Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

An Indian Perspective with a Focus on Rabeprazole for High-risk Patients

Piyush Gupta[1], Anil Verma[2], Ajay Bhalla[3]

[1]Senior Consultant, Department of Gastroenterology, Max Hospital, Delhi, India, [2]Senior Consultant, Department of Gastroenterology, Sarvodaya Super Speciality Hospital Ghaziabad, Uttar Pradesh, India, Senior Consultant, Department of Gastroenterology, Yatharth Hospital, Noida, Uttar Pradesh, India

Abstract

Rabeprazole, a proton pump inhibitor (PPI), stands out for its pharmacokinetic properties and clinical benefits in managing gastrointestinal (GI) complications in patients with cardiovascular disease (CVD) and diabetes mellitus (DM). Unlike other PPIs, Rabeprazole is metabolized through a nonenzymatic pathway, minimizing drug interactions and ensuring consistent efficacy irrespective of CYP2C19 genetic variations. It offers rapid acid suppression due to its high pKa (~5.0) and quicker onset of action, achieving acid inhibition within hours of administration. Rabeprazole manages gastroesophageal reflux disease (GERD), in patients with CVD and DM. In diabetic patients, it benefits beyond acid suppression, including improved glycaemic control, enhanced insulin sensitivity, and reduced glycated haemoglobin (HbA1c) levels. Its long-term use has been linked to increased gastrin production, promoting pancreatic β-cell regeneration and glycaemic stability. For patients with CVD, combining Rabeprazole with antithrombotic therapies reduces GI bleeding risks without increasing cardiovascular events. Its stable pharmacokinetics across renal impairment and favourable safety profile make it suitable for high-risk populations. These properties position Rabeprazole as a preferred PPI for managing acid-related disorders and improving the quality of life (QoL) in patients with CVD and DM. A nationwide survey was conducted involving experts across India. Expert insights were reviewed and consolidated into a set of expert opinions. This survey highlights the advantages of Rabeprazole, including rapid acid suppression, minimal drug interactions, and benefits in improving glycaemic control and reducing GI bleeding risk in high-risk populations. The expert opinions received unanimous support, endorsing Rabeprazole as a preferred PPI for patients with CVD and DM.

Key words: Proton pump inhibitors; Cardiovascular risk; Polypharmacy; CYP450 enzyme; Clopidogrel; Rabeprazole

INTRODUCTION

Rabeprazole is a proton pump inhibitor (PPI) that reduces stomach acid production.[1] Rabeprazole, chemically known as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl] sulfinyl]-1 H-benzimidazole sodium salt, works by binding to the hydrogen/potassium adenosine triphosphatase (H^+/K^+-ATPase) enzyme, also known as the proton pump, on the surface of gastric parietal cells in the stomach lining.[1] This binding blocks the activity of the pump, thus effectively stopping acid production and increasing gastric pH.[1] The overall prevalence of gastroesophageal reflux disease (GERD) symptoms in the general adult population is nearly 30%, with about 12.5% experiencing symptoms at least once weekly over the year.[2] Increasing age correlates with a higher frequency of GERD symptoms, particularly notable in those over 55 years of age, where the rate reaches 17.2%.[2] While the link between diabetes mellitus (DM) and gastrointestinal (GI) complications is well-documented, the prevalence of GERD in asymptomatic DM patients remains insufficiently investigated.[3] GERD causes symptoms including heartburn, chest pain, cough, and sore throat, with potential complications such as oesophagitis and Barrett's esophagus if untreated. It impacts quality of life (QoL) and poses a growing societal burden, especially in developed countries. PPIs are the first-line therapy recommended for treatment.[4] This review article presents expert insights from practicing Indian physicians on the use of PPIs for managing gastric

Access this article online

www.ijss-sn.com

Month of Submission : 04-2025
Month of Peer Review : 05-2025
Month of Acceptance : 06-2025
Month of Publishing : 06-2025

Corresponding Author: Dr. Ajay Bhalla, Yatharth Hospital, Noida, Uttar Pradesh, India

complications, with a specific focus on high-risk groups such as individuals with cardiovascular disease (CVD) and DM. Key areas of exploration include their effectiveness in reducing the risk of GI bleeding associated with antiplatelet or anticoagulant treatments, their safety during prolonged use, and their influence on metabolic health and potential drug interactions in these susceptible populations.

METHODS

A nationwide survey was conducted to evaluate key issues concerning the use of PPIs in patients with CVD and DM. The comprehensive questionnaire is available as supplementary material. The objective was to assess current evidence and gather expert opinions on the role of PPIs in managing gastric complications. A total of 54 experts from across India participated, sharing their insights, which were subsequently reviewed and consolidated into a comprehensive set of expert recommendations. These recommendations received unanimous support from all participants.

Pharmacokinetic Properties that Make Rabeprazole a Preferred Choice

Rabeprazole has an overall bioavailability of 52%, which remains consistent regardless of food or antacid intake.[1] It binds extensively to plasma proteins, with binding rates between 94.8% and 97.5%.[1] Unlike many other medications, rabeprazole is metabolized through a non-enzymatic pathway, which minimizes the risk of interactions with drugs that are processed by cytochrome P450 (CYP) enzymes.[1] Rabeprazole has a notably high pKa of approximately 5.0 and a rapid onset of action compared to other PPIs.

