DOI:10.1016/j.mcna.2018.08.002
[21]. Andrawes M, Andrawes W, Das A, Siau K. Proton Pump Inhibitors (PPIs)—An Evidence-Based Review of Indications, Efficacy, Harms, and Deprescribing. Medicina. 2025 Aug 31;61(9):1569. DOI:10.3390/medicina61091569
[22]. Seo S, Jung HK, Gyawali CP, Lee HA, Lim HS, Jeong ES, Kim SE, Moon CM. Treatment response with potassium-competitive acid blockers based on clinical phenotypes of gastroesophageal reflux disease: a systematic literature review and meta-analysis. Journal of Neurogastroenterology and Motility. 2024 Jul 30;30(3):259. DOI: 10.5056/jnm24024
[23]. Koo TH, Fass R. A systematic review and meta-analysis of randomized controlled trials: the effect of potassium-competitive acid blockers on nighttime symptoms of gastroesophageal reflux disease. Esophagus. 2026 Jan 12:1-7. DOI:.0.1007/s10388-025-01181-0
[24]. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. Therapeutic advances in drug safety. 2013 Jun;4(3):125-33. DOI:10.1177/2042098613482484
[25]. Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, Chiriac SA, Ciobica A, Boiculese L. Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis. World journal of gastroenterology. 2017 Sep 21;23(35):6500. DOI: 10.3748/wjg.v23.i35.6500

[26]. Zheng Z, Lu Z, Song Y. Long-term proton pump inhibitors use and its association with premalignant gastric lesions: a systematic review and meta-analysis. Frontiers in Pharmacology. 2023 Aug 25;14:1244400. DOI:10.3389/fphar.2023.1244400
[27]. 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 Nov 1;167(6):1228-38. DOI:10.1053/j.gastro.2024.06.038
[28]. Khan Z, Alastal Y, Khan MA, Khan MS, Khalil B, Shrestha S, Kamal F, Nawras A, Howden CW. On-demand therapy with proton pump inhibitors for maintenance treatment of nonerosive reflux disease or mild erosive esophagitis: a systematic review and meta-analysis. Gastroenterology Research and Practice. 2018;2018(1):6417526. DOI:10.1155/2018/6417526
[29]. Vakil N, Niklasson A, Denison H, Rydén A. Gender differences in symptoms in partial responders to proton pump inhibitors for gastro-oesophageal reflux disease. United European Gastroenterology Journal. 2015 Oct;3(5):443-52. DOI:10.1177/2050640614558343
[30]. Shirley M. Vonoprazan: a review in Helicobacter pylori infection. Drugs. 2024 Mar;84(3):319-27. DOI:10.1007/s40265-023-01991-5
[31]. Zhong Y, Hou C, Zhang J, Wang L, Xiong D, Zhong H, Luo X. Vonoprazan-related adverse events: a pharmacovigilance study based on the FDA adverse event reporting system. Frontiers in Medicine. 2025 Dec19;12:1688914.DOI:10.3389/fmed.2025.1688914
[32]. Yang E, Ji SC, Jang IJ, Lee S. Evaluation of CYP2C19-Mediated Pharmacokinetic Drug Interaction of Tegoprazan, Compared with Vonoprazan or Esomeprazole: E. Yang et al. Clinical Pharmacokinetics. 2023 Apr;62(4):599-608. DOI:10.1007/s40262-023-01228-4
[33]. Laine L, Sharma P, Mulford DJ, Hunt B, Leifke E, Smith N, Howden CW. Pharmacodynamics and pharmacokinetics of the potassium-competitive acid blocker vonoprazan and the proton pump inhibitor lansoprazole in US subjects. Official journal of the American College of Gastroenterology| ACG. 2022 Jul 1;117(7):1158-61. DOI:10.14309/ajg.0000000000001735
[34]. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert opinion on drug metabolism & toxicology. 2018 Apr 3;14(4):447-60. DOI:10.1080/17425255.2018.1461835
[35]. Scarpignato C, Leifke E, Smith N, Mulford DJ, Lahu G, Facius A, Howden CW. A population pharmacokinetic model of vonoprazan: evaluating the effects of race, disease status, and other covariates on exposure. The Journal of Clinical Pharmacology. 2022 Jun;62(6):801-11. DOI:10.1002/jcph.2019
[36]. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut Liver. 2017 Jan 15;11(1):27-37.. PMID: 27840364; PMCID: PMC5221858. DOI:10.5009/gnl15502
[37]. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease–where next?. Alimentary pharmacology & therapeutics. 2005 Jul;22(2):79-94. DOI:10.1111/j.1365-2036.2005.02531.x
[38]. Ouyang M, Zou S, Cheng Q, Shi X, Zhao Y, Sun M. Comparative efficacy and safety of potassium-competitive acid blockers vs. proton pump inhibitors for peptic ulcer with or without Helicobacter pylori infection: a systematic review and network meta-analysis. Pharmaceuticals. 2024 May 28;17(6):698. DOI:.10.3390/ph17060698
[39]. 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. Clinical and Translational Gastroenterology. 2024 Nov 1;15(11):e00776. DOI:10.14309/ctg.0000000000000776
[40]. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Official journal of the American College of Gastroenterology| ACG. 2013 Mar 1;108(3):308-28. DOI:10.1038/ajg.2012.444
[41]. Mizuno H, Inagaki S, Yamada K, Kamiyamamoto S. Follow-up study of vonoprazan maintenance therapy for reflux esophagitis: A 96-week evaluation in patients with PPI-refractory disease. Biomedical Reports. 2025 Jul 30;23(4):160 DOI: 10.3892/br.2025.2038
[42]. Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJ, Vaezi M, Sifrim D, Fox MR, Vela MF, Tutuian R. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018 Jul 1;67(7):1351-62. DOI: 10.1136/gutjnl-2017-314722
[43]. Chandan S, Deliwala S, Mohan BP, Ramai D, Dhindsa B, Bapaye J, Kassab LL, Chandan OC, Facciorusso A, Adler DG. Vonoprazan versus lansoprazole in erosive esophagitis—A systematic review and meta-analysis of randomized controlled trials. Indian Journal of Gastroenterology. 2023 Aug;42(4):475-84. DOI: 10.1007/s12664-023-01384-2
[44]. Miyazaki H, Igarashi A, Takeuchi T, Teng L, Uda A, Deguchi H, Higuchi K, Tango T. Vonoprazan versus proton-pump inhibitors for healing gastroesophageal reflux disease: a systematic review. Journal of gastroenterology and hepatology. 2019 Aug;34(8):1316-28.DOI: 10.1111/jgh.14664
[45]. Howden CW, Hunt RH. Relationship between gastric secretion and infection. Gut. 1987 Jan;28(1):96. DOI: 10.1136/gut.28.1.96
[46]. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. Cmaj. 2008 Aug 12;179(4):319-26.DOI: 10.1503/cmaj.071330