Faster absorption

Rabeprazole demonstrates a quicker absorption rate than other PPIs. Studies indicate that the time to reach maximum concentration (T_{max}) for rabeprazole can range from 0.25 to 1.5 h, which is significantly faster than the 2–8 h observed with conventional formulations of other PPIs such as Omeprazole.[4] It begins to block active proton pumps within 5 min, achieving almost complete inhibition quickly. Peak plasma concentrations are typically reached within 3–4 h of administration.[1]

Extended duration of action

Rabeprazole irreversibly inhibits the H^+/K^+-ATPase enzyme in gastric parietal cells, leading to sustained acid suppression for 24–48 h after administration.[5] This long-lasting effect allows for once-daily dosing in most cases, improving patient compliance and convenience.[5]

Rabeprazole effectively suppresses gastric acid secretion in a dose-dependent manner. Studies in patients with severe renal impairment have shown that its pharmacokinetics are unaffected, therefore, dose adjustments are not necessary in this population.[1] When administered in doses of 10 or 20 mg once daily, the pharmacokinetics, including maximum plasma concentration of a drug (C_{max}) and area under the curve, remain linear and stable with repeated dosing.[1] Rabeprazole has a plasma half-life of 1–2 h, and the time to reach peak concentration (t_{max}) remains consistent across different doses.[1]

Gastric Protection in CVD and DM

GERD prevalence, causes, and impact on QoL

GERD is a common GI condition in which stomach contents frequently flow back into the esophagus. It affects millions of people globally, with an estimated global prevalence of 13.9% in 2020.[6] Studies show the prevalence of GERD in India is approximately 15.6%. GERD can result from several structural and functional factors that weaken the anti-reflux barrier located at the esophagogastric junction, including the lower oesophageal sphincter (LES) and crural diaphragm.[6] This weakening allows acidic stomach contents to reach the esophagus, causing irritation. The severity of GERD is closely related to the level and duration of acid exposure in the esophagus.[6]

Gastroesophageal reflux in patients with DM without GI symptoms

GI complications in DM often arise from altered GI motility patterns. The study aimed to assess the prevalence of asymptomatic GERD in patients with DM, recognizing that GI complications frequently occur in this population and are often underdiagnosed due to their asymptomatic presentation.[3]

In a prospective study, 20 patients with DM who exhibited no symptoms of GERD were enrolled. GERD diagnosis was primarily confirmed through 24-h ambulatory pH monitoring.[3] Patients, free of GERD symptoms and dyspepsia, were initially screened with a dyspepsia questionnaire and assessed for fasting glucose levels, glycated hemoglobin (HbA1c), and body mass index (BMI).[3] Further evaluations included oesophageal manometry and 24-h ambulatory pH monitoring. Analysis using 24-h ambulatory pH monitoring indicated a 40% prevalence of GERD in asymptomatic DM patients.[3] The prevalence of asymptomatic GERD among DM patients was notably higher than that of the general population ($P < 0.05$).[3] These findings suggest the common occurrence of GI complications within this group.[3] This highlights the importance of proactive screening and management for GERD in patients with DM, regardless of symptom presentation.[3] Targeted dietary strategies,

lifestyle adjustments, and pharmacologic treatment may improve the QoL and reduce the risk of GERD-related complications in this population.[3]

Prevalence of GI symptoms in patients with DM

GI symptoms are more common in people with DM than in the general population, with reported prevalence rates varying widely, often exceeding 70% in outpatient samples.[7] The prevalence of GI symptoms may differ between type 1 and type 2 DM, with some studies suggesting patients with type 1 diabetes DM experience less heartburn but more constipation.[7] Factors, such as BMI, sex, psychological comorbidities, and age can influence the prevalence of GI symptoms.[7]

Prevalence of GI issues in patients with CVD

GI issues are common among patients with CVD, with many attributing coronary artery disease (CAD) symptoms to GI problems, leading to delayed diagnosis and poor outcomes.[8] Patients with CAD undergoing antithrombotic therapy are at high risk of GI bleeding, which has been linked to increased cardiovascular (CV) events and mortality.[8] The use of multiple drugs to manage CV conditions can cause upper GI symptoms, and some GI treatments may increase CV risk due to drug–drug interactions.[8]

Efficacy and safety of PPI in patients with CAD

The meta-analysis assessed the efficacy and safety of combining PPIs with an antithrombotic regimen in patients with CAD, compared to using antithrombotic therapy alone.[9] The primary efficacy outcome assessed was the occurrence of major adverse CV and cerebrovascular events (MACCE), whereas the primary safety outcome focused on GI events.[9] Secondary outcomes included rates of all-cause mortality, CV mortality, myocardial infarction (MI), stent thrombosis, significant bleeding from gastroduodenal lesions, and gastroduodenal ulcer formation.[9]

A total of 19 trials with 43,943 patients were included in the analysis. Results did not indicate any significant increase in the risk of MACCE (relative risk [RR] 1.05; 95% confidence interval [CI] 0.96–1.15), all-cause mortality (RR 0.84; 95% CI 0.69–1.01), CV mortality (RR 0.88; 95% CI 0.69–1.12), MI (RR 0.98; 95% CI 0.88–1.09), stent thrombosis (RR 1.01; 95% CI 0.76–1.34) or gastroduodenal ulcer formation (RR 0.40; 95% CI 0.13–1.29) among patients receiving PPIs compared to those who did not.[9] However, the combined PPI and antithrombotic therapy significantly reduced the risk of GI events (RR 0.34; 95% CI 0.21–0.54) and major bleeding from gastroduodenal lesions (RR 0.09; 95% CI 0.03–0.28) compared to antithrombotic therapy alone.[9]

For patients with CAD, the addition of PPIs to an antithrombotic regimen may help reduce the risk of GI events and bleeding from gastroduodenal lesions without affecting the rates of MACCE, mortality, MI, stent thrombosis, or gastroduodenal ulcers.[9]

Symptoms of GERD

Heartburn and regurgitation are common symptoms of GERD, but it can also cause other symptoms such as chest pain, epigastric pain, nausea, vomiting, belching, bloating, early fullness, and pain when swallowing.[6] These symptoms often occur during both day and night, with night-time symptoms frequently leading to sleep disturbances like early or interrupted waking.[6]

Other factors influencing GERD

In addition to anatomical factors, various other factors contribute significantly to the development of GERD.[6] These include age over 50, low socioeconomic status, tobacco use, excessive alcohol consumption, certain connective tissue disorders, pregnancy, and the use of specific medications, such as benzodiazepines, nonsteroidal anti-inflammatory drugs (NSAIDs), and aspirin.[6] Because GERD has a significant impact on a patient's QoL, treatment focuses on restoring QoL and reducing the disease's socioeconomic impact.[6] The primary goals of managing GERD are to control symptoms, prevent symptom recurrence, and minimize the risk of GERD-related complications, such as dysphagia, bleeding, and esophageal strictures.[6]

How rabeprazole differs from other PPIs?

- Metabolism pathway: Unlike most PPIs that are primarily metabolized by the hepatic CYP enzyme system, rabeprazole is mainly metabolized through a nonenzymatic pathway, with minimal involvement of CYP enzymes (such as CYP2C19 and CYP3A4).[6]
- Predictability: The effectiveness of rabeprazole is not influenced by genetic variations in the CYP2C19 isoenzyme, making its antisecretory activity more predictable compared to other PPIs.[6]
- Activation at higher pH: Rabeprazole has a higher pKa value (~5.0), allowing it to be activated at higher pH levels more rapidly than other PPIs, resulting in a faster onset of acid inhibition.[6]

Long-term use of PPI in patients with DM

PPIs are powerful agents that suppress acid production by targeting the H^+ and K^+-ATPase enzymes in the gastric parietal cells.[10] They are widely prescribed to manage conditions such as GERD, peptic ulcers, and GI issues associated with NSAID use.[10] Under normal circumstances, high gastric acid levels trigger a feedback mechanism that inhibits gastrin release. However, by reducing gastric acid secretion, PPIs disrupt this feedback,

leading to increased gastrin production.[10] Research has shown that PPIs can raise plasma gastrin levels and insulin while also lowering HbA1c. Two retrospective studies have indicated that individuals with type 2 DM who used PPIs had improved A1c levels and better glycaemic control compared to those who did not use PPIs.[10]

The role of rabeprazole in patients with DM includes

Acid suppression

Rabeprazole is noted for its high accumulation and rapid transformation into its active form, which results in effective acid suppression.[11]

In a study comparing rabeprazole and omeprazole, the acid secretion was suppressed by rabeprazole (20 mg) by 72% after 11 h and 64% after 23 h, in contrast to omeprazole (20 mg), and the benefit was sustained throughout the therapeutic intervention period of 8 days.[11]

Comparison with other PPIs

Rabeprazole, compared with other PPIs such as omeprazole, pantoprazole, and esomeprazole, shows superior acid suppression and longer maintenance of intragastric pH > 4.[11]

Potential benefits

Rabeprazole may offer significant benefits in managing diabetes by improving glycemic control and reducing the risk of GI issues.[11] PPIs may help improve blood sugar control in individuals with type 2 DM by enhancing insulin sensitivity, which can lower blood glucose levels. Research suggests that this effect of PPIs could also reduce the risk of long-term diabetes complications, such as neuropathy, stroke, and CVD.[11]

Gastrin and glycaemic control

PPIs elevate serum gastrin levels, which may improve glucose tolerance by promoting pancreatic β cell neogenesis and replication.[12]

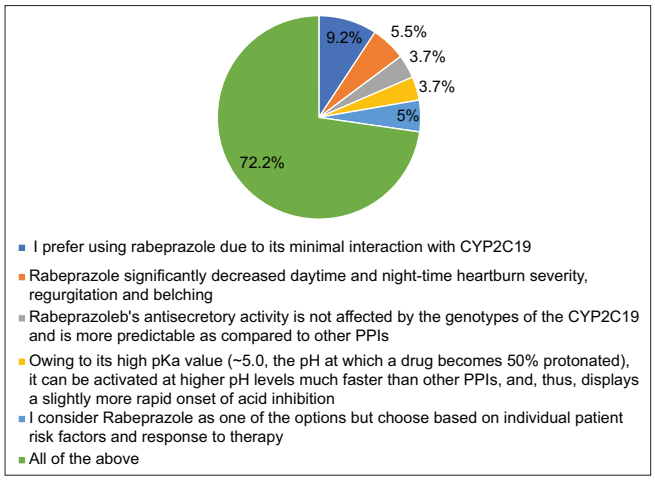

Figure 1: Statements that reflect clinical experience when prescribing rabeprazole

Clinical studies

Several studies have shown significant improvements in HbA1c levels and fasting plasma glucose in patients with type 2 DM taking PPIs.[12]

EXPERT OPINIONS AND DISCUSSION

Statements that Best Reflect the Clinical Approach for Immediate Relief when Prescribing Rabeprazole to GI Patients

The majority of respondents (72.2%) selected "All of the statements" [Figure 1], indicating that most clinicians consider multiple factors when prescribing rabeprazole. These factors include its minimal interaction with CYP2C19, which may reduce potential drug interactions (9.2% of respondents). It has the ability to significantly decrease both daytime and night-time heartburn severity, as well as symptoms such as regurgitation and belching (5.5%). Its antisecretory activity is not influenced by CYP2C19 genotypes, making its effect more consistent compared to other PPIs (3.7%). Its higher pKa value (~5.0) allows it to be activated at higher pH levels, which may lead to a quicker onset of acid inhibition (3.7%). Clinicians choose rabeprazole based on individual patient risk factors and response to therapy (5%). Rabeprazole undergoes nonenzymatic conversion into a thioether, with minimal involvement of the enzymes CYP2C19 and CYP3A4 in its hepatic metabolism. Genetic variations in CYP2C19 or potential drug interactions are less likely to affect rabeprazole compared to other PPIs.[13] The data indicates that most clinicians consider rabeprazole due to its predictable action, rapid onset of acid suppression, and minimal interaction with metabolic enzymes, making it a favorable choice.

Statement that is True for PPI Metabolism

The majority of respondents (83.3%) selected "All of

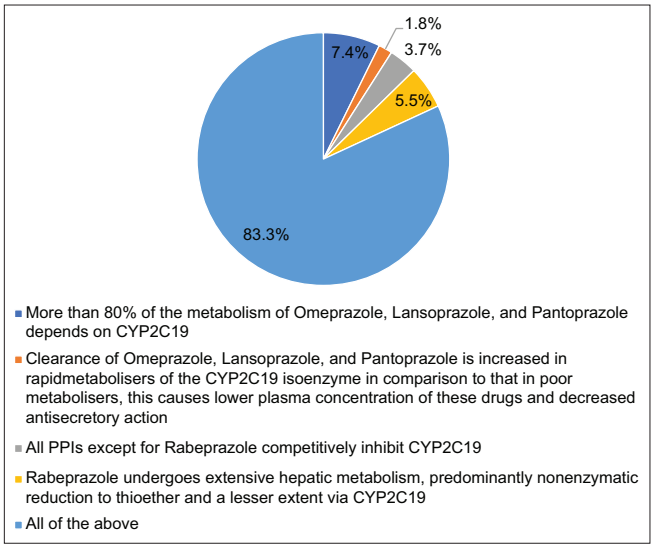

Figure 2: Statements true for proton pump inhibitor metabolism

the statements as true" [Figure 2], indicating that most clinicians agree with multiple aspects of PPI metabolism and the role of CYP2C19. The included statements are as follows: More than 80% of the metabolism of omeprazole, lansoprazole, and pantoprazole depends on CYP2C19 (7.4%), highlighting the significant role of CYP2C19 in the metabolism of these PPIs.[14] The clearance of omeprazole, lansoprazole, and pantoprazole is increased in rapid metabolizers of CYP2C19 compared to poor metabolizers, leading to lower plasma concentrations and decreased antisecretory effects (3.7%), showing how genetic variations affect drug levels and efficacy. All PPIs except rabeprazole competitively inhibit CYP2C19 (1.8%), suggesting that rabeprazole has a unique profile among PPIs regarding CYP2C19 interaction. Rabeprazole undergoes extensive hepatic metabolism, primarily through nonenzymatic reduction to a thioether, with only a minor role for CYP2C19 (5.5%), emphasizing rabeprazole's reliance is less on CYP2C19 for metabolism. Clinicians generally recognize the complex relationship between CYP2C19 and PPI metabolism, particularly with the distinct metabolic pathway of rabeprazole.

Most Appropriate PPI in Decreasing GI Bleeding/Acid Secretion in Patients Prescribed with Drugs that Metabolise through CYP2C19 Isoenzyme

According to clinicians, rabeprazole dominates as the most preferred PPI, with a significantly large portion of responses (90.74%; Figure 3). Pantoprazole holds the second-largest segment, though the preference is much lower than rabeprazole (7%). Esomeprazole has a minimal preference of 2%, whereas lansoprazole and omeprazole were not preferred by any of the clinicians. This indicates a strong consensus for rabeprazole as the most appropriate choice among the listed PPIs for reducing GI bleeding. Rabeprazole differs from traditional PPIs in its metabolic pathway.[15] Unlike other PPIs, it is primarily degraded through non-enzymatic routes rather than relying on the CYP450 enzyme system.[15] This unique metabolism minimizes its interaction with clopidogrel and ensures that it does not interfere with Clopidogrel's antiplatelet function.[15]

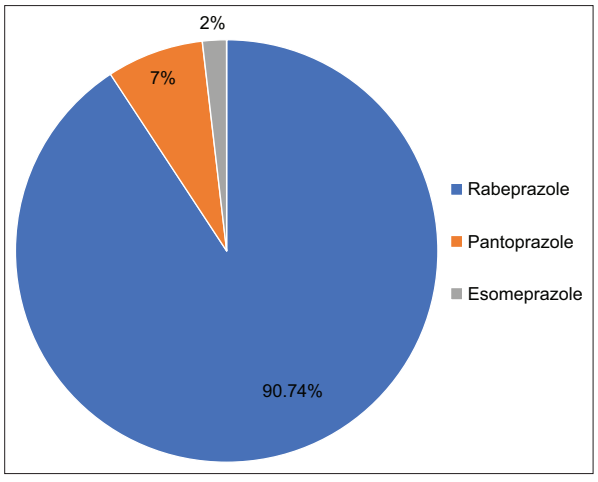

Figure 3: Most appropriate proton pump inhibitor in decreasing gastrointestinal bleeding

Statements that Best Support the Efficacy of Rabeprazole in Patients with GERD Taking Antihypertensive Drugs

The majority of respondents (66.7%) selected all of the statements [Figure 4], indicating broad agreement with multiple statements regarding the use of rabeprazole. Calcium channel blockers (CCBs), particularly nifedipine, increase the risk of GERD by significantly reducing the tone of the LES, which increases oesophageal acid exposure and reduces esophageal peristalsis (18.5% of respondents). Antacid drug therapy with rabeprazole could reduce both systolic and diastolic blood pressure in patients with GERD and hypertension (1.9%). The mean ratios of 24-h pH ≥3 holding time were significantly longer with rabeprazole, attributed to its higher pKa compared to other PPIs, resulting in superior inhibition of gastric acid (13%).

The administration of CCBs should be avoided in patients with GERD.[16] This highlights that certain antihypertensive medications can exacerbate GERD symptoms.[16] Antacid therapy effectively normalize esophageal pH and significantly reduces elevated blood pressure, indicating that managing GERD may help in stabilizing blood pressure in patients with essential hypertension. Rabeprazole may also have a potential benefit beyond acid suppression.[17] Rabeprazole has a higher pKa value (5) compared to other PPI (pKa ~4), making it less reliant on low pH for conversion to its active form.[18] This property enables rabeprazole to activate more rapidly across a broader pH range.[18] Consequently, its

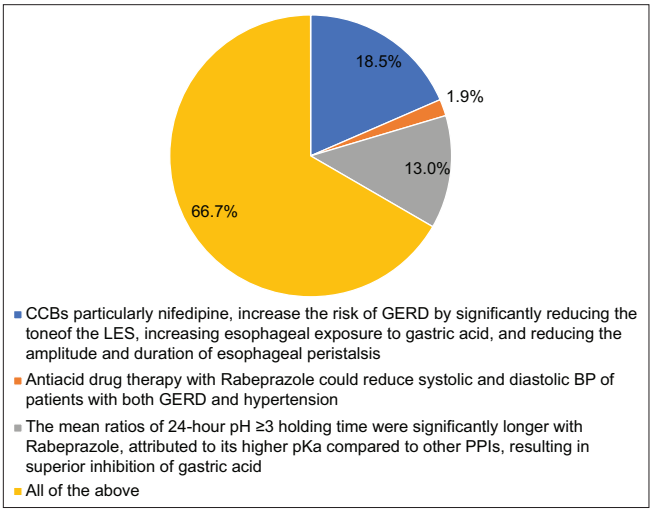

Figure 4: Statements that support the efficacy of rabeprazole in patients with gastroesophageal reflux disease taking antihypertensive drugs

higher pKa accounts for the faster onset of proton pump inhibition compared to other PPIs.[18] This emphasizes that rabeprazole has enhanced acid suppression due to its pharmacokinetic properties.[18] Clinicians generally support the use of rabeprazole in patients with GERD on antihypertensive medications, recognizing its efficacy in reducing acid exposure, mitigating GERD symptoms potentially worsened by certain antihypertensives, and offering additional benefits in blood pressure control.

Therapeutic Indications of Rabeprazole in Patients with CVD

Common indications include dyspepsia, unexplained chest discomfort or pain, GERD, peptic ulcer bleeding, gastric acid secretion, and aspirin-related mucosal injury, according to 91% of experts [Figure 5]. The individual contributions of peptic ulcer bleeding, gastric acid secretion, and aspirin-related mucosal injury remain minimal at 2% each. GERD alone accounts for only 4%. This shift emphasizes that rabeprazole is largely prescribed for multifactorial indications in CVD patients, rather than for isolated conditions. Rabeprazole is a well-tolerated and effective PPI widely used in the management of acid-related GI disorders. It has demonstrated significant efficacy in the treatment of peptic ulcers, not only promoting their healing but also reducing the risk of relapse.[19] Rabeprazole is considered a valuable alternative to H2 receptor antagonists (anti-H2) due to its superior acid suppression and longer duration of action.[19] In addition, it serves as an important therapeutic option among PPIs for managing various conditions associated with excessive gastric acid production, such as GERD and NSAID-induced gastric ulcers.[18] Its rapid onset of action and favorable safety profile make it a preferred choice in both short-term and long-term treatment strategies for these conditions.[18]

Preferred PPI while Co-Prescribing in Patients with Hypertension/DM Complaining of GERD

Rabeprazole was the most preferred PPI for co-prescription in hypertensive or diabetic patients with GERD, accounting for 94% of the prescriptions. In comparison, esomeprazole was chosen in only 6% of cases, whereas lansoprazole and pantoprazole were not recommended for these patients. The primary objective of co-prescribing PPIs for cardiac patients is to reduce the risk of GI bleeding, a common adverse effect of dual antiplatelet therapy (DAPT).[20] PPIs such as pantoprazole, omeprazole, and lansoprazole undergo extensive hepatic metabolism, predominantly through CYP enzymes CYP3A4 and CYP2C19.[20] Despite its structural similarity to other PPIs, rabeprazole exhibits distinct metabolic properties.[20] Studies have shown that the metabolic activation of clopidogrel depends heavily on CYP2C19 and CYP3A4.[20] This has raised concerns that PPIs could impair Clopidogrel's antiplatelet efficacy, potentially increasing the risk of major adverse CV events (MACE).[19,20] However, rabeprazole is a weaker competitive inhibitor of CYP2C19 compared to other PPIs.[19,20] Consequently, its use has not been associated with a significant increase in MACE risk or heterogeneity.[20] These findings support the CV safety of rabeprazole, making it a safer option among PPIs in patients requiring concomitant clopidogrel therapy.[20]

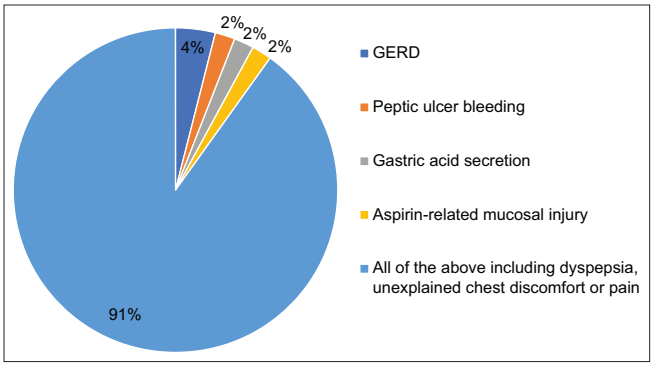

Figure 5: Indications for rabeprazole in patients with cardiovascular disease

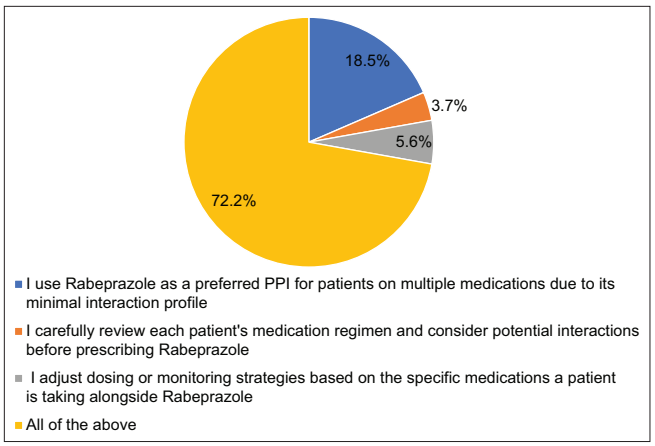

Figure 6: Approach toward the use of rabeprazole in patients undergoing polypharmacy

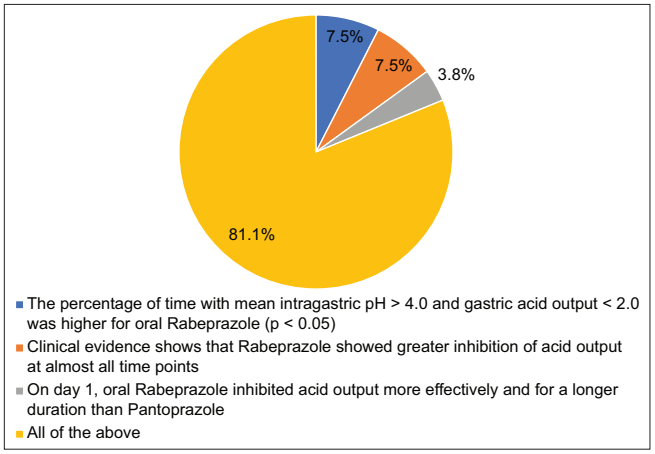

Figure 7: Rabeprazole can be prescribed to be taken any time of the day

Rabeprazole in Patients Undergoing Polypharmacy

The majority of respondents (72.2%) agree with all of the statements [Figure 6]. A smaller portion (18.5%) prefers to prescribe rabeprazole to patients on multiple medications due to its minimal interaction profile. Very few (5.6%) prefer to adjust dose or monitoring strategies based on the specific medications a patient is taking alongside rabeprazole. The smallest group (3.7%) emphasizes carefully reviewing each patient's medication regimen and considering potential interactions before prescribing rabeprazole. This suggests that a majority of respondents consider all of the listed factors—minimal interaction profile, a careful review of the medication regimen, and dosing adjustments based on other medications—when prescribing rabeprazole. The drug–drug interaction between clopidogrel and esomeprazole was observed in 23 patients (18%), posing a risk of therapy failure and diminishing clopidogrel's protective CV benefits. This interaction is pharmacokinetic in nature, as esomeprazole inhibits CYP2C19, the enzyme that metabolizes clopidogrel, reducing the levels of clopidogrel's active metabolite. To mitigate this risk, it is strongly advised to replace esomeprazole with alternative PPIs such as rabeprazole or pantoprazole.[21]

Rabeprazole can be taken at any Time of the Day

The responses highlight a strong preference for the cumulative benefits of rabeprazole [Figure 7]. 7.5% of respondents agreed that mean intragastric pH > 4.0 and gastric acid output <2.0 support the flexibility in prescribing rabeprazole. This finding underscores its effectiveness in maintaining an optimal gastric environment for longer durations ($P < 0.05$). 7.5% of respondents supported the evidence showing superior inhibition of acid output across almost all time points. This shows that it has consistent efficacy regardless of administration timing. On day 1, 3.8% of respondents acknowledged that rabeprazole provided more effective and prolonged acid output inhibition than pantoprazole. No respondents opted for significant differences in mean time-matched pH values during the first 8.3 h ($P < 0.05$). A significant number of (81%) respondents selected "All of the above," indicating that most clinicians value the combined clinical evidence supporting the flexibility of rabeprazole. This consensus reinforces the idea that the pharmacodynamic properties of rabeprazole, such as effective acid suppression, prolonged duration of action, and greater inhibition at multiple time points, are sufficient to justify its use at any time of the day.

Fastest-acting PPI in your Clinical Practice

A majority (92.6%) of respondents prefer or prescribe rabeprazole. A small percentage (7.4%) prefer esomeprazole, indicating that it is far less preferred than rabeprazole. No respondents indicated a preference for pantoprazole or lansoprazole, suggesting that these PPIs are not favored as the fastest-acting PPIs. This dominance suggests that Rabeprazole is the preferred PPI, most likely due to its effectiveness, tolerability, or other benefits such as a lower potential for drug interactions. Rapid activation of rabeprazole across a broad pH range explains its faster onset of effective acid suppression compared to other PPIs such as omeprazole, lansoprazole, and pantoprazole.[18] Rabeprazole may provide improved 1st-day acid suppression compared with esomeprazole.[18] Rabeprazole, in both 10 mg and 20 mg doses, demonstrates superior gastric pH control, maintaining pH levels above 4 and 3 for longer durations and achieving a higher area under the gastric pH-time curve on the 1st day of treatment compared to other PPIs. These findings highlight its rapid onset of acid suppression. Notably, comparisons with omeprazole and esomeprazole indicated improved nocturnal acid control on day 1 with rabeprazole.[21] In a multicenter, open-label study, 2,579 patients diagnosed with erosive oesophagitis were treated with rabeprazole 20 mg once daily for 8 weeks. On the 1st day of treatment, rabeprazole significantly reduced the severity of symptoms, including daytime and night-time heartburn, regurgitation, and belching. Complete relief from daytime heartburn was reported in 64.0% of patients, and 69.2% experienced relief from night-time heartburn. By the 7th day, these improvements were even more pronounced, with 81.1% achieving complete relief from daytime heartburn and 85.7% from night-time heartburn.[22]

Rabeprazole offers the advantage of fewer drug–drug interactions, making it highly suitable for patients on multiple medications. It also has the added benefit of promoting mucin secretion for enhanced gastric protection.

Rabeprazole stands out as the only PPI that increases gastric mucin levels. In cases of reflux oesophagitis, mucin secretion is notably reduced. Treatment with rabeprazole at a dose of 20 mg once daily for 8 weeks resulted in a marked improvement in oesophageal mucin secretion rates, both under basal conditions (during initial saline exposure) and after a mucosal challenge with HCl/pepsin, replicating the typical gastroesophageal reflux environment. In addition, a double-blind, placebo-controlled study demonstrated that a 7-day course of rabeprazole (20 mg QD) significantly boosted gastric mucin secretion by 167%.[23] A double-blind study involving 21 asymptomatic volunteers investigated the impact of rabeprazole on gastric mucin content, mucus, and its viscosity. Rabeprazole administration resulted in a significant increase in mucus content in both pentagastrin-

stimulated (3.36 ± 0.39 vs. 1.50 ± 0.32 mg/mL, $P < 0.001$) and basal (3.31 ± 0.38 vs. 2.28 ± 0.36 mg/mL, $P < 0.01$) conditions. Mucin levels were also notably higher with rabeprazole, showing a 2.6-fold increase under stimulated conditions (0.96 ± 0.08 vs. 0.36 ± 0.06 mg/mL, $P < 0.0001$) and a 41% rise in basal conditions (0.82 ± 0.09 vs. 0.58 ± 0.09 mg/mL, $P < 0.05$). In addition, gastric juice viscosity significantly increased in both stimulated ($P < 0.01$) and basal ($P < 0.05$) conditions during rabeprazole treatment. These findings suggest that rabeprazole enhances gastric mucus and mucin production and may provide added clinical benefits in safeguarding the upper GI tract against acid-related challenges.[24]

CONCLUSION

Minimal CYP2C19 Interaction

Many experts emphasized that rabeprazole metabolism primarily involves non-enzymatic reduction, minimizing variability in efficacy and drug interactions, especially in polypharmacy scenarios.

Efficacy in Managing Acid-related Disorders

Common indications include GERD, dyspepsia, peptic ulcer bleeding, and unexplained chest pain. Superior acid suppression from day 1 and prolonged action compared to pantoprazole were consistently mentioned.

Safety and Compatibility in Patients with CVD and DM

Experts prefer rabeprazole due to its minimal impact on hypertensive and diabetic patient regimens. The reduction of aspirin-related mucosal injuries is a specific advantage cited for CVD patients.

Flexible Dosing

Several experts validated the ability to take rabeprazole at any time of day, citing consistent intragastric pH > 4.0 and superior acid inhibition.

Rapid Onset of Action

Experts attributed that rabeprazole has effectiveness at high pKa (~5.0), ensuring faster activation and quicker relief from symptoms.

Rabeprazole Versus Pantoprazole

While some experts still recommend pantoprazole for CYP2C19-metabolised drug scenarios, Rabeprazole has broader advantages, including superior acid inhibition and safety profile, which were more commonly endorsed.

Rabeprazole Versus Esomeprazole

Experts occasionally prefer esomeprazole in certain patient groups, but acknowledge the suitability of rabeprazole for most scenarios.

Clinical Evidence Supporting Rabeprazole

High intragastric pH maintenance (>4.0) and a significant reduction in gastric acid output across time points. Scientific evidence supports strong acid suppression from the first dose, maintaining efficacy over time, and superior efficacy compared to pantoprazole in achieving prolonged acid suppression.

Recommendations

Rabeprazole is widely recommended for patients requiring reduced GI bleeding risk, especially those on CYP2C19-metabolised drugs. Its predictable antisecretory activity, minimal drug interaction profile, and safety in patients with CVD and DM make it a reliable option for polypharmacy patients. Experts recommend rabeprazole as a first-line PPI due to its dosing flexibility, which allows for administration at any time of the day.

ACKNOWLEDGMENT

We would like to acknowledge Scientimed Solutions Pvt. Ltd. for assistance in developing the manuscript.

REFERENCES

1. Changani M, Soni A, Kumar L, Patel S. Randomized, open labelled, two-treatment, two-period, single-dose crossover bioavailability & bioequivalence study to compare two formulations of rabeprazole in healthy male subjects. Am J Pharmacol Ther 2019;3:8-12.
2. Moshkowitz M, Horowitz N, Halpern Z, Santo E. Gastrooesophageal reflux disease symptoms: Prevalence, sociodemographics and treatment patterns in the adult Israeli population. World J Gastroenterol 2011;17:1332-5.
3. Bilgic NM, Ozel AM, Bayramicli OU, Bulur A. Frequency of gastrooesophageal reflux in diabetic patients without gastrointestinal symptoms. Med Sci Discov 2024;11:67-72.
4. Bae S, Kwon J, Lee MH, Yu KS, Lee S. Development of a fast onset proton pump inhibitor: Comparison of fixed-dose combination of rabeprazole and sodium bicarbonate (ypi-011) to the conventional enteric-coated rabeprazole. Drug Des Devel Ther 2023;17:497-506.
5. Bethesda L. Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Available from: https://www.ncbi.nlm.nih.gov/books/nbk548154 [Last accessed on 2025 Apr 26].
6. Lawate P, Jilawar N, Vyas K, Pebbili KK, Desai S, Rathod R, *et al*. Effectiveness of rabeprazole and other proton pump inhibitors in managing gerd with varying severity: A retrospective, real-world EMR-based study (POWER GERD study). J Assoc Physicians India 2023;71:37-44.
7. Du YT, Rayner CK, Jones KL, Talley NJ, Horowitz M. Gastrointestinal symptoms in diabetes: Prevalence, assessment, pathogenesis, and management. Diabetes Care 2018;41:627-37.
8. Dalal J, Dutta AL, Hiremath J, Iyengar SS, Mohan JC, Ooman A, *et al*. Cardiovascular compatibility of proton pump inhibitors: Practice recommendations. Cardiol Ther 2023;12:557-70.
9. Shang YS, Zhong PY, Ma Y, Bai N, Niu Y, Wang ZL. Efficacy and safety of proton pump inhibitors in patients with coronary artery diseases receiving oral antiplatelet agents and/or anticoagulants: A systematic review and meta-analysis. J Cardiovasc Pharmacol 2022;80:1-12.
10. Han N, Oh M, Park SM, Kim YJ, Lee EJ, Kim TK *et al*. The effect of proton pump inhibitors on glycated hemoglobin levels in patients with type 2 diabetes mellitus. Can J Diabetes 2015;39:24-8.
11. Khuntia M, Mishra S, Chand S, Sahoo A, Swain SK, Mahapatra H.

Long-term PPI (proton pump inhibitor) use in patients with diabetes. NeuroQuantology 2022;20:3729-40.
12. Takebayashi K, Inukai T. Effect of proton pump inhibitors on glycemic control in patients with diabetes. World J Diabetes 2015;6:1122-31.
13. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: From CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol 2018;14:447-60.
14. Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, *et al.* Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. Clin Pharmacol Ther 2021;109:1417-23.
15. Jia RJ, Wang XP, Zhang ZH, Cui HH, Qin R, Du DY, *et al.* Effect of Rabeprazole and rebamipide in the treatment of upper gastrointestinal hemorrhage associated with dual antiplatelet therapy in elderly patients with coronary heart disease. Clin Appl Thromb Hemost 2022;28:1-7:10760296221130746.
16. Seretis C, Seretis F, Gemenetzis G, Liakos N, Pappas A, Gourgiotis S, *et al.* Calcium channel blockers and esophageal sclerosis: Should we expect exacerbation of interstitial lung disease. Case Rep Gastroenterol 2012;6:82-7.
17. Li ZT, Ji F, Han XW, Wang L, Yue YQ, Wang ZG. The role of gastroesophageal reflux in provoking high blood pressure episodes in patients with hypertension. J Clin Gastroenterol 2018;52:685-90.
18. Robinson M. Review article: pH, healing and symptom relief with Rabeprazole treatment in acid-related disorders. Aliment Pharmacol Ther 2004;20:30-7.
19. Niu Q, Wang Z, Zhang Y, Wang J, Zhang P, Wang C, *et al*. Combination use of clopidogrel and proton pump inhibitors increases major adverse cardiovascular events in patients with coronary artery disease: A meta-analysis. J Cardiovasc Pharmacol Ther 2017;22:142-52.
20. Dalal J, Desai S, Pebbilli KK. Cardiac safety of proton pump inhibitors when used with antiplatelet agents. Indian J Clin Cardiol 2024;5:344-9:26324636241287665.
21. Robinson M, Barone J. Review article: Comparative pharmacodynamic review of rabeprazole-focus on day 1 data. Aliment Pharmacol Ther Symp Ser 2006;2:315-26.
22. Robinson M, Fitzgerald S, Hegedus R, Murthy A, Jokubaitis L, FAST TRIAL INVESTIGATORS). Onset of symptom relief with rabeprazole: A community-based, open-label assessment of patients with erosive ooesophagitis. Aliment Pharmacol Ther 2002;16:445-54.
23. Agrawal A, Sethi V. Rabeprazole: The Unique PPIs. J Clin Endocrinol Metab 2023;2:1-8.
24. Skoczylas T, Sarosiek I, Sostarich S, McElhinney C, Durham S, Sarosiek J. Significant enhancement of gastric mucin content after rabeprazole administration: Its potential clinical significance in acid-related disorders. Dig Dis Sci 2003;48:322-8.

How to cite this article: Gupta P, Verma A, Bhalla A. An Indian Perspective with a Focus on Rabeprazole for High-risk Patients. Int J Sci Stud 2025;13(3):23-31.

Source of Support: Nil, **Conflicts of Interest:** None declared